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204 Common Viral Respiratory Infections, Other Than COVID-19

TABLE 203-1 Recommended Treatments for Genital Warts Caused by Human Papillomavirusa TREATMENT IMIQUIMOD CRYOTHERAPY INTERFERON SURGICAL REMOVAL LASER Effectiveness Good Good Good Excellent Excellent Recurrence Frequent Frequent Frequent Frequent Frequent Adverse effects Frequent, mild to moderate Mild, well tolerated Frequent, moderately severe Mild, well tolerated Mild to moderate, well tolerated Availability Fair Good Fair Good Fair Cost Expensive Inexpensive Very expensive Moderately expensive Very expensive aImiquimod can be self-administered. All other treatments must be administered by a clinician. immune responses are blunted by specific viral mechanisms. Numerous therapeutic vaccines that are being developed are designed to enhance the cell-mediated response to the HPV E6 and E7 oncoproteins, which are expressed in HPV-associated cancers. Such vaccines would enhance the ability to treat HPV-associated cancers, conditions that are very difficult to treat with current modalities. However, while progress has been made, no HPV vac cine is currently available for treatment of HPV infection or HPVassociated disease. Other Therapies Both trichloroacetic acid and bichloroacetic acid are caustic agents that destroy warts by coagulation of proteins. Nei ther of these agents is recommended for treatment. Sinecatechins (15% ointment) and podophyllotoxin (0.05% solution or gel and 0.15% cream) are occasionally used for external genital warts, but other modalities listed above are as or more effective and are better tolerated. RECOMMENDATIONS FOR TREATMENT Table 203-1 lists available treatments for genital warts. An optimal therapy for HPV-related genital tract disease that combines high efficacy, low toxicity, low cost, and low recurrence is not available. For genital warts of the penis or vulva, cryotherapy is the safest, least expensive, and most effective modality. However, all available modalities for treatment of genital warts carry high rates of recur rence. Guidelines for the treatment of anogenital warts can be found on the CDC website (https://www.cdc.gov/std/treatment-guidelines/ anogenital-warts.htm). Women with vaginal lesions should be referred to a gynecologist experienced in colposcopy and treatment of these lesions. Treat ment of cervical disease involves careful inspection, biopsy, and histopathologic grading to determine the severity and extent of disease. Women with evidence of HPV-associated cervical disease should be referred to a gynecologist familiar with HPV and experi

enced in colposcopy. Optimal follow-up of these patients includes colposcopic examination of the cervix and vagina on a yearly basis. Guidelines from the American College of Obstetricians and Gyne cologists are available for the treatment of cervical dysplasia and cancer. For anal or perianal lesions, cryotherapy or surgical removal is safest and most effective. Anoscopy and/or sigmoidoscopy should be performed in patients with perianal lesions, and suspicious lesions should be biopsied to rule out malignancy. ■ ■COUNSELING PATIENTS REGARDING

HPV DISEASE Most sexually active adults will be infected with HPV during their lives. The only way to avoid acquiring an HPV infection is to abstain from sexual activity, including intimate touching and oral sex. Practicing safe sex (partner reduction, use of condoms) may help reduce HPV transmission. Most HPV infections will be controlled by the immune system and cause no symptoms or disease. Some infections lead to genital warts and cervical precancers. Genital warts can be treated for cosmetic reasons and to prevent spread of infection to others. Even after resolution of genital warts, latent HPV may persist in normalappearing skin or mucosa and thus theoretically may be transmitted to uninfected partners. Precancerous cervical lesions should be treated to prevent progression to cancer.

■ ■FURTHER READING Akhatova A et al: Prophylactic human papillomavirus vaccination: From the origin to the current state. Vaccines (Basel) 10:1912, 2022. Clifford GM et al: Carcinogenicity of human papillomavirus (HPV) types in HIV-positive women: A meta-analysis from HPV infection to cervical cancer. Clin Infect Dis 64:1228, 2017. Garland SM et al: Impact and effectiveness of the quadrivalent human papillomavirus vaccine: A systematic review of 10 years of real-world experience. Clin Infect Dis 63:519, 2016. Gavinski K, DiNardo D: Cervical cancer screening. Med Clin North Am 107:259, 2023. Gelbard MK, Munger K: Human papillomaviruses: Knowns, mysteries, and unchartered territories. J Med Virol 95:e29191, 2023. Giuliano AR et al: Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. N Engl J Med 364:401, 2011. Gravitt PE, Winer RL: Natural history of HPV infection across the CHAPTER 204 lifespan: Role of viral latency. Viruses 9:265, 2017. Palefsky J et al: Treatment of anal high-grade squamous intraepithe lial lesions to prevent anal cancer. N Engl J Med 386:2273, 2022. Rosenblum HG et al: Declines in prevalence of human papilloma virus vaccine-type infection among females after introduction of vaccine — United States, 2003–2018. MMWR Morb Mortal Wkly Rep 70:415, 2021. Schiffman M et al: Carcinogenic human papillomavirus infection. Common Viral Respiratory Infections, Other Than COVID-19
Nat Rev Dis Primers 2:16086, 2016. Section 13 Infections Due to DNA and RNA Respiratory Viruses James E. Crowe, Jr.

Common Viral

Respiratory Infections,

Other Than COVID-19 The most common and frequent infections in humans are respiratory virus infections. Influenza viruses and coronaviruses have been the agents responsible for the largest infectious disease pandemics. These viruses are easily transmitted by contact, droplets, and fomites. Fur thermore, transmission can occur before the appearance of symptoms. These viruses are also associated with a large reproductive number (the number of secondary infections generated from one infected individual to others). Some classical respiratory viruses (e.g.,

rhinoviruses) enter the body through the respiratory tract, replicating and causing disease only in cells of the respiratory epithelium. Other, more systemic viruses (e.g., measles virus and severe acute respiratory syndrome coronavirus [SARS-CoV]) spread via the bloodstream and cause systemic disease;

however, they also may enter through and cause disease in the respi ratory tract. Although infections with systemic viruses often induce lifelong immunity against disease, respiratory viruses that do not cause high-grade viremia usually can reinfect the same host many times throughout life. Reinfection with the same virus is common because of incomplete or waning immunity after natural infection. Hundreds of different viruses cause infection of the respiratory tract, and within each virus type, there can be a nearly unlimited diversity of field strains that vary antigenically, geographically, and over time (e.g., antigenically drifting influenza viruses or coronaviruses). Specific antiviral treat ment options are limited, and only a few licensed vaccines are available. For further discussion of common respiratory virus infections, see Chap. 37 and syndrome-specific chapters. For further discussion of SARS-CoV-2 virus infections, see Chap. 205.

Common viral respiratory infections can be categorized in several ways, including by site of anatomic involvement, disease syndrome, or etiologic agent. ANATOMIC SITES IN THE HUMAN RESPIRATORY TRACT The type of respiratory disease that develops during virus infection is dictated to a large degree by the cell types and tissue organization in the respiratory tract. The vocal cords mark the transition between the upper and lower respiratory tracts. The upper respiratory tract is a complex anatomic system with interconnected structures, including the sinuses, middle-ear spaces, Eustachian tubes, conjunctiva, naso pharynx, oropharynx, and larynx. The tonsils and the adenoids are large collections of lymphoid tissue in the pharynx that participate in immunity but also are susceptible to infections. The lower respiratory tract structures include the trachea, bronchi, bronchioles, alveolar spaces, and lung tissue, including epithelial cells and blood vessels. The epithelial cell types that line the respiratory tract are varied in morphol ogy and function, and their susceptibility to different virus infections varies. The principal types of cells in the major airways are ciliated or nonciliated epithelial cells, goblet cells, and Clara cells. Smooth-muscle cells form major tissue structures around the epithelial structures of the large airways of the lower respiratory tract down to the level of the bronchioles, and these cells are reactive to intrinsic and extrinsic signals, including viral infection or exposure to allergens or pollut ants. The pathologic process of wheezing is driven by smooth-muscle contraction and obstruction of airways caused by mucus accumulation and epithelial sloughing in the lumen. Reactive airways causing wheez ing are most often due to constriction of lumen size at the level of the bronchioles (which have the narrowest lumen diameter of the airways). The lung does not have smooth-muscle or ciliated cells but instead possesses pneumocytes of types I and II. Pneumonia (Chap. 131) is an infection of the pneumocytes in the lung tissue and the alveolar spaces. The alveolar spaces also contain cells of the monocyte lineage, such as macrophages, which patrol the air spaces. PART 5 Infectious Diseases DISEASE SYNDROMES Since different respiratory viruses tend to have a predilection for repli cation in differing cells or regions of the respiratory tract, it is possible for the well-trained clinician with epidemiologic information to under stand the most likely associations of viruses with clinical syndromes. The clinical diagnoses for virus infections in the upper respiratory tract are rhinitis or the common cold, sinusitis, otitis media, conjunctivitis, pharyngitis, tonsillitis, and laryngitis. Some upper respiratory tract infections affect more than one upper respiratory tract anatomic site during a single infection, such as the classical pattern of pharyngo conjunctival fever

during adenovirus infection. Lower respiratory tract syndromes also can be associated easily with anatomic region, including tracheitis, bronchitis, bronchiolitis, pneumonia, and exacer bations of reactive airway disease or asthma. Bronchiolitis is a disease condition characterized by trapping of air in the lungs with difficulty in expiration (i.e., wheezing); it is caused by inflammation or infec tion of the bronchioles, the smallest and most highly resistant airways. Again, mixed syndromes occur, such as laryngotracheitis, usually termed croup. Croup, a disease condition characterized by difficulty

in inspiration associated with a barky cough, is caused by inflamma tion or infection of the larynx, trachea, and bronchi. When respiratory symptoms occur in the context of a respiratory viral illness with signifi cant systemic signs, infection with particular agents can be suspected (e.g., influenza, measles, SARS-CoV, SARS-CoV-2, or hantavirus pul monary syndrome [HPS]), with exposure history taken into account. ETIOLOGIC AGENTS ■ ■RESPIRATORY VIRUSES CAUSING DISEASE IN IMMUNOCOMPETENT HOSTS Children have more frequent respiratory virus infections than adults; thus, it was natural that many early discoveries about the viral causes of respiratory infections came from pediatric studies. The principal causes of acute viral respiratory infections were determined in large epidemio logic studies in the 1960s and 1970s, when cell culture of infectious agents became available. More recently, studies of viral epidemiology have been conducted in adults, especially in special populations such as the elderly, nursing home residents, and immunocompromised individuals. Rapid antigen detection tests (based on immunoassays for detection of viral proteins) became available for respiratory syncytial virus (RSV) and influenza virus in the 1980s. With the availability of sensitive and specific molecular tests, such as reverse transcription combined with the polymerase chain reaction (RT-PCR), studies in the past several decades have greatly increased the extent to which we understand the causes of viral respiratory infections. Multiplex panels of RT-PCR tests capable of detecting a dozen or more viruses are com monly available for clinical testing of respiratory secretions. Nested multiplex PCR assays performed in two stages provide sensitive tests that have been especially helpful in studies of infection in adults, who often shed much lower concentrations of virus in secretions than do children. Typically, influenza viruses, RSV, and human metapneumo virus (hMPV) are the most common causes of serious lower respira tory tract disease in otherwise healthy subjects; parainfluenza viruses (PIVs) and adenoviruses also cause substantial disease. Rhinoviruses (the most common cause of the common cold syndrome) have been increasingly associated with lower respiratory tract syndromes. Rhino virus infection is so common, even in asymptomatic individuals, that it has been hard to establish clear figures for the role of rhinovirus in lower respiratory disease. COVID-19 and the associated public health measures deployed in 2020−2021 altered the epidemiology of respira tory viruses such that conventional viruses were greatly reduced in incidence, exhibited altered seasonality, or even disappeared (influenza type B Yamagata lineage viruses) in the years immediately following. Generally, about two-thirds of cases of respiratory illness in a research setting can be associated with a specific viral agent. Besides the viruses mentioned above (and discussed below), several additional viruses identified with molecular tools have been associated with respiratory illness. Still, our diagnostic tools remain suboptimal since a specific infectious agent is not identified in approximately one-third of clinical respiratory illnesses in large surveillance studies. It is likely that in most of these cases pathogens are not detected because of the very low titers of virus in patient samples at the time of clinical presentation, which may occur after the period of peak virus shedding. It is also possible that novel agents are yet to be identified. As emerging tools for metage nomic and “virome” studies (with sequencing of all nucleic

acids in a sample) are applied in these settings in coming years, new agents and new associations with disease will probably be discovered. ■ ■RESPIRATORY VIRUSES CAUSING DISEASE IN IMMUNOCOMPROMISED HOSTS Special populations of patients are susceptible not only to the conven tional respiratory viruses discussed above but also to agents causing symptoms during reactivation of latent viruses or new infections with opportunistic agents. Most prominently, reactivating latent viruses, such as herpes simplex virus (HSV) and cytomegalovirus (CMV) and adenoviruses, cause disease in immunocompromised humans. Patients at most risk are those with hematopoietic stem cell or solid organ transplantation, leukopenia caused by chemotherapy, or advanced

HIV-AIDS. In immunosuppressed patients with pneumonia, CMV is the virus recovered most frequently during deep respiratory tract diag nostic procedures such as bronchoalveolar lavage. These patients also are highly susceptible to more frequent and more severe disease caused by common respiratory viruses, including RSV, hMPV, PIVs, influenza viruses, rhinoviruses, and adenoviruses. Conventional acute respira tory viruses can cause chronic and sometimes fatal infections in these populations. Nosocomial transmission of respiratory viruses occurs in hematopoietic stem cell transplantation units, and the frequency of transmission can be high, with entire units affected. ■ ■SPECIFIC VIRAL CAUSES OF RESPIRATORY DISEASE Orthomyxoviridae: Influenza Viruses (See also Chap. 206) Influenza virus infection and influenza syndrome usually are associ ated with fever, myalgias, fatigue, sore throat, headache, and cough. Influenza causes severe and even fatal pneumonia, particularly in elderly patients, nursing home residents, immunocompromised per sons, and very young children. Influenza pneumonia has an unusually high rate of complication by bacterial superinfection, with staphylo coccal and streptococcal bacterial pneumonia occurring in as many as 10% of cases in some clinical series. Influenza is a single-stranded, segmented, negative-sense, RNA genome virus of the family Orthomyxoviridae. There are four (sero) types of influenza viruses: A, B, C and D. Influenza A and C viruses infect multiple species, whereas influenza B virus infects humans almost exclusively. Type D viruses primarily infect cattle and are not known to infect humans. Type A viruses appear to be the most virulent for humans and most commonly cause severe disease manifestations, although type B viruses cause substantial morbidity. Based on antibody response, influenza A viruses can be subdivided into 18 different hem agglutinin (H) surface protein subtypes and 11 neuraminidase (N) sur face protein subtypes. The subtypes that have caused major pandemics in humans are H1N1, which caused the 1918 pandemic; H2N2, which caused the 1957 pandemic; H3N2, which caused the 1968 pandemic; and H1N1pdm2009, which caused the 2009 pandemic. Currently, two type A subtypes (H1N1 and H3N2) and one type B lineage (Victoria) cause annual seasonal epidemics. Major pandemics caused by new influenza viruses are always pos sible. Many highly pathogenic influenza viruses circulate in aquatic birds. Occasionally, avian viruses infect humans directly after close contact with infected wild birds or poultry. Co-housing of pigs (which have both avian and human influenza virus receptors) with poultry may increase the risk of reassortment of human and animal or bird viruses; reassortment can make the zoonotic viruses more fit for repli cation in humans. Several outbreaks of avian influenza have occurred in limited numbers of humans to date, and there is the risk of a world wide pandemic with avian influenza viruses if a strain acquires the potential to spread efficiently from human to human. H5N1 influenza virus infection of humans, predominantly by direct chicken-to-human transmission, occurred during an epizootic in Hong Kong’s poultry population in 1997. The disease affected many types of wild and domestic birds and caused a high rate of systemic disease and death in infected humans. This virus, carried in the

gastrointestinal tract of wild birds, has spread throughout Asia and beyond and continues to evolve antigenically. An H5N1 virus was detected widely in dairy cattle in the United States in 2024 and inferred to be a highly pathogenic avian influenza (HPAI) virus. Avian H7N7 and H7N9 viruses also have caused zoonotic outbreaks. A significant outbreak of H7N9 virus infec tion began in China in March 2013, with high mortality, and there have been six outbreaks to date, the largest in 2016−2017 with 766 human infections. H7N9 is considered to have high potential to cause a future pandemic. H1N2 virus is endemic in pigs and affects humans with close contact. An H3N2 variant virus that differs antigenically from seasonal human viruses is endemic in pigs and occasionally infects children who have close contact with pigs in the United States. H3N8 is a subtype of equine influenza viruses that can infect humans who are in close contact with pigs. Rare human cases caused by H6, H9, and H10

subtype viruses have been reported. Type B influenza viruses co-circulate in humans during seasonal epidemics. Type B viruses mutate less frequently than type A viruses. The slower evolution of type B viruses is probably linked to the fact that they are almost exclusively human pathogens. There is only one B type of influenza, but these viruses began to diverge into two antigenically distinguishable lineages in the 1970s. The two virus lineages were named after the initial designated representative strains—B/Victoria/2/87 and B/Yamagata/16/88—and can be distinguished by serologic or genotyping laboratory tests. The evolution of B viruses over time spurred the inclusion of two type B virus antigens in seasonal influenza vaccines, expanding some multiva lent vaccines from trivalent (H1N1, H3N2, B) to a quadrivalent format. During the COVID-19 pandemic, the diversity of influenza in humans has been reduced, as strains in lineage B/Yamagata and one clade of H3N2 known as 3c3.A were not detected. In 2023, the World Health Organization recommended future vaccines to be trivalent with only B/Victoria for the type B component.

Pneumoviridae/Paramyxoviridae (the formal species names of family Pneumoviridae were updated in 2023; Table 204-1)

• RESPIRATORY SYNCYTIAL VIRUS Human RSV (hRSV) (species name Human orthopneumovirus hominis) is a single-stranded, negativesense, nonsegmented, RNA genome virus of the genus Respirovirus (formerly Pneumovirus) in the family Paramyxoviridae. Infection is ubiquitous, affecting most humans in the first several years of life and causing reinfections throughout life. RSV is among the most trans missible viruses of humans. Disease epidemics occur yearly, typically between October or November and March in temperate regions. RSV is one of the most common viral causes of severe lower respiratory tract illness in the elderly and in children; it is among the most important causes of hospitalization of elderly and infant patients throughout the world. There is only one serotype of RSV, but antigenic variability does occur in circulating field strains. In immune serum reciprocal crossneutralization studies, the two antigenic subgroups, A and B, appear to be ~25% antigenically related; this relatedness may partially explain the susceptibility of humans to reinfection, which is very common and can be caused by viruses of the same subgroup or even the same strain. However, reinfection in otherwise healthy adults usually is associated with mild disease confined to the upper respiratory tract. Severe lower respiratory tract disease is common in the elderly, especially in frail institutionalized elderly populations. Immunocompromised patients of any age also are at risk of severe or prolonged disease, especially recipi ents of hematopoietic stem cell transplants. Wheezing is common with primary infection in children (bronchiolitis), and there is a strong asso ciation of RSV infection early in life and subsequent

asthma, although it is unclear whether severe childhood RSV causes asthma or is the first manifestation of reactive airway disease. RSV causes exacerbations of asthma and is associated with acute exacerbations of chronic obstruc tive pulmonary disease (COPD), also referred to as acute exacerbations of chronic bronchitis (AECB). CHAPTER 204 Common Viral Respiratory Infections, Other Than COVID-19
HUMAN METAPNEUMOVIRUS hMPV (species name Metapneumo virus hominis) was discovered only in 2001 but probably has always been present in human populations. Infection occurs first in early childhood, and reinfections are common throughout life. This virus is similar in many respects to RSV, but it now is classified in the fam ily Pneumoviridae and is a member of the genus Metapneumovirus. It causes both upper and lower respiratory disease. It appears to be TABLE 204-1 Family Pneumoviridae, Human Pathogens with Current Species Names, the International Committee on Taxonomy of Viruses: 2023 Release CURRENT SPECIES NAME FORMER SPECIES NAME(S) GENUS Metapneumovirus Metapneumovirus hominis Human metapneumovirus (hMPV) Orthopneumovirus Human orthopneumovirus hominis Human respiratory syncytial virus (hRSV) or Human orthopneumovirus

somewhat less virulent than RSV, causing about half as much severe lower respiratory tract disease, probably because it does not possess the nonstructural genes that RSV expresses in infected cells to abrogate the effect of host innate immune effectors like interferons. The clinical features of lower respiratory tract infections caused by hMPV are like those of such infections caused by other paramyxoviruses, most often including cough, coryza, and wheezing. Like RSV, hMPV plays an important role in exacerbations of asthma or COPD and causes pneu monia or wheezing in frail and institutionalized elderly individuals and immunocompromised patients.

Paramyxoviridae (the formal species names of family Para myxoviridae were updated in 2023; Table 204-2) • HUMAN PARAINFLUENZA VIRUSES The human PIVs (hPIV) are a group of four distinct serotypes (designated 1–4) of single-stranded, negativesense RNA viruses belonging to the family Paramyxoviridae. hPIV3 (species name Respirovirus pneumoniae) most commonly causes severe disease, and repeated infection is common throughout life, although secondary infections often are mild or asymptomatic. Primary infec tions in children manifest as laryngotracheitis (croup), while subse quent infections typically are limited to the upper respiratory tract. hPIVs are detected with sensitive RT-PCR tests or, more classically, by cell culture with immunofluorescent microscopy or hemadsorption in reference laboratories. MEASLES VIRUS (See also Chap. 211) Measles virus (species name Morbillivirus hominis) is also a paramyxovirus but of the genus Morbil livirus. This virus causes a systemic infection known as rubeola but also can manifest with respiratory symptoms. Measles virus probably is the most contagious respiratory virus infection of humans: it is transmitted efficiently not only by direct contact with infected persons or fomites (like other respiratory viruses) but also by small-particle aerosols. Mea sles virus infection is preventable by vaccination, but the pathogen is so transmissible that cases are inevitable—even in the United States— whenever vaccination rates fall below 90–95% in a population. The virus causes systemic illness, sometimes including severe pneumonia, when primary infection occurs in an unvaccinated adult or an immu nocompromised person of any age. Therefore, vigilance in maintaining high vaccination rates is critical. With primary infection, the illness in children is typically milder; however, mortality rates in lower-resource countries are high, especially among persons with underlying risk fac tors, including malnutrition. PART 5 Infectious Diseases Symptoms of measles include ≥3 days of high fever and a classical set of upper and lower respiratory tract symptoms

sometimes termed “the 3 Cs”: cough, coryza, and conjunctivitis. Unlike most respiratory viruses, measles virus circulates in the bloodstream and thus causes TABLE 204-2 Family Paramyxoviridae Human Pathogens with Current Species Names, the International Committee on Taxonomy of Viruses: 2023 Release CURRENT SPECIES NAME FORMER SPECIES NAME(S) GENUS Respirovirus Respirovirus laryngotracheitidis Human respirovirus 1 or human parainfluenza virus type 1 (hPIV1) Respirovirus pneumoniae Human parainfluenza virus type 3 (hPIV3) or Human respirovirus 3 Orthorubulavirus Orthorubulavirus parotitidis Mumps virus or Mumps orthorubulavirus Orthorubulavirus laryngotracheitidis Human parainfluenza type 2 (hPIV2) or Human orthorubulavirus 2 Orthorubulavirus hominis Human parainfluenza type 4a (hPIV4a) or Human orthorubulavirus 4 Human parainfluenza type 4b (hPIV4b) or Human orthorubulavirus 4 Orthorubulavirus mammalis Parainfluenza type 5 (PIV5) or Mammalian orthorubulavirus 5

disseminated infection with systemic manifestations. Usually, a charac teristic diffuse maculopapular rash appears within days of fever onset. Koplik’s spots (see Fig. A1-2)—typical mucosal lesions in the mouth that appear briefly—are considered diagnostic of measles infection in the setting of the typical rash and fever. Picornaviridae A wide variety of picornaviruses cause respiratory disease, including nonpolio enteroviruses, rhinoviruses, and parecho viruses (Chap. 210). The designations of these viruses can be confus ing: the Enterovirus, rhinovirus, and Parechovirus species names were changed (with the approval of the International Committee on Tax onomy of Viruses) to remove references to host species names (such as the formerly used terms human, simian, etc.), and they are frequently updated. These changes are summarized in Table 204-3. The genus Enterovirus consists of 15 species, including the enteroviruses and rhinoviruses affecting humans. The genus Parechovirus contains six species, one of which—Parechovirus A—encompasses 19 types: human parechoviruses (HPeVs) 1 and 2 are common human pathogens. These viruses exhibit seasonal patterns that differ from those of most other acute respiratory viruses. Rhinovirus infections occur year-round. Enterovirus infections occur most commonly in the summer months in temperate areas. RHINOVIRUSES Rhinoviruses have single-stranded, positive-sense RNA genomes. Rhinoviruses A through C represent species in the Enterovirus genus of the family Picornaviridae. Rhinoviruses are the most common viral infective agents in humans and the most frequent cause of the common cold. Field isolates of rhinovirus are exception ally diverse; they can be classified by serotyping into >100 serotypes or, alternatively, by genotyping into many genotypes that cause cold symptoms. The viral particles are icosahedral in structure and are non enveloped. Rhinoviruses are responsible for at least half of all cases of the common cold. Rhinovirus-induced common colds may be compli cated in children by otitis media and in adults by sinusitis. Most adults, in fact, have radiographic evidence of sinusitis during the common cold, which resolves without therapy. Therefore, the primary disease is probably best termed rhinosinusitis. Rhinovirus infection is associated with exacerbations of reactive airway disease in children and asthma TABLE 204-3 Enterovirus, Rhinovirus, and Parechovirus Species Names, the International Committee on Taxonomy of Viruses: 2023 Release GENUS CURRENT SPECIES NAME FORMER SPECIES NAME(S) Enterovirus

(15 species) Enterovirus alphacoxsackie: consists of 25 serotypes, including coxsackieviruses and some nonpolio enteroviruses that cause respiratory disease Human enterovirus A; Enterovirus A Enterovirus betacoxsackie: consists of 63 serotypes, including some coxsackieviruses, echoviruses, and nonpolio enteroviruses Human enterovirus B; Enterovirus B Enterovirus coxsackiepol: consists of 23 serotypes, including the polioviruses Human enterovirus C; Enterovirus C Enterovirus

deconjuncti: consists of multiple serotypes and includes enterovirus D68 Human enterovirus D; Enterovirus D Enterovirus alpharhino Human rhinovirus A; Rhinovirus A Enterovirus betarhino Human rhinovirus B; Rhinovirus B Enterovirus cerhino Human rhinovirus C; Rhinovirus C Parechovirus

(6 species) Parechovirus ahumpari: consists of 19 types (1–19); human parechoviruses (HPeVs) 1 and 2 are common human pathogens Parechovirus A; HPeV-1 and HPeV-2 were formerly classified in the genus Enterovirus as echoviruses 22 and 23, respectively

in adults. It is not clear whether rhinovirus is restricted to the upper respiratory tract and only indirectly induces inflammatory responses that affect the lower respiratory tract or whether the viruses spread to the lower respiratory tract. In the past, it was thought that these viruses did not often replicate or cause disease in the lower respiratory tract. However, recent studies have discerned strong epidemiologic associa tions of rhinoviruses with wheezing and asthma exacerbations, includ ing episodes severe enough to require hospitalization. Rhinovirus C (species Enterovirus cerhino) has been associated with more severe disease syndromes, such as pneumonia or exacerbation of COPD. Rhi noviruses likely can infect the lower airways to some degree, inducing a local inflammatory response. Another possibility is that significant local infection of the upper respiratory tract may induce regional elaboration of mediators that causes lower airway disease. The associa tion of rhinovirus infection with lower respiratory tract illness is dif ficult to study because diagnosis by cell culture is not sensitive. RT-PCR diagnostic tests are difficult to interpret because they are often positive for prolonged periods and even asymptomatic individuals may have a positive test. Comprehensive serologic studies to confirm infection are difficult because of the large number of serotypes. Nevertheless, most experts believe rhinoviruses are a common cause of serious lower respiratory tract illness. ENTEROVIRUSES Nonpolio enteroviruses are common and distrib uted worldwide. Although infection often is asymptomatic, these viruses cause outbreaks of clinical respiratory disease, sometimes with fatal consequences. The species Enterovirus alphacoxsackie (formerly Enterovirus A) consists of 25 serotypes, including coxsackieviruses and some nonpolio enteroviruses that cause respiratory disease. Cox sackieviruses cause oral lesions and often are associated in children with hand-foot-and-mouth disease. The pharyngitis associated with this infection characteristically manifests with herpangina, a clinical syndrome of ulcers or small vesicles on the palate that often involves the tonsillar fossa and is associated with fever, difficulty swallowing, and throat pain. Outbreaks commonly occur in young children during the summer. Enterovirus A71 also causes large outbreaks of hand-footand-mouth disease, especially in Asia, sometimes leading to neurologic complications and even death. The species Enterovirus betacoxsackie (formerly Enterovirus B) consists of >90 serotypes, including the echo viruses (echo being an acronym for enteric cytopathic human orphan, which may be an archaic notion since most echoviruses are associated with human diseases, most commonly in children). Echoviruses can be isolated from many children with upper respiratory tract infections during the summer months. Echovirus 11 has been associated with laryngotracheitis or croup. Epidemiologic studies also have associated echoviruses with epidemic pleurodynia, an acute illness characterized by sharp chest pain and fever. The species Enterovirus coxsackiepol (formerly Enterovirus C) consists of 23 serotypes, including the polio viruses. The species Enterovirus deconjuncti (formerly Enterovirus D)

consists of five serotypes, including enterovirus D68, which has been associated with wheezing and a polio-like syndrome in children marked by acute flaccid myelitis. PARECHOVIRUSES The genus Parechovirus comprises six species, one of which is Parechovirus ahumpari (formerly Parechovirus A), which can affect humans. The most common member of the genus Parecho virus, human parechovirus 1 (HPeV-1), is a frequent human pathogen. The genus also includes the closely related human parechovirus 2 (HPeV-2). HPeVs usually cause mild respiratory or gastrointestinal illness. Most infections occur in young children. The seroprevalence of HPeV-1 and HPeV-2 is high among adults. Adenoviridae Viruses of the family Adenoviridae infect both humans and animals. As their designation indicates, adenoviruses were first isolated in human lymphoid tissues from surgically removed adenoids. In fact, some serotypes establish persistent asymptomatic infections in tonsil and adenoid tissues, and virus shedding can occur for months or years. These double-stranded DNA viruses are <100 nm in diameter and have nonenveloped icosahedral morphology. The large double-stranded DNA genome is linear and nonsegmented. The seven

major human adenovirus species (designated A through G) fall into over 50 immunologically distinct serotypes. Human respiratory tract infections are caused mainly by the B and C species. Adenovirus infec tions can occur throughout the year. Many serotypes cause sporadic outbreaks, while others appear to be endemic in particular locations. Respiratory illnesses include mild disease such as the common cold and lower respiratory tract illnesses including croup, bronchiolitis, and pneumonia. Conjunctivitis is associated with infection by the B and D species. A particular constellation of symptoms referred to as pharyngoconjunctival fever is frequently associated with acute adenovirus infection. In contrast, gastroenteritis has been associated most frequently with virus serotypes 40 and 41 of species F. Immu nocompromised patients are highly susceptible to severe disease dur ing infection with respiratory adenoviruses. The syndrome of acute respiratory disease (ARD), especially common in stressful or crowded living conditions, was first recognized among military recruits during World War II and has continued to be a problem when vaccination has been suspended temporarily because of lapses in vaccine supply. ARD is most often associated with adenovirus types 4 and 7. Adenovirus vaccine containing live adenovirus types 4 and 7 taken orally as two tablets, which prevents most illness caused by these two virus types, is only available for U.S. military personnel 17−50 years of age. It is recommended by the Department of Defense for military recruits entering basic training or other military personnel at high risk for adenovirus infection.

Coronaviridae SARS-CoV-2 emerged in an outbreak in Wuhan, China, that spread worldwide, causing the severe pandemic of COVID-19. SARS-CoV-2 is discussed separately in Chap. 205. CHAPTER 204 Other members of the genus Coronavirus also contribute to respira tory illness, including severe disease. Dozens of coronaviruses affect animals. In the twentieth century, only two representative strains of human coronaviruses were known to cause disease: 229E (HCoV229E) and OC43 (HCoV-OC43). An outbreak of infection with SARS-associated coronavirus (SARS-CoV) first showed that animal coronaviruses have the potential to cross from other species to humans, with devastating effects. The one major SARS-CoV epidemic to date (2002−2003) encompassed >8000 cases, with mortality rates approach ing 10%. SARS-CoV causes a systemic illness with a respiratory route of entry. In contrast to most other viral pneumonias, SARS lacks upper respiratory symptoms, although cough and dyspnea occur in most patients. Typically, patients present with a nonspecific illness manifest ing as fever, myalgia, malaise, and chills or rigors; watery diarrhea may occur as well. Investigators have reported the identification of a fourth

human coronavirus, HCoV-NL63. Evidence is emerging that this new group 1 coronavirus is a common respiratory pathogen of humans, causing both upper and lower respiratory tract illness. HCoV-HKU1 was first described in January 2005 after its detection in a patient with pneumonia. Several cases of respiratory illness have been associated with this virus, but its infrequent identification suggests that this group 2 coronavirus has caused a low incidence of illness to date. The Middle East respiratory syndrome coronavirus (MERS-CoV), first isolated in 2012, causes severe disease in humans, with ~35% mortality and >2500 cases reported to date. MERS-CoV is a zoonotic virus (transmitted between animals and people). The virus likely emerged from bats in the Middle East, although studies have shown that humans are infected through direct or indirect contact with an intermediate host—infected dromedary camels. Common Viral Respiratory Infections, Other Than COVID-19
Herpesviridae Several herpesviruses cause upper respiratory infec tions, especially infection of the oral cavity. Herpes simplex pharyngitis is associated with characteristic clinical findings, such as acute ulcer ative stomatitis and ulcerative pharyngitis. HSV types 1 and 2—human herpesvirus (HHV) 1 (species Simplexvirus humanalpha1) and HHV2 (species Simplexvirus humanalpha2), respectively—both cause oral lesions (Chap. 197), although >90% of oral infections are caused by HSV-1. Primary oral disease can be severe, especially in young children, who sometimes are admitted for rehydration therapy because of poor oral intake. A significant proportion of individuals suffer recurrences

of symptomatic disease consisting of vesicles on the lips. Epstein-Barr virus (EBV) mononucleosis syndrome (Chap. 199) is often marked by acute or subacute exudative pharyngitis; in some cases, tonsillar swelling in EBV pharyngitis is so severe that airway occlusion appears immi nent. Most of the viruses in the family Herpesviridae—including CMV

(Chap. 200); EBV; varicella-zoster virus (VZV; Chap. 198); and HHV-6, -7, and -8 (Chap. 200)—can cause severe disease in immunocompro mised patients, especially hematopoietic stem cell transplant recipients.

Parvoviridae: Human Bocavirus Human bocavirus (HBoV) was identified in 2005 in respiratory samples from children with lower respiratory tract disease. Sequence analysis of the genome revealed that the virus is a member of the genus Bocaparvovirus (subfamily Parvo virinae, family Parvoviridae). This virus has been identified as the sole agent in a limited number of respiratory samples from individuals with respiratory tract disease, especially hospitalized young children, but the virus is also commonly found by RT-PCR tests in respiratory samples from healthy subjects. Retroviridae: HIV Pharyngitis occurs with primary HIV infection and may be associated with mucosal erosions and lymphadenopathy (Chap. 208). Papovaviridae: Polyomaviruses Polyomaviruses are small, dou ble-stranded, DNA-genome, nonenveloped icosahedral viruses that may be oncogenic. Two major polyomaviruses, JC and BK viruses, are known to infect humans. Of adults in the United States, ≥80% are sero positive for these viruses. JC virus can infect the respiratory system, kidneys, or brain. BK virus infection causes a mild respiratory infec tion or pneumonia and can involve the kidneys of immunosuppressed transplant recipients. PART 5 Infectious Diseases EPIDEMIOLOGY ■ ■AGE Age (along with the associated factor of prior exposure history) is a major determinant of risk for symptomatic disease during respiratory virus infection. Primary infection with most of the acute respiratory viruses often is more severe than secondary infection. Indeed, reinfec tion with most of these viruses occurs throughout life, but primary

infection is much more likely to be associated with severe lower respi ratory tract disease, while secondary infection typically is asymptom atic or associated with upper respiratory tract symptoms only. As these infections are ubiquitous, most primary infections (and thus many of the severe cases) occur during the first few years of life. Later, exposure to young children (in populations such as parents of young children and daycare workers) is a risk factor for frequent reinfection. Despite a lifetime of previous exposures, the risk of severe disease increases with age in the elderly, probably because of immune senescence and general medical decline. ■ ■SEASON Infections with most of the conventional respiratory viruses (e.g., influ enza virus, RSV, and hMPV) occur in winter. Typically, there is one dominant virus sweeping through a local community at any one time, a pattern that suggests some population-level interference with trans mission. However, outbreaks can be closely spaced, and co-circulation of different viruses or antigenically diverse strains of one virus does occur. In the United States, some regional differences in seasonality have been noted; for example, RSV often appears in Florida and other southeastern states first. Seasons are, of course, reversed in the North ern and Southern hemispheres, so that winter epidemics occur roughly from November to March in the United States but from April to August in Australia; therefore, “winter” epidemics are almost always occurring somewhere in the world. Seasonal variances differ in the tropics, where acute respiratory viral infections are more common in the rainy season. The pandemic starting in 2020 caused by SARS-CoV-2 disrupted the seasonality of the common respiratory viruses for several years. SARS-CoV-2 outbreak patterns do not follow traditional seasonal

patterns like other respiratory viruses, with peaks caused by antigenic variants at any time of the year thus far. ■ ■RISK FACTORS FOR DISEASE Infection with these viruses is nearly universal, but disease expression varies among individuals infected with identical viruses. Therefore, investigators have sought to identify risk factors for severe disease. Most single risk factors identified have a moderate effect on the inci dence of severe disease, but an accumulation of factors is associated with high risk. Underlying lung disease is a major factor, especially diseases associated with the need for chronic oxygen supplementation. COPD is one of the most profound risk factors. Other severe underly ing medical conditions, especially cardiovascular disease, also enhance risk. Smoking (or exposure to wood smoke), low socioeconomic status, and male gender all contribute to minor increases in the risk of lower respiratory tract illness. Obesity causes a chronic state with features of inflammation that are associated with impaired immunity, reduced response to vaccination, and higher susceptibility to severe disease. Close exposure to infected people is a major factor. For instance, living in close quarters (e.g., housing for military trainees, college dormi tories, or nursing homes) puts groups of individuals at risk for rapid outbreaks. A breakdown in isolation and hand-washing compliance procedures can lead to cycles of nosocomial transmission of infection in hospital inpatient wards and intensive care units. In assessments of severe lower respiratory tract illness, a history of travel to an area with unusual agents should be considered carefully (e.g., exposure to avian influenza outbreaks in Asia, exposure to MERS-CoV in the Middle East). In 2020−2021, the dominance of the SARS-CoV-2 outbreak and the associated health measures deployed reduced the incidence of con ventional respiratory viruses. ■ ■TRANSMISSION Most respiratory viruses are transmitted by two principal modes: fomites or large-particle aerosols of respiratory droplets spread directly from person to person by coughing or sneezing. Fomite transmission occurs indirectly when infected respiratory droplets are deposited on the hands or on inanimate objects and surfaces, with subsequent transfer of secretions to a susceptible person’s nose or conjunctiva. Most respiratory viruses do not spread by small-particle

aerosols across rooms or down halls, although measles virus and VZV do spread in this manner. Therefore, contact and droplet precautions are sufficient to prevent transmission in most settings; hand washing is especially critical in health care settings during the winter. Intensive studies of the SARS-CoV-2 pandemic are ongoing (see previous sections on COVID-19), but many experts agree that exposure to large-particle droplets likely is one of the major ways that SARS-CoV-2 spreads. APPROACH TO THE PATIENT Common Viral Respiratory Infections The principal interventions that make a difference in the care of patients with acute respiratory virus infections are supportive, and these factors should be managed meticulously. Hypoxia is managed with supplemental oxygen and respiratory failure with mechanical ventilation. Because the tachypnea and fever that often accompany pneumonia and wheezing frequently result in dehydration, fluid management is important. The astute clinician can narrow the etio logic possibilities based on epidemiologic knowledge; information about viruses circulating in the community (widely available from local reference laboratories, county and state health departments, and the U.S. Centers for Disease Control and Prevention [CDC]); and the patient's exposure history, age, and immunologic status, including vaccination status. Proper use of rapid diagnostic tests is important. When diagnostic tests are applied only to samples from individuals at high risk of exposure to an infectious agent in the appropriate season, the positive predictive value of the test is increased. A central medical decision is whether to use a specific antibacterial or antiviral agent to treat a respiratory infection.

Antibiotics do not improve the outcome of uncomplicated respi ratory virus infections in otherwise healthy subjects. Some viral infections, especially influenza, can be complicated by secondary bacterial infection. There are only a limited number of licensed antiviral drugs, which should be used when a specific viral etiology is determined. Antiviral treatment generally is effective only when administered early in the course of illness. CLINICAL MANIFESTATIONS The common cold is characterized by nasal congestion, sneezing, rhinorrhea, cough, and sore throat. Laryngitis is accompanied by hoarseness or dysphonia. Acute bronchitis is characterized by a dry or productive cough of <3 weeks' duration (most prevalent in winter) in the absence of signs and symptoms of pneumonia and of evidence of pneumonia on chest radiography and is primarily caused by viruses. Bacteria play a more prominent role in chronic bronchitis. Bronchiol itis is an acute illness with wheezing and evidence of upper respiratory infection, primarily seen in the winter in infants and young children. The typical clinical manifestations of acute pneumonia include cough, sputum production, dyspnea, and chest pain. More systemic signs and symptoms also occur in pneumonia, including fever, fatigue, sweats, headache, myalgia, and occasionally nausea, abdominal pain, and diarrhea. DIAGNOSIS The clinical diagnosis of a respiratory syndrome and the anatomic location of infection are based on history, physical examination, and radiography. A specific viral etiology can be determined by specific diagnostic tests. The gold standard for diagnosing a respiratory viral infection is virus isolation, performed by inoculation of cell cultures with fresh secretions and use of multiple cell types in a reference labo ratory staffed by experienced technologists. Direct or indirect fluores cent antibody detection can be used to visualize virus-infected cells in nasal secretions. Rapid antigen-based diagnostic tests are used to detect influenza virus or RSV proteins in nasopharyngeal secretions. The most sensitive tests typically are RT-PCR molecular diagnostic tests that amplify and detect the presence of viral genomic RNA or DNA in respiratory secretions. Multiplex panels assaying a sample for a dozen or more common respiratory viruses are available. These tests must be used and interpreted carefully because of their extreme sensitivity. If care is not taken, it is relatively easy to contaminate a PCR test in the laboratory with small amounts of DNA from a previous reaction. In addition, because a viral genome can sometimes persist in nasal

secre tions for weeks after an infection resolves, a positive test may indicate a recently resolved rather than a currently acute infection. Despite these limitations, PCR tests generally are considered the most sensitive and specific tests available. Chest radiographs should be obtained for all patients with suspected pneumonia. TREATMENT Common Viral Respiratory Infections INFLUENZA (SEE ALSO CHAP. 206) Several drugs are licensed in the United States for the treatment or prophylaxis of influenza. Neuraminidase inhibitors act on both influenza A and B viruses by serving as transition-state analogues of the viral neuraminidase that is needed to release newly budded virion progeny from the surface of infected cells. The cell surface normally is coated heavily with the viral receptor sialic acid. Osel tamivir is administered orally twice daily and is effective for the prevention or treatment of uncomplicated influenza in otherwise healthy adults. Observational studies indicate that oseltamivir also may be beneficial during serious illness. The drug is generally well tolerated, with primarily gastrointestinal toxicity. Zanamivir, a pow der that is administered through oral inhalation, exhibits effective ness like that of oseltamivir. Moreover, zanamivir is active against

some influenza virus strains that are resistant to oseltamivir. Inhala tion of zanamivir powder may cause bronchospasm in patients with COPD or asthma. Peramivir is a neuraminidase inhibitor that acts as a transition-state analogue inhibitor of the influenza neuramini dase enzyme that is administered intravenously as a single 600-mg dose. It is efficacious in acute, uncomplicated influenza and was approved by the U.S. Food and Drug Administration (FDA) in 2014 for treatment of individuals who cannot take oral or inhaled medica tions. Laninamivir was approved in Japan for prophylaxis (2013) or treatment (2010) of influenza; it is under investigation in the United States. It is a polymeric zanamivir conjugate that is delivered by oral inhalation, and it exhibits greater potency and longer retention times than conventional zanamivir. Baloxavir marboxil is a relatively new class of drug for influenza. It is a prodrug whose metabolism releases the active agent baloxavir acid that inhibits influenza virus cap-dependent endonuclease activity in infected cells. This activity is used by the virus for a process in which the first 10–20 residues of a host cell RNA are removed and used as the 5′ cap and primer to initiate the synthesis of the influenza mRNA (a process sometimes termed “cap snatching”). Baloxavir marboxil was approved by the FDA in 2018 for treatment of acute uncomplicated flu within 2 days of illness onset in otherwise healthy people 12 years and older or those at high risk of developing flu-related complications. In 2020, the FDA approved an updated indication to include postexposure prevention of influenza for people ≥12 years old after contact with an infected person. The adamantanes amantadine and rimantadine were used in the past for the treatment of influenza A infection. These drugs interfere with the ion channel activity caused by the M2 protein of influenza A viruses, which is needed for viral particle uncoating after endocytosis. Widespread resistance occurred in many currently circulating influenza A viruses. RSV INFECTION Ribavirin is a nucleoside antimetabolite prodrug whose activation by kinases in the cell results in a 5′-triphosphate nucleotide form that inhibits RNA replication. The drug was licensed in an aerosol formula in the United States in 1986 for treatment of children with severe RSV-induced lower respiratory tract infection. The efficacy of aerosolized ribavirin therapy remains uncertain despite several clinical trials. Most centers use it infrequently, if ever, in otherwise healthy infants with severe RSV disease. Intravenous ribavirin has been used for adenovirus, hantavirus, measles virus, PIV, and influ enza virus infections, although a good risk/benefit profile has not been clearly established for any of these uses. OTHER VIRAL TARGETS Pleconaril, an oral drug with good bioavailability for treatment of infections caused by picornaviruses, has been tested for treatment of rhinovirus infection. This drug acts by binding to a

hydrophobic pocket in the VP1 protein and stabilizing the protein capsid, pre venting release of viral RNA into the cell. Pleconaril reduces mucous secretions and other symptoms and is being further examined for this indication. Acyclovir and related compounds are guanineanalogue antiviral drugs used in the treatment of herpesvirus infec tions. HSV stomatitis in immunocompromised patients is treated with famciclovir or valacyclovir, and immunocompetent patients with severe oral disease compromising oral intake are sometimes treated with these agents. These compounds have also been used prophylactically to prevent the recurrence of outbreaks, with mixed results. Intravenous acyclovir is effective against HSV or VZV pneu monia in immunocompromised patients. Systemic therapy of CMV infection in immunocompromised patients has been studied with numerous small-molecule inhibitor drugs, including ganciclovir, valganciclovir, foscarnet, and cidofovir. The clinical utility of these drugs in the immunocompetent host is uncertain. The nucleotide analogue cidofovir also has activity against many other viruses, including adenoviruses. Intravenous cidofovir has been effective in the management of severe adenoviral infection in immunocompro mised patients but may cause serious nephrotoxicity.

CHAPTER 204 Common Viral Respiratory Infections, Other Than COVID-19

COMPLICATIONS: CO-INFECTIONS Co-infections with two or more viruses can occur because of the over lap in the winter season of these viruses in temperate areas. In general, in careful studies using cell culture techniques for virus isolation, two or more viruses were isolated from respiratory secretions of otherwise healthy adults with acute respiratory illness in ~5–10% of cases. There is little evidence that more severe disease occurs during co-infections. The incidence of positive results in two molecular diagnostic tests (generally RT-PCR for these RNA viruses) is expected to be higher than that of culture because, as discussed above, molecular tests can remain positive for an extended period after shedding of infectious virus has ended.

PREVENTION ■ ■VACCINES Numerous vaccines against influenza viruses have been licensed. In the United States, trivalent and quadrivalent inactivated intramuscular vaccines (covering H3N2, H1N1, and one or two B antigens) and a live attenuated trivalent vaccine for intranasal administration are available (although components of the live attenuated vaccine were only ~3% effective during the 2013−2016 seasons and that vaccine was not avail able during the 2016–2018 seasons). Vaccines are effective when the vaccine strains chosen for inclusion are highly related antigenically to the epidemic strain, but occasional antigenic mismatches cause negligible efficacy of a vaccine component. Antigenic drift caused by point mutations in the hemagglutinin (HA) and neuraminidase (NA) molecules leads to antigenic divergence, requiring the production of new vaccines each year. The segmented influenza genome allows reas sortment of two viruses during co-infection of one individual or ani mal; sometimes the consequence is a major antigenic shift resulting in a pandemic. On average, pandemics occur every 20–30 years. There is current concern about the potential for an H5N1 or H7N9 pandemic, and experimental vaccines are being tested for these and other avian influenza viruses. PART 5 Infectious Diseases Vaccines were developed for adenovirus serotypes 4 and 7 and were approved for prevention of epidemic respiratory illness among military recruits. Essentially, these vaccines consisted of unmodified viruses given by the enteric route in capsules instead of by the respiratory route—the natural route of infection leading to disease. Inoculation by the altered route resulted in an immunizing asymptomatic infection. Most U.S. military recruits are vaccinated against adenovirus, and epi demic disease recurs in the absence of vaccination. Two vaccines for RSV are now available (Arexy [GlaxoSmithKline] and

Abrysvo [Pfizer]) based on recombinant subunit protein formula tions of the virus surface fusion (F) protein. Both can be used to protect older adults. The CDC recommends a single dose of either vaccine for adults aged 60 and older who decide with their health care provider that RSV vaccination is right for them. Arexy also can be used in indi viduals 50 through 59 years of age who are at increased risk for lower respiratory tract disease caused by RSV. Abrysvo can be used to pro tect young infants through maternal immunization, leading to passive transfer of enhanced levels of serum antibodies from mother to fetus; a single dose is recommended for pregnant women between 32 and 36 weeks of pregnancy. There are no licensed vaccines against rhinoviruses; as there is little or no cross-protection between serotypes, it will be challenging to develop a vaccine covering >100 serotypes. Efforts to develop seasonal coronavirus vaccines are in the preclinical stage. SARS-CoV-2 vaccines are discussed in Chap. 205. ■ ■PASSIVE PROTECTION WITH IMMUNOTHERAPY Palivizumab, a humanized mouse monoclonal antibody to the F protein of RSV, was licensed for prevention of RSV hospitalization in high-risk infants, in half or more of whom it was effective. Experimen tal treatment of both immunocompetent and immunocompromised RSV-infected individuals with antibody was reported, but the efficacy of this approach has not been established. A next-generation RSV neu tralizing antibody with higher potency and an extended half-life of

~3 months (nirsevimab) was approved in 2023 for all infants younger than 8 months of age born during RSV season or entering their first RSV season and some young children who are at increased risk for severe RSV disease and entering their second RSV season. ■ ■ISOLATION PROCEDURES, PERSONAL PROTECTIVE EQUIPMENT, AND HAND WASHING Most respiratory viruses are spread by direct contact—i.e., bodysurface to body-surface contact and physical transfer of microorgan isms between a susceptible person and an infected person. Poor hand hygiene is probably the most common cause of contact transmission of viruses, which occurs often in family, school, and workplace settings. Transmission between health care workers and patients also takes place when hand-washing compliance is low. Fomites (objects or substances capable of carrying infectious organisms), including instruments, stethoscopes, and other objects in medical environments, can contrib ute to transmission. Small-particle-mediated airborne transmission can occur but is probably not the dominant mode of transmission for most respiratory viruses. Particle size affects the epidemiology of airborne pathogens. The composition and size distribution of the generated particles affect the duration of suspension of the infectious agents in the air, the distance across which they can be transported, the interval during which the virus remains infectious, and the site of deposition in the airway of a susceptible host. Direct exposure to large-particle aerosols (e.g., exposure at close range—up to 3 ft—to a cough or sneeze) causes some transmission. Particles of small size can remain suspended in the air for long periods; for instance, particles of ~1 μm can remain suspended for hours. However, in general, only a few respiratory viruses are thought to be transmitted by small-particle aerosols. Protection from transmission in health care environments can be achieved by proper implementation of and adherence to estab lished procedures for the appropriate level of precaution. Standard and Contact Precautions Standard precautions, the basic level of infection control that is always used in the care of all patients, reduces the risk of transmission of viruses from respiratory tract secretions and mucous membranes. Contact precautions, the second level, require a single room for the patient when possible and the use of additional personal protective equipment, including the wearing of clean, nonsterile gloves when touching a patient or coming into contact with secretions. Fluid-resistant nonsterile gowns are used to protect skin and clothing during activities in which contact with secretions is anticipated, and providers should wear each gown for the care of only one patient. A

face mask is used when there is potential for direct contact with respiratory secretions. Eye protection (goggles or face shields) is worn in anticipation of potential splashing of respira tory secretions. Good hand hygiene should always follow any patient contact, including washing for 20 s with soap and warm water or clean ing with an alcohol-based hand rub. Providers should attempt to avoid the contamination of clothing and the transfer of microorganisms to other patients, surfaces, or environments. Droplet Precautions Large-particle droplets are generated during sneezing and coughing and during the performance of some medical procedures, such as airway suctioning in critical care units or bron choscopy. Such droplets may contain viruses, but their range is usually limited to about 3 ft. Transmission of large-particle droplets occurs when they are deposited on the nasal mucosa or conjunctivae. To pre vent transmission in these settings, providers should implement drop let precautions. They should wear a face mask, such as a surgical mask, for close contact (within 3–6 ft of the patient). Patients also should wear a face mask when exiting the examination room and should avoid coming into close contact with other patients. Airborne Precautions Airborne transmission occurs through the dissemination of airborne droplet nuclei (particles of ≤5 μm) or evapo rated droplets containing viruses that can remain suspended in the air for long periods. Certain viruses that are carried by the airborne route can be inhaled by a susceptible host in the same room or over a long distance from the source patient, depending on environmental factors

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