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Viral Respiratory Illnesses

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Respiratory viruses are probably the most common cause of symptomatic human infections. Adults experience an average of one to three and children two to seven respiratory illnesses each year.[39, 57, 152] Among children, respiratory viruses are the major cause of lower respiratory tract illness and have been associated on a worldwide basis with significant morbidity, physician visits, hospitalization, and death.[68, 152, 167] Among adults, viral respiratory infections occur primarily as upper respiratory tract illness, but they also result in significant morbidity, lost time from work, and some mortality.[151, 152, 159, 167]

No effective preventive measures or specific therapies are available, except those used for influenza. Nevertheless, during the 1980s new technologies and improved understanding of the epidemiology and biology of these viruses are likely to make possible rapid diagnosis and improved treatment and control of these infections.

These developments will make it increasingly important for the clinician to have a clear understanding of viral respiratory illness. In this article our present understanding of the clinical and epidemiologic characteristics of viral respiratory tract illness in adults, techniques for diagnosis, and vaccines and drugs available for treatment and prevention are described.

THE ORGANISMS

Adenoviruses

The adenovirus group is comprised of 41 presently recognized human serotypes plus many serologically intermediate strains. These nonenvel-

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oped viruses have a diameter of 60 to 100 nm, contain linear double-stranded DNA, and belong to the family Adenoviridae.[59, 114, 116, 186] The virus is quite stable and can be stored for prolonged periods at −20° C. Adenoviruses cause the widest variety of illnesses of any respiratory virus (Table 1). Most of these illnesses occur in all age groups, although they are most common among children, in whom approximately 50 per cent of infections are asymptomatic. Acute respiratory disease (ARD) in military recruits,[47, 192] epidemic keratoconjunctivitis (EKC),[34, 36, 75, 119] and venereal disease[36, 95, 125] are primarily adult illnesses.

Adenoviruses are endemic in all populations at all times of the year. They also cause small outbreaks of respiratory disease in the winter and spring, outbreaks of swimming pool–associated pharyngoconjunctival fever in the summer, and outbreaks of EKC associated with industrial eye trauma or ophthalmologic procedures at any time of the year.

The virus can be transmitted by the fecal-oral route, aerosolized droplets, fomites, contaminated swimming pool water, and transplanted organs. The incubation period ranges from 2 to 14 days. After onset of illness, virus can be shed for variable periods depending on the site cultured. Virus can be isolated from respiratory specimens for 1 to 7 days during respiratory illness, from eye swabs or corneal scrapings for up to 16 days during EKC, and from stool specimens for 1 to 12 weeks during any adenoviral illness.[59, 114] Adenoviruses have also been shown to establish latent infection in tonsillar, lymphoid, and renal tissues, and probably can cause illness following reactivation in immunosuppressed patients, much as herpesviruses do.[59, 114]

The most sensitive test for adenovirus respiratory infection is isolation, which can be accomplished in most virus laboratories. Rapid antigen detection tests such as immunofluorescence (FA), radioimmunoassay (RIA), and enzyme-linked immunosorbent assay (ELISA) have generally not been sufficiently sensitive for respiratory specimens, detecting only 60 to 65 per cent of infections confirmed by viral isolation.[94, 146] Serum can be tested by several methods for either type- or group-specific antibodies.[116]

Coronaviruses

Coronaviruses, recognized as a new group of viruses in 1968, are enveloped, single-stranded RNA viruses, 70 to 130 nm in diameter belonging to the family Coronaviridae. Coronaviruses are increasingly recognized as a cause of diseases in humans and animals.[103, 139, 149, 177] At least four strains are respiratory pathogens of humans. Two of these strains, 229E and OC43, have been characterized biochemically and shown to be a major cause of upper respiratory tract illness (URI) in children and adults.[92, 110, 118, 126] Occasionally, they have been associated with pneumonia and pleurodynia in children and adults.[176, 202] OC43 has also been reported to cause fever, pancreatitis, and pericarditis in adults.[176] Although their mode of transmission has not been well studied, it is presumed to be by the respiratory route. Since the human coronaviruses are difficult to isolate, available information derives largely from serologic studies.[149] Diagnostic tests for the coronaviruses are not generally available.

Table 1. *Adenovirus Infections in Adults*

SYNDROME	SIGNS AND SYMPTOMS		ADENOVIRUS SEROTYPES INVOLVED		REFERENCES
	Frequent	*Less Frequent*	*Frequent*	*Less Frequent*	
Upper respiratory tract illness (URI)	Coryza, pharyngitis, fever, malaise	Rash, otitis media, gastroenteritis	1–3,5,7	4,11,18,21,29,31	105,186
Lower respiratory tract illness (LRI)	Bronchitis, pneumonia, fever, coryza, cough	Bronchiolitis	3,4,7,21	1,2,5,35	55,99,106,131,172,184
Acute respiratory disease	Fever, malaise, myalgia, coryza, tracheobronchitis	Pneumonia	4,7	14,21,35	47,192
Pharyngoconjunctival fever	Fever, pharyngitis, conjunctivitis	Coryza, headache, diarrhea, rash	3,4,7	1,11,14,16,19,37	9,15,33,130,135
Epidemic keratoconjunctivitis	Keratitis, headache, preauricular nodes	Coryza, pharyngitis, gastroenteritis	8,19,37	3,4,7,10,11,21	34,36,75,119
Acute hemorrhagic conjunctivitis	Subconjunctival hemorrhages, chemosis, follicles	Preauricular nodes, fever, coryza	11	2,4,7,8,19,37	101
Cystitis	Cystitis (often hemorrhagic)	Fever, pharyngitis	11	7,21,34,35	155
Venereal disease	Ulcerative genital lesions	Cervicitis	2,19,37	1,5,7,11,18,31	36,95,125
Neurologic disease	Meningitis	Encephalitis, Reye's syndrome	7	3,32	59,178
Immunocompromised host	URI, LRI, diarrhea, cystitis	Hepatitis	11,34,35	2,5,7,21,31	10,54,100,185,187,207

Influenza Viruses

The influenza viruses comprise three types, A, B, and C viruses, plus subtypes and strains within the types. These enveloped viruses contain single-stranded RNA, have a diameter of 80 to 100 nm, and belong to the family Orthomyxoviridae.[46] Influenza viruses in diagnostic specimens lose infectivity within several days at room temperature but maintain infectivity at 4° C for up to one week.[3] Influenza is the only infectious disease that is consistently associated with significant increases in national mortality during epidemics. Infection with influenza viruses may be asymptomatic (up to 50 per cent of infected individuals) or cause symptoms ranging from the common cold to fatal pneumonia.[43, 44, 188] The severity of illness partly depends on the levels of pre-existing antibody to the infecting strains, age of the individual, and presence of chronic underlying disease.[112, 120]

Infection confers long-term strain-specific immunity, but the frequent changes in surface antigens of the influenza viruses result in life-long susceptibility to additional infections. Minor changes in the hemagglutinin (H) or neuraminidase (N) antigens of influenza A or B may be associated with epidemics, and major changes in the H or N antigens of influenza A lead to worldwide pandemics.

Currently, influenza A (H3N2) viruses are the most important influenza viruses from both a clinical and epidemiologic standpoint. They infect persons in all age groups and have been associated with excess mortality in seven of nine periods of epidemic activity in the United States since emerging in 1968.[12, 13, 162] Influenza A (H1N1) virus has caused illness primarily among children, adolescents, and young adults following its reemergence in 1977[162] and has not been associated with excess mortality. Influenza B viruses tend to cause epidemics at 2- to 3-year intervals and primarily affect young persons, although the elderly may also experience illnesses; excess mortality was observed during the 1979–80 influenza season.[164] Influenza C viruses have been associated only with mild, sporadically occurring illness.[148]

Small-particle aerosol is believed to be the most common mode of transmission of the influenza viruses.[1] The incubation period varies from 18 to 72 hours.

Diagnosis of influenza is often based solely on a consistent clinical picture and presence of an influenza epidemic in the community. Infection can be most reliably confirmed by viral isolation in primary monkey kidney cells or embryonated hen's eggs, although FA staining of respiratory specimens can detect 80 to 90 per cent of those infections confirmed by isolation.[63] Influenza infection can also be detected in most instances by a rise in type- or subtype-specific antibodies.[46]

Parainfluenza Viruses

Four serotypes and two subtypes of parainfluenza, types 1, 2, 3, 4a, and 4b, have been identified. These enveloped viruses have a diameter of 150 to 200 nm, contain a single strand of RNA, and belong to the family Paramyxoviridae.[20] Parainfluenza viruses lose infectivity at room temperature within several days and can maintain infectivity for as long as one week at 4° C.[37, 38] Parainfluenza viruses are probably second only to rhi-

noviruses as a cause of respiratory illnesses in humans.[28, 71, 150] The spectrum and epidemiology of disease varies with the age of the population and the serotype.

Only respiratory syncytial virus is more common than parainfluenza 3 as a cause of pneumonia and bronchiolitis in children under 2 years of age; parainfluenza 3 virus may be isolated throughout the year, but peaks of illness often occur in the fall and spring.[26, 64, 70, 150] Parainfluenza virus types 1 and 2, which are the leading cause of croup in children and a significant cause of childhood pneumonia, produce a peak incidence of infection at 2 to 6 years of age and occur primarily in epidemics.[58, 70, 71, 109] Parainfluenza 4 is less frequently isolated, but serologic studies suggest it is a common infection, apparently causing mild or asymptomatic infections.[65, 122] Most persons have been infected with the parainfluenza viruses by age 5 and then have recurrent infections throughout life. Reinfections in adults usually cause a mild upper respiratory tract infection but can also cause more severe illness, including pneumonia.[22, 51, 150, 156, 203] The rate of reinfection decreases as the titer of serum neutralizing antibody increases. Protection from reinfection appears to be better correlated with antibody in nasal secretions than with antibody in serum.[22, 193]

The mode of transmission of parainfluenza virus has not been well studied, although transmission appears to be by direct person-to-person and/or droplet aerosol spread.[158, 201] The incubation period ranges from 2 to 7 days, and virus can be isolated for up to 7 days or longer after onset of illness.[22, 60] FA, RIA, and ELISA tests are capable of detecting viral antigens in 75 to 95 per cent of respiratory secretions which yielded virus by isolation with few false-positive results.[63, 180] Isolation in the clinical setting is complicated by the fact that the most sensitive cell line, primary rhesus monkey kidney, is not generally available. Serologic diagnosis of parainfluenza viral infections is hampered by heterologous antibody responses among the four types and with mumps virus, and by inconsistent homologous antibody responses.[20]

Rhinoviruses

Over 100 different serotypes of rhinovirus have been identified so far. Rhinoviruses are small, 20 to 30 nm in diameter, contain single-stranded RNA, are nonenveloped, and belong to the family Picornaviridae.[91] They are relatively stable viruses and can survive as long as three days on dry environmental surfaces.[174] Rhinoviruses are believed to be the most common respiratory pathogen of man, causing primarily mild upper respiratory symptoms, such as the common cold, but also causing lower respiratory tract illness, including pneumonia, in adults and children.[67, 77, 109, 151, 170] Approximately 75 per cent of infections are symptomatic. In temperate climates, rhinovirus infections occur throughout the year, with peaks in the fall and spring. During these peak seasons, multiple types of rhinoviruses may be simultaneously present in a community.[93]

Higher numbered types and untypable rhinoviruses appear to be becoming more common than the lower numbered types, suggesting that there is antigenic drift among rhinoviruses.[56] Reinfection, as demonstrated by infection in the presence of type-specific serum neutralizing antibody, also occurs. The rate of reinfection, however, decreases with increasing

titers of neutralizing antibody.[45, 97] Antigenic drift, reinfection, and the numerous serotypes may all contribute to the frequency of rhinovirus infections.

Rhinoviruses are readily transmitted by autoinoculation with hands contaminated by direct person-to-person contact or by fomites.[79, 98] The most efficient site of inoculation is the nasal mucosa or conjunctiva.[8, 32] The incubation period is one to three days, and virus can be most readily isolated for four to six days and sometimes up to four weeks after onset.[45, 56, 77]

Identifying rhinovirus infections can be difficult. Because of the numerous serologic types, neither testing for antibody rises in serum nor for presence of antigen in respiratory secretions is presently practical. Isolation of rhinoviruses can also be difficult since they may grow poorly even in normally sensitive cell lines.[29]

Respiratory Syncytial Virus

Although several strains of respiratory syncytial virus (RSV) are known,[27, 102] strain differences have not yet been shown to have epidemiologic or clinical significance.[5] RSV is an enveloped virus with a diameter of 120 to 200 nm, contains single-stranded RNA, and belongs to the family Paramyxoviridae.[169] It is a labile virus; the titer of RSV drops by about 100-fold within 2 days at room temperature and 100-fold within 4 to 6 days at 4° C.[90] RSV is the most important cause of lower respiratory tract disease—pneumonia and bronchiolitis—in children under 2 years of age worldwide and is the only respiratory virus other than influenza that causes epidemics each year. These epidemics occur from late fall to spring and last from 2 to 5 months.[68, 123, 157]

The role that host immune responses play in the pathogenesis of RSV disease is unclear. RSV is unique among viral diseases in its ability to cause serious illness among infants despite the presence of maternal neutralizing antibody.[140] Reinfection with RSV occurs throughout life. In older children and adults, serum neutralizing antibody does not prevent but may ameliorate the illness.[96, 168] Antibody in respiratory secretions may play a larger role in preventing infection.[117, 145] In adults, RSV usually causes a mild upper respiratory tract infection although it can also produce more severe illness, including pneumonia, especially in the elderly.[17, 85, 88, 136]

RSV is transmitted by direct person-to-person spread and/or by droplet aerosol spread and fomites.[82, 84] Symptoms occur about four to five days after initial infection, and virus can usually be isolated from the respiratory tract for three to five days or longer. Isolation of RSV can be accomplished in most virology laboratories. ELISA and FA tests for RSV antigens in respiratory specimens have been shown to be sensitive (85 to 90 per cent compared with isolation), specific, and practical.[63, 141] Infection can also be demonstrated by a rise in serum antibody titer by several different tests.[169]

Other Viruses That Cause Respiratory Illness

Many viruses can cause respiratory illness alone or as part of other syndromes. Herpes simplex, especially type 1, and Epstein-Barr virus (EBV) are significant causes of pharyngitis; rubella, rubeola, and varicella can cause symptoms of an upper respiratory tract infection before onset of their typical rashes; and mumps can cause an upper respiratory tract infec-

tion with or without the more typical parotitis. BK virus, a nonenveloped, double-stranded DNA virus in the family Papovaviridae, has recently been associated with respiratory illness. Infection of the respiratory tract with BK virus is common, and BK virus may cause 4 to 8 per cent of all acute respiratory disease.[73]

Virtually all of the 67 enterovirus types, including polioviruses, coxsackie A and B viruses, echoviruses, and enterovirus 68–71, can cause respiratory tract illness (i.e., upper respiratory tract infection, pharyngitis, pneumonia, and acute respiratory disease in military recruits).[58, 74, 104, 127, 153, 154, 161, 171, 179] Enterovirus infections occur most commonly in children during the summer and fall months, with about 50 per cent of these infections being symptomatic.

THE SYNDROMES

The viral respiratory syndromes are artificial categories taken from a continuum of illness ranging from asymptomatic infection to life-threatening pneumonia. Although artificial, these categories do provide a convenient way to discuss the causative agents and the general epidemiologic features of viral respiratory disease from a clinical perspective.

Upper Respiratory Tract Infections

Viral upper respiratory tract illness (URI), or the common cold, is probably the most common human infection and is a major cause of morbidity, visits to physicians, and time lost from work in the United States.[39, 152, 159] URI is characterized by nasal discharge, nasal obstruction, sneezing, sore throat, and cough with or without fever. The illness usually lasts 5 to 7 days but can persist for several weeks or longer. The most common complications of viral URI are sinusitis and otitis media, which were estimated to occur in 0.5 to 1.9 per cent, respectively, of family members in one study.[39]

In temperate climates, the prime season for URI begins in late summer and early fall and continues into late spring. The season consists of (1) sequential outbreaks of infections caused by different viruses such as respiratory syncytial virus, influenza viruses, coronaviruses, and rhinoviruses; and (2) endemic infections with other viruses such as adenoviruses and parainfluenza 3 virus. Thus, at any given time the virus likely to be responsible for this syndrome varies greatly.

The most commonly identified agents of URI among adults are rhinoviruses, followed by coronaviruses (Table 2). These viruses may also cause a significant portion of the URI of unknown etiology since they are more difficult to identify than some of the other viruses. Infection with rhinoviruses and coronaviruses is relatively less common in children, and infection with respiratory syncytial virus, parainfluenza viruses, and adenoviruses is more common.[24, 31, 109, 118]

Pharyngitis

Although pharyngitis is often part of other symptom complexes, such as the common cold or influenza syndrome, it can be caused by a different

Table 2. *Etiologic Agents of Respiratory Syndromes in Adults*

AGENT	ESTIMATES OF PER CENT OF TOTAL ILLNESS		
	URI (Common Cold)	*Acute Pharyngitis/Tonsillitis*†	*Influenza Syndrome*‡
Adenovirus	1–2	2–3	3
Coronavirus	7–20	—	—
Enterovirus	1–8	—	—
Herpes simplex virus	0–1	9–24	1–6
Influenza virus	3–10	3–5	35
Mycoplasma pneumoniae	2	1–2	1
Parainfluenza virus	2–8	2–3	2–9
Respiratory syncytial virus	1–4	—	4
Rhinovirus	15–40	—	—
Group A streptococcus	3	18–26	1
Unknown	40–50	35–50	30–50

*Data from references 24, 50, 69, 93, 126, and 149.
†Data from references 50, 51, and 69.
‡Data from references 50 and 69.

group of etiologic agents (see Table 2). Although the usual clinical features of the pharyngitis and the accompanying symptoms are different among the agents, the overlap in the clinical picture makes it impossible to determine the causative agent on clinical grounds alone. However, certain symptom complexes are likely to be viral: pharyngitis with vesicles, pharyngitis with rhinorrhea and nasal obstruction, and pharyngitis with conjunctivitis. In temperate climates, the peak season for pharyngitis coincides with that for URI.

Influenza Syndrome

Influenza syndrome is characterized by the abrupt onset of fever, headache, severe myalgias, malaise, and prostration.[42, 44, 162] These manifestations typically resolve within one to five days although cough, nasal congestion, and sore throat may then become more prominent. Cough and lassitude can persist for up to two weeks, even in uncomplicated cases, and most affected individuals recover spontaneously or with symptomatic therapy. Lower respiratory tract complications may occur in up to 10 per cent of patients,[61] particularly in the elderly and in those with certain chronic disorders. Other complications, including myositis with myoglubinuria,[144] myocarditis,[165] encephalitis,[143] and Reye's syndrome,[30] rarely occur with influenza viral infection.

Influenza viruses are the most common cause of the influenza syndrome in civilian populations, although adenoviruses have been a major cause in military training camps.[50, 204] Other respiratory viruses, including coronavirus,[126] have also been implicated in the influenza syndrome (see Table 2).

Bronchitis

Symptoms of tracheobronchitis (cough and expectoration) without pneumonia are commonly associated with viral respiratory infections, especially with influenza and parainfluenza viruses, respiratory syncytial vi-

rus, and adenovirus.[151, 189] Some persons with viral respiratory infections appear to be at increased risk of bronchitis. Smokers, for example, may have an increased frequency and duration of coughing after rhinovirus and influenza infections,[78, 115] and patients with asthma and chronic bronchitis may experience exacerbations of their illnesses with viral respiratory infections.[138, 147, 191]

Associated signs and symptoms, such as fever, rhinorrhea, myalgias, and pharyngitis, are usually present during the first three to six days of the illness, while cough and expectoration may last for several additional weeks. Acute bronchitis most commonly occurs during the viral respiratory season (fall, winter, and spring) and is usually caused by respiratory viruses or *Mycoplasma* pneumonia.

Pneumonia

Large-scale investigations during the past two decades suggest that viruses are relatively uncommon causes of pneumonia in adults, accounting for 25 to 50 per cent of nonbacterial pneumonias and only 12 per cent of all radiologically proven pneumonias.[41, 52, 53, 156, 190] All of the respiratory viruses except coronaviruses have been implicated in community-acquired viral pneumonia,[17, 67, 136, 156, 203] but only influenza virus has been established as a common cause.[43, 44, 175]

Primary influenza pneumonia has been observed with both A and B virus types and can be a severe or relatively mild illness.[42, 44] Severe primary influenza pneumonia has been reported most commonly in elderly patients, individuals with chronic lung and heart diseases, and, in some epidemics, in women during the late stages of pregnancy,[61, 133, 175, 182] but this type of pneumonia has also been detected in patients with no underlying predisposition. It is characterized by a rapid and relentless progression of respiratory distress with diffuse alveolar and interstitial infiltrates. Most patients die despite intensive supportive care. Mild influenza pneumonia most commonly occurs in younger patients[44, 175] and is characterized by persistent cough, no respiratory distress, and sparse segmental infiltrates. These patients usually recover completely.

Secondary bacterial pneumonia and mixed viral and bacterial pneumonia accompany influenza infection more frequently than does primary influenza pneumonia.[7, 44, 133] The elderly and patients with certain chronic underlying disorders are at highest risk.[49, 112] Secondary bacterial pneumonia usually presents with recrudescence of fever and productive cough 5 to 14 days after the onset of influenza syndrome, and a chest roentgenogram shows an area of consolidation. *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Hemophilus influenzae* are the most common pathogens.[7, 183]

DIAGNOSIS OF VIRAL RESPIRATORY ILLNESSES

With the advent of specific antiviral chemotherapy and increased awareness of nosocomial viral infections, the diagnosis of viral infections is becoming increasingly important. Diagnostic tests available to the clinician include serologic and antigen detection tests and viral isolation. Serologic testing has the advantage that serum specimens are generally easier to

handle and transport, but this testing requires both acute and convalescent sera for comparison of antibody titers. Consequently, results are usually not available when clinically useful. No IgM tests for the rapid diagnosis of the respiratory viruses have yet been developed for general use. Serologic testing is also hampered by inconsistent antibody response after reinfection and the unavailability of screening tests for rhinoviruses and coronaviruses. A major advantage of rapid antigen detection tests for clinical specimens is that they can be completed in one to two days, while results are still clinically useful. As with serologic testing, however, screening tests are not available for rhinoviruses and coronaviruses.

Viral isolation, on the other hand, does not require specific tests for a particular virus, though some may not be detected if the appropriate cell culture is not used, and some, such as coronavirus, are almost never isolated. Generally, viral isolation is more sensitive than antigen detection but takes longer and is more expensive.

Using any of these tests effectively requires that specimens be collected at the appropriate time, handled correctly, and results interpreted in light of the sensitivity and specificity of the particular test.[25] For detecting changes in antibody titer, an acute-phase serum should be drawn as soon as possible after the onset of illness, preferably within three to four days, and a convalescent-serum two to four weeks later. For antigen detection tests and viral isolation, the specimen should be collected as soon as possible after the onset of illness, preferably within three to four days. For both viral isolation and antigen detection, a nasopharyngeal aspirate or wash is preferable to a nasopharyngeal or throat swab. For identifying RSV, one study showed nearly a 3-fold increase in isolation rate with a nasopharyngeal wash compared with a nasopharyngeal swab.[81] Isolation of most respiratory viruses from respiratory secretions generally provides an etiologic diagnosis, although care is needed in interpreting the significance of adenovirus and herpesvirus isolation since shedding may be prolonged. For all tests the sensitivity and specificity depend on the skill of the person performing the test, especially for FA, and the quality of the reagents. Thus, the results from one laboratory may be quite different from those of another, and the clinician should be aware of the sensitivity and specificity of the tests as performed in the laboratory he or she uses.

Diagnosis of viral respiratory infections is likely to increasingly rely on rapid detection tests for clinical specimens. For antigen detection, monoclonal antibodies are likely to be commonly used as reagents since they can provide sensitivity and specificity comparable to that of animal antiserum without variability in its quality. Tests for detecting viral DNA or other virus-specific components in clinical specimens are also being developed and may further improve our ability to detect viral respiratory infections.[200, 206]

NOSOCOMIAL INFECTIONS

Nosocomial viral infections are increasingly recognized as an important problem. Studies have shown that they cause significant morbidity, prolongation of hospitalization, and death, especially among infants and

children.[198] Respiratory viruses are probably the most important of the viral nosocomial pathogens and often occur as part of community outbreaks. The epidemiology of outbreaks of nosocomial viral respiratory infections is just beginning to be understood, and guidelines for their prevention and control are being developed.[195, 197]

Influenza has been recognized as a nosocomial pathogen for some time and has been well documented to cause outbreaks in nursing homes and hospitals.[72, 89, 199] It spreads in an explosive fashion, presumably by aerosol, and once introduced into the hospital is very difficult to control. Thus, although the effectiveness of preventive measures has not been well studied, measures such as vaccination of hospital and nursing home staff and restriction of visitors with influenza like–illness are most likely to be effective if initiated when influenza is in the community but before a nosocomial outbreak occurs. Once a confirmed outbreak occurs, amantadine prophylaxis can be given to unvaccinated patients and staff, and patients with influenza can be isolated.[108, 195]

Respiratory syncytial virus has been shown to be a major nosocomial pathogen in pediatric hospitals, causing significant morbidity and death in children under the age of 2, especially in those with compromised cardiac function.[83, 134] It has also been associated with outbreaks among the elderly in chronic-care facilities, causing significant morbidity and some deaths.[17, 66, 136] Spread of this pathogen requires close contact, which may occur through infected hospital staff and fomites.[82, 83] Respiratory syncytial virus does not spread as rapidly as influenza, and thus its spread in the hospital is more likely to be preventable. Separating infected from uninfected patients, cohorting staff to ill patients, strict hand washing, and use of gowns by staff may prevent spread of an outbreak.[86]

The parainfluenza viruses have been implicated in outbreaks in pediatric hospitals[62, 158, 201] and among the elderly in chronic-care facilities.[16] The spread and, therefore, the prevention and control of parainfluenza viruses are presumed to be similar to those for respiratory syncytial virus.

Adenoviruses have been implicated in nosocomial outbreaks among children and adults, often spreading from patients to staff.[15, 99, 130, 172] They usually occur sporadically and not as part of recognized community outbreaks. To prevent and control outbreaks of adenovirus infections, infected and uninfected patients should probably be separated, staff members should wear gowns and gloves, and strict hand washing should be enforced.[197]

Coronaviruses and rhinoviruses are not known to be important nosocomial pathogens, but both have been implicated in nosocomial outbreaks of respiratory illness.[176, 196]

PREVENTION, CONTROL, AND TREATMENT OF VIRAL RESPIRATORY INFECTIONS

Prevention, control, and treatment of viral respiratory infections have met with limited success. Vaccines and chemotherapeutic agents for general use have been developed only for influenza. Another approach to prevention and control of these viruses is to interrupt their transmission.

Studies on the use of disinfectants, as applied to the hands or environmental surfaces, have shown either equivocal results or the technique is not practical for widespread use.[76, 80] Studies of nosocomial respiratory syncytial virus and adenovirus infections suggest that interruption of transmission is possible by separating infected from uninfected patients and by the use of gowns and gloves and strict handwashing by staff members.[86, 130] Additional studies on methods to interrupt transmission of the respiratory viruses, especially in the hospital, are needed.

Vaccines

In the United States, only vaccines for influenza and adenovirus infection have been licensed. The licensed influenza vaccine consists of inactivated virus, and use of the vaccine has been strongly recommended only for individuals at greatest risk of serious pulmonary complications or death following influenza. Such individuals include the elderly and those with certain chronic underlying diseases, including acquired or congenital heart disease, chronic obstructive pulmonary disease, renal impairment, diabetes mellitus, severe anemia, and conditions that compromise the immune system. Unfortunately, only about 20 per cent of some 48 million people in high-risk groups are vaccinated each year.[18] Unlike other vaccines, the component strains must be updated frequently to keep pace with antigenic changes in influenza viruses. The influenza vaccines stimulate an increase in antibody titer in 50 to 90 per cent of recipients, often associated with comparable degrees of protection from infection.[2, 14, 121, 142, 163, 173]

Live attenuated oral vaccines for adenoviruses 4, 7, and 21 are being used in military personnel and have been very effective in reducing acute respiratory disease in recruits.[47, 192]

Experimental vaccines have been developed for a number of the respiratory viruses. Considerable research has been devoted to the development of live attenuated influenza vaccines that are administered intranasally.[4, 121] It is hoped that by simulating natural infection, live vaccines will be more effective than inactivated ones. The vaccines tested to-date, however, have often failed to induce an adequate antibody response in seropositive individuals, and some have been associated with a high rate of adverse reactions, particularly in seronegative individuals.

The many serotypes of rhinoviruses have thus far precluded the development of vaccines for these viruses. Since natural infection with respiratory syncytial virus, parainfluenza virus, and coronavirus induces short-term immunity, and reinfections occur throughout life, the prospects for vaccines against these viruses are less than promising. However, infections caused by respiratory syncytial virus and parainfluenza virus are major health problems in infants and young children worldwide, and considerable effort is being made to develop vaccines for this age group.[194] Inactivated vaccines for respiratory syncytial virus were found not to be protective and may have predisposed recipients to more severe illness during subsequent natural infection.[23] Live attenuated vaccines for respiratory syncytial virus are currently being evaluated for parenteral and intranasal administration.[6, 205] Thus far, none of these vaccines has been shown to be effective. Vaccines for the parainfluenza viruses are being developed.[194]

The use of recombinant technology, cloning, and peptide synthesis may in the future contribute to improved vaccines for respiratory viruses.[21, 113, 128]

Chemotherapy

Antiviral chemotherapy is available for the treatment and prophylaxis of influenza A infection. Amantadine hydrochloride (Symmetrel)* has been shown to be effective in both the treatment and prophylaxis of influenza A infections, probably by interfering with the penetration step of viral replication.[107, 160] When 200 mg per day of amantadine is begun within the first 24 to 48 hours of illness, the duration of uncomplicated illness and virus shedding is shortened and the extent of small-airway abnormalities is reduced. It is unknown whether amantadine is effective in treating primary influenza A pneumonia. When taken daily for the duration of an epidemic of influenza A (generally 6 to 8 weeks), amantadine has been shown to be 50 to 70 per cent effective in preventing infection[107] but should not be considered a substitute for vaccination.[112] Amantadine is primarily excreted unmetabolized in the urine. Thus, it may accumulate when renal function is impaired.[107] Side effects, the most common of which include difficulty in concentration, confusion, hallucinations, anxiety, insomnia, anorexia, and dyspepsia, occur in 10 to 33 per cent of adults.[160]

Studies of several investigational antiviral drugs have yielded promising results. Rimantadine, an analog of amantadine, appears to be as effective in the treatment and prophylaxis of influenza as amantadine.[40] Ribavirin, a synthetic ribonucleoside, has exhibited in vitro and in vivo activity against a number of viruses including influenza A and B and respiratory syncytial virus.[111, 166] In clinical studies of infections caused by influenza A and B and respiratory syncytial virus, it has achieved promising results when administered as an aerosol by face mask.[87, 124, 137] Interferon administered by nasal spray before and after challenge with rhinovirus appeared to delay the onset and decrease the severity of symptoms of infection in volunteers.[181]

Other investigational drugs, including isoprinosine for prophylaxis and treatment of infections due to influenza A (H3N2),[132] enviroxime for rhinoviruses,[129] and vitamin C for the common cold,[19, 48] have so far not been shown to be effective.

CONCLUSIONS

Viral respiratory illness is likely to continue to be a fact of life for some time, with symptomatic therapy the only intervention available to the clinician in most instances. However, for the patient with more serious illness, the patient with compromised immune, cardiac, or respiratory systems, and the hospitalized patient, developments in the 1980s and 1990s are likely to permit effective intervention. For the seriously ill and the

*Use of trade names is for identification only and does not imply endorsement by the Public Health Service or by the United States Department of Health and Human Services.

immunocompromised patient, diagnosis of a viral respiratory infection may permit the clinician to discontinue antibiotics and to initiate appropriate antiviral therapy. For the hospitalized patient, diagnosis of a viral respiratory infection may alert the medical staff to the possibility of a nosocomial outbreak and prompt them to initiate appropriate control measures. The diagnosis, control and treatment of viral respiratory infections will become more than just a scientific curiosity—they will be an important part of the clinician's armamentarium.

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