78. COMMON VIRAL RESPIRATORY ILLNESSES

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RHINOVIRUSES

Etiology

The rhinoviruses are the most frequently isolated agents associated with the "common cold." They are small RNA-containing viruses of the picornavirus group. Rhinoviruses are acid labile and grow optimally at temperatures of 33–34°C. They grow poorly at 37°C and do not survive the acid pH of the human gastrointestinal tract. Because the surface temperature of the nostrils is approximately 34°C, these viruses are ideally adapted as agents of upper respiratory tract disease.

Over 100 serotypes of rhinovirus have been documented. Infection with each may lead to respiratory illness. Disease caused by one serotype of rhinovirus does not prevent further infection with heterologous serotypes.

Pathogenesis and Pathology

The major pathologic lesion in acute rhinovirus disease is viral rhinitis characterized by hyperemic and edematous mucosal membranes and exudation of serous and mucinous fluid. Histologically, edema of subepithelial connective tissue is seen with sparse infiltration of neutrophils, lymphocytes, eosinophils, and plasma cells. There is increased mucus production by the submucosal glands. Although virus can be recovered from cultures of the pharynx and saliva, it is probable that the virus recovered represents contamination of secretions rather than virus replication at these sites.[1] There is no evidence that rhinoviruses replicate in the lower respiratory tract. However, rhinovirus infection does seem to exacerbate chronic bronchitis and has been shown to cause pulmonary function abnormalities in cigarette smokers and normal adult volunteers.[2]

Epidemiology

Rhinoviruses are responsible for the majority of acute respiratory infections of man and therefore may be the most common of all viral infections. Rhinovirus infections begin in infancy and continue into adult life at a population rate of approximately 0.5 infections per person-year. Rhinovirus-specific antibody can be detected in the first year of life and reaches a peak in young adults, probably because of repeated exposure to children with recurrent disease. Rhinovirus infections are most prevalent during early fall and continue throughout the colder months in temperate climates, similar to the seasonal epidemiology of most respiratory viruses. Infections are most frequent in populations in which interpersonal spread of virus through droplet nuclei and close physical contact are facilitated, such as families, nursery and elementary schools, military barracks, and nursing homes. Rhinoviruses are also very efficiently transmitted by autoinoculation of mucosal surfaces with either hands or fomites contaminated by virus-containing secretions.[3–5]

Manifestations

Rhinoviruses produce the typical "common cold syndrome" characterized by rhinorrhea, nasal obstruction, sneezing, pharyngitis, and cough. Most rhinovirus colds last approximately 1 week with peak symptoms occuring on the second and third days of illness. Cough may be more severe and prolonged in cigarette smokers and patients with preexisting pulmonary disease. In one-quarter of infected patients, symptoms may persist for up to 2 weeks. Secondary bacterial infections rarely occur as complications of rhinovirus illness. Systemic symptoms such as fever, malaise, and fatigue are not common, differentiating rhinovirus respiratory illness from influenza and paramyxovirus illness. Rhinovirus pharyngitis is less severe than that associated with β-hemolytic streptococcal disease or adenoviral infections.

There are no particular laboratory parameters diagnostic for rhinovirus disease. Early in the acute illness, total leukocyte count may be elevated with polymorphonuclear cells predominating. Increased erythrocyte sedimentation rates have been demonstrated as rhinovirus infections progress. The lower respiratory tract is not directly infected, and therefore radiographic changes are not seen.

Diagnosis

Specific etiologic diagnosis depends on demonstration of characteristic viral cytopathic effects in appropriate tissue culture cell lines followed by type-specific identification of the virus by neutralization with intersecting pools of antisera. The usual cell lines for rhinovirus recovery are human diploid lines such as WI-38. Direct virus isolation is quite cumbersome and is further complicated by the fact that cultures must be maintained at 33–34°C for rhinovirus detection rather than the standard 37°C used by most clinical virus laboratories. Because a large number of serotypes may cause disease, diagnosis on the basis of rising antibody titer is impractical. Techniques for demonstration of rhinovirus antigens in respiratory secretions are not currently used. The diagnosis of rhinovirus illness is thus made clinically, based on the likelihood that the majority of common colds are caused by rhinoviruses.

The differential diagnosis of rhinovirus illness is discussed in Chapter 77 and outlined in Table 77-2. The major pathogens that may cause similar disease are influenza virus, the parainfluenza viruses, respiratory syncytial virus, adenoviruses, *Mycoplasma pneumoniae*, and group A β-hemolytic streptococcal syndromes in small children.

N. Gleicher (ed.), *Principles of Medical Therapy in Pregnancy*

Treatment and Prevention

Treatment of rhinovirus infections consists mainly of bed rest, good hydration, and symptomatic relief. Disease is generally mild and self-limited; therefore, administration of medication to pregnant patients should not be necessary. Acetaminophen may be used if fever or pharyngitis are bothersome. Two experimental antiviral agents, enviroxime and dichloroflavan, are active in vitro against rhinoviruses but have not been proved clinically useful to date. The use of these drugs in pregnant women has not been studied, and potential effects on fetal development must be investigated. Therefore, specific antiviral chemotherapy for relatively mild rhinovirus illness cannot be advocated at this time.

There are no currently available vaccines for prevention of rhinovirus infection. Good hand washing and appropriate care with rhinovirus-contaminated fomites, such as facial tissues, are the best measures to reduce spread of rhinovirus disease.

Fetal Aspects

Rhinovirus infections in pregnant women are mild and self-limited. There is no viremic phase of the infection, and systemic manifestations are virtually non-existent. No metabolic or direct infectious insult to the fetus should be expected, and no complications of pregnancy from rhinovirus infections have been reported.

PARAINFLUENZA VIRUSES

Etiology

The parainfluenza viruses are members of the paramyxovirus group. They are RNA-containing viruses consisting of a lipoprotein envelope with hemagglutinin spikes surrounding a nucleocapsid. Four serotypes of parainfluenza virus have been defined on the basis of differential hemagglutination inhibition.[6] Each serotype of parainfluenza virus is associated with characteristic clinical and epidemiologic features, although the diseases caused by each serotype overlap in many respects, and in adults all fall within the general category of nonspecific viral respiratory illness.

The parainfluenza viruses are principally pathogens of children, in whom they may cause serious respiratory disease. Adults infected with parainfluenza viruses more often manifest the "common cold" syndrome. Parainfluenza type 1 is the principal cause of croup (laryngotracheobronchitis) in children. Parainfluenza virus type 3 is the second most common virus isolated from infants less than 6 months of age with bronchiolitis. Parainfluenza virus type 2 causes upper respiratory and pharyngeal illness, but disease caused by parainfluenza type 2 is generally less severe than that caused by parainfluenza type 1. Infections with parainfluenza type 4 are infrequently diagnosed and do not appear to cause significant morbidity.

Pathogenesis and Pathology

The pathogenesis of parainfluenza virus infections has been incompletely studied. Local multiplication of the virus in respiratory mucosal cells probably causes most of the manifestations of the disease. Parainfluenza virus antigens can be demonstrated in ciliated columnar epithelial cells in respiratory secretions of sick children using fluorescent antibody staining. Pathologic examination of lung tissue from infants dying with severe parainfluenza virus pneumonia shows general histologic findings associated with viral pneumonitis.[7] There are no pathognomonic lesions or inclusions associated with parainfluenza virus disease. The predilection of these viruses for the subglottic region and subsequent edema leading to clinical croup has not been explained. Viremia has occasionally been documented with parainfluenza infections, but its occurrence is rare.

Epidemiology

Parainfluenza viruses are found worldwide. Primary infections occur in infants and preschool children. Reinfection can occur throughout childhood and adult life despite the presence of preexisting antibody. By the age of 8 years, the majority of children have antibody to types 1, 2, and 3. Most adults have antibody to all four types of parainfluenza virus, which probably accounts for the mild disease caused by these viruses in older patients.[8]

Transmission of parainfluenza virus infection is by person-to-person contact and large droplet nuclei. Thus, outbreaks of disease are most likely to occur where there are many serosusceptible young children, such as day-care centers, nursery schools, and institutions for children. Because parainfluenza virus disease is mild in older children and adults, outbreaks of disease in grammar schools, military recruit centers, and nursing homes are reported less commonly. Attack rates of 96% have been reported in seronegative children, 67% in children with low levels of antibody, and 33% in individuals with high titers of serotype-specific antibody.

Parainfluenza viruses cause approximately 5–15% of respiratory infections in children and are responsible for fewer than 5% of infections in adults with respiratory disease.

Manifestations

The incubation period of parainfluenza virus infections varies from 3 to 6 days. Adult patients, who usually are reinfected rather than experiencing primary infections, present with nonspecific upper respiratory complaints of coryza and pharyngitis. Laryngitis may be more prominent than with other respiratory viruses. Disease in adults is usually self-limited and resolves spontaneously over several days.

Primary infections generally occur in children and are almost always symptomatic. Clinical manifestations may range from afebrile upper respiratory syndromes to severe, life-threatening lower respiratory tract illnesses. Parainfluenza virus 1 and, less commonly, parainfluenza virus 2 are associated with laryngeal and subglottic infection presenting as croup (laryngotracheobronchitis). Subglottic edema may become so severe that life-threatening airway obstruction occurs. Parainfluenza 3 infects infants rather than the 6-month- to 3-year-old children affected by croup. Babies with parainfluenza type 3 infections can present with severe viral pneumonia and bronchiolitis,

which may require hospitalization and mechanical ventilatory support.

There are no specific laboratory findings associated with parainfluenza virus infections. Young children with primary infections may present with elevated white blood cell counts early in the course of their illness, which return to normal after 2 to 3 days. Abnormalities seen on chest radiographs are not specific. Lateral and PA neck films may be useful to distinguish viral croup (subglottic edema) from acute bacterial epiglottitis.

Diagnosis

The specific diagnosis of parainfluenza virus infection depends on isolation of the virus in tissue culture. Samples of a patient's respiratory secretions may be collected on a cotton swab and placed in transport medium containing protein. The specimen is then inoculated into either primary monkey kidney or human embryonic kidney cells. Parainfluenza viruses do not reliably produce cytopathic effects, so virus is detected by hemadsorption of guinea pig erythrocytes to infected cultures. The serotype of the virus is determined by hemagglutination inhibition, hemadsorption inhibition, or complement-fixation assays. Although evidence for infection may be obtained serologically by screening acute and convalescent sera for titer rises to the parainfluenza viruses, heterotypic rises often occur to all serotypes when infection with one serotype occurs, limiting the use of this technique. Diagnosis of parainfluenza virus infections may also be made by demonstrating viral antigens in respiratory secretions using serotype-specific fluorescent antibody reagents.

The differential diagnosis of parainfluenza virus infections includes disease caused by other viruses that cause upper respiratory infections and *Mycoplasma pneumoniae*. These are outlined in Chapter 77, Table 77-2. In children with severe illness, bacterial pneumonia may be considered in the differential diagnosis. A young child with inspiratory stridor may have either viral croup or epiglottitis caused by *Hemophilus influenzae*. Bacterial epiglottitis is not limited to childhood, and several case reports of fatal disease remind the physician to consider infectious agents in the differential diagnosis of acute airway obstruction in adults.

Treatment and Prevention

Treatment of parainfluenza infections is symptomatic. In reinfected adults, disease is mild, and medication should not be required. Primary infection may be more severe, and some children require hospitalization for maintenance of adequate hydration and ventilation. Pregnant women have not been shown to be at increased risk of infection or its complications. Transmission of the virus from mother to neonate might result in severe disease for the infant, however. A recent case report describes the use of ribavirin, an antiviral agent effective against the parainfluenza viruses and respiratory syncytial virus, to improve the course of parainfluenza virus illness in a child with severe combined immunodeficiency. This agent might therefore be useful in the perinatal period. Ribavirin, however, is embryotoxic and teratogenic in animals, and its use in pregnancy is specifically contraindicated.

Vaccine use for prevention of parainfluenza illness has not been widely accepted. Inactivated vaccines have been shown to elicit good antibody response, but secondary infections may occur despite high titers. Live attenuated virus vaccines have been used experimentally and are more efficacious than inactivated preparations in adults. These attenuated vaccines have not been extensively evaluated in children.

Fetal Aspects

There have been no reported complications of pregnancy or fetal anomalies reported in association with parainfluenza virus infections.

RESPIRATORY SYNCYTIAL VIRUS

Etiology

Respiratory syncytial virus is an RNA virus of the paramyxovirus group. It is intermediate in size between larger parainfluenza viruses and smaller influenza virus particles. The virion consists of a single-stranded RNA genome within a lipid membrane studded with glycoprotein projections. The RSV is a relatively labile virus that is inactivated rapidly at 55°C and retains only 10% of its infectivity after 24 h at 37°C. The virus withstands freeze–thawing poorly and rapidly loses infectivity at low pH. There is only one serotype of RSV. Although antigenic variants have been demonstrated using hyperimmune ferret serum, human serum possessing neutralizing antibodies specific for one "strain" of RSV neutralizes all other variants.[9,10]

Pathogenesis and Pathology

Human infection with respiratory syncytial virus occurs through the upper respiratory tract, with the nose and eye being equally sensitive routes of inoculation. Virus multiplication occurs in the respiratory epithelium, and the infection is spread throughout the respiratory tree by cell-to-cell transfer of virus along intracytoplasmic bridges. Respiratory synctial virus infection may progress to involve the lower respiratory tract and conducting airways at all levels.

The effect of RSV infection on the respiratory epithelium may be seen in pathologic specimens from infants and young children dying with bronchiolitis and pneumonia. In RSV bronchiolitis, peribronchiolar mononuclear infiltrates, necrosis of the epithelium of small airways, lumenal plugging, and hyperinflation and air trapping can be seen. In RSV pneumonia, interstitial mononuclear cell infiltration is found. Lymphocytic infiltration of bronchiolar cell walls may also be present. Edema and necrosis of the lung parenchyma lead to alveolar filling, consolidation, and collapse.

Most adults infected with RSV develop "common colds." Young children, however, may suffer from severe and at times fatal RSV illness. Infants with the worst clinical illness possess RSV-specific passively transferred maternal antibody. Similarly, infants immunized with in-

activated virus develop very severe disease when challenged by infection with naturally occurring virus. In both of these situations virus shedding is prolonged, and high titers of virus may be recovered. Interferon production is poor, with detectable levels demonstrable in the nasal secretions of only a small percentage of infected infants. It appears that, at least in part, the pulmonary damage associated with RSV infection may be immune mediated.

Epidemiology

Respiratory syncytial virus infections occur in yearly outbreaks in most urban areas. Peak isolation of virus occurs in the midwinter to early spring. These epidemics are characterized by sharp onset and last 2 to 5 months. Infections with respiratory syncytial virus are observed worldwide. The virus is recovered most commonly from small children and is the major cause of viral pneumonia and bronchiolitis in infancy and early childhood.

Serologic surveys show that specific neutralizing antibody is passively transferred to virtually all infants. Antibody titers are identical in infants and mothers at birth, with passively transferred antibody gradually declining over the first 6 months of life. After 7 months of age, antibody titers develop as a result of natural infection. At 1 year of age, 25% to 50% of children have demonstrable neutralizing antibodies to RSV; 95% of 5-year-olds and virtually 100% of adults have serologic evidence of prior RSV infection.

Reinfections with respiratory syncytial virus are frequently seen. The most common pattern of spread of RSV is by introduction of the virus into a household by a school-age child with a cold. Adult family members then develop asymptomatic infection or mild colds, but infant siblings are at risk of severe disease. Attack rates within families are higher in lower socioeconomic groups, most probably reflecting both larger family size and increased population density. Nosocomial RSV infections are frequently observed in pediatric wards, and nursery outbreaks have been documented.

Manifestations

The incubation period for respiratory syncytial virus infection varies from 2 to 8 days, with most patients becoming symptomatic at 4 to 6 days post-infection. Clinical symptoms vary with age. Wheezing is prominent in pediatric disease. As noted above, infants and young children may develop severe lower respiratory illness manifesting acute pneumonitis, bronchiolitis, and bronchitis. These infections are particularly severe in those infants aged 2 to 5 months and may be fatal.

Adults reinfected with RSV most often present with the "common cold." Respiratory syncytial virus accounted for one-quarter of the viruses recovered from medical students complaining of colds. In military recruits, two-thirds of those soldiers shedding RSV complained of upper respiratory tract infections, and the rest were asymptomatic. Respiratory syncytial virus infections may be increased in severity in adults with intensive exposure to young children shedding the virus, possibly because of a larger inoculum. These patients, often the parents or physicians caring for young children with RSV disease, complain of moderately severe illness, which may limit their normal level of activity. They may describe their illnesses as more severe than the normal cold, and the course of the illness may be prolonged to nearly 2 weeks. Approximately one-third of these adults with more severe RSV disease are febrile. Since pregnant women often have children at home, they may fall into the group of adults at risk for more severe disease. There are no data to suggest that pregnancy per se is a risk factor for severe RSV infection.

Although RSV infection has been reported in neonates and in neonatal intensive care units, infections observed during the first month of life are generally mild.[11] Babies who have been born prematurely, especially those with lung disease, have been reported to develop more severe lung disease with later infection. Similarly, infants with cyanotic congenital heart disease have increased morbidity and mortality when infected with RSV than otherwise normal infants.[12]

Diagnosis

Specific diagnosis of respiratory syncytial virus disease depends on isolation of the virus in tissue culture. Samples for inoculation are best obtained by nasal wash, as these samples have higher yields than standard nasopharyngeal swabs. Because RSV is very labile, specimens should be kept on ice, not frozen, and inoculated onto HEp-2 cells as soon as possible after the specimen is obtained. Characteristic cytopathic effects consisting of syncytia formation and eosinophilic inclusions may be observed in approximately 4 days. Presumptive evidence of RSV infection may be obtained by staining smears of respiratory secretions or recently inoculated tissue culture tubes with fluoresce conjugated antibodies to RSV. Because illness so frequently occurs in spite of preexisting neutralizing antibodies, serologic tests to document infection are not helpful.

The differential diagnosis for RSV infection is that outlined in Table 77-2. In the general adult population, RSV infection is indistinguishable from infection with any other common respiratory virus. Epidemiologic considerations, such as the patient having a child with bronchiolitis, may allow presumptive etiologic diagnosis.

There are no specific laboratory findings associated with RSV infection. Children may have leukocytosis early in their course. Adults have normal blood smears and radiographic findings. In children with pneumonia and bronchiolitis, hyperinflation and patchy infiltrates, particularly in the upper lobes, may be seen in chest X ray.

Treatment and Prevention

Treatment of respiratory syncytial virus infections is supportive. Good hydration and fever control should be maintained. Infants with severe RSV disease often require hospitalization for hydration and may progress to require oxygen and ventilatory support. Amantadine, rimantadine, and ribavirin all are antiviral agents with in vitro activity against RSV. Several recent clinical trials have shown that aerosolized ribavirin has provided some symptomatic relief for infants with RSV pneumonia and bronchiolitis.[13,14] The use of this drug is still investigational, and its risk to pregnant women and the fetus is

great. Ribavirin is embyotoxic and teratogenic in animal toxicity tests. There is no reason to believe that pregnant women should acquire severe illness. No specific treatment should be required.

There are no specific ways to prevent RSV infection. Vaccine development has been hampered by concern for the presumed immune mediation of the severe lower respiratory disease that occurs in the first 6 months of life. As with most common respiratory viral illnesses, the best advice regarding prevention is to avoid when possible crowded places and congregations of young children during the winter months. In hospital outbreaks of RSV infection, good hand washing has provided the best control of spread of infection.

Fetal Aspects

There is no specific risk to the fetus associated with respiratory syncytial virus infection. Most maternal illness is mild, and no viremia has been reported. Infants are generally protected from severe lower respiratory disease during the first month of life. Infants with congenital heart disease or babies born prematurely may acquire severe RSV disease; however, these infections generally occur after the perinatal period.

CORONAVIRUS INFECTIONS

Etiology

The first strains of human coronavirus were isolated between 1965 and 1967 from patients in two centers investigating the etiology of common colds. The agents discovered were fastidious viruses that grew only in human respiratory tract organ culture or in cultured human embryonic kidney cells. They were classified as a new group in 1968. Coronaviruses are large RNA viruses with lipid-soluble coats that mature by budding into cytoplasmic vesicles. The virions are pleomorphic, and the external surface of the virus membrane is studded with projections that give the virion the appearance of a solar corona, hence their name. Because of the difficulty of isolating these viruses in cell lines routinely used for diagnosis, the actual description of clinical isolates is limited. Fewer than 50 viruses have been recovered in tissue or organ culture. Two prototype strains have been used to investigate the epidemiology of coronavirus infections, OC43 and 229E. They represent distinct serotypes. Two additional serotypes also probably exist, but infections attributable to these viruses are less well studied.[15,16]

Pathogenesis and Pathology

Coronavirus infections are generally associated with mild disease; therefore, little is known about the pathology of the infection. The virus appears to replicate superficially in tracheal organ cultures and interferes with cilial function. Other pathologic findings have not been described. Presumably, superficial replication of virus in respiratory epithelial cells occurs in natural infection. Virus is excreted by infected volunteers following a 2- to 4-day incubation period. Symptoms begin as virus is detectable in nasal secretions and continue from 1 to 4 days.

Epidemiology

Serologic evidence for coronavirus infection has been found in each geographic location studied, and coronaviruses are thus inferred to be distributed worldwide. Spread of infection is by inhalation of droplet nuclei or infected aerosols. Related animal viruses can be spread by the fecal–oral route, and there have been some recent reports suggesting prolonged enteric carriage of these viruses in human infants. In volunteer studies, coronavirus infection can easily be transmitted by nasal inoculation. Of patients inoculated by this route, virtually all will develop evidence of infection documented by seroconversion, but only 45–50% will become symptomatic.

Like most agents causing acute respiratory infections, coronaviruses are associated with outbreaks of illness during the winter and early spring months. Sporadic infections have been documented throughout the year. Early data suggest that coronavirus epidemics occur every 2 to 4 years. Age-specific attack rates are highest for young school children. In one serologic study of the prevalence of coronavirus infection conducted in Washington, D.C., 2% of infants and toddlers were seropositive, and only 48% of adults possessed neutralizing antibodies for coronaviruses. Coronavirus infections continue throughout the third, fourth, and fifth decades of life, causing 10–15% of adult "common colds."

Manifestations

Coronaviruses are the etiologic agents of approximately 15% of the common colds seen in adults. They produce a mild upper respiratory disease similar to that caused by rhinovirus infection. Headache, rhinorrhea, sore throat, and cough may be present. Fever is usually absent. Experimentally infected volunteers describe their illness as a mild cold. Lower respiratory tract symptoms are not present in infected adults; however, coronaviruses have been isolated from a few infants with pneumonia, and serologic evidence of coronavirus infection has been documented in approximately 5% of babies with pneumonia.[17] Gastroenteritis is associated with coronavirus infection in other species, and occasionally gastroenteritis may accompany common colds caused by coronaviruses. Several reports have associated coronavirus infection with outbreaks of necrotizing enterocolitis in neonatal intensive care units, again suggesting that gut disease may be caused by this virus group.[18]

Diagnosis

Laboratory diagnosis of coronavirus infection is difficult because these viruses do not grow in the tissue culture cell lines used in routine virus diagnostic labs. Several specialized experimental cell lines have been used by investigators studying the incidence and manifestations of coronavirus infection and can be obtained for special studies. Antibody titers are determined using complement fixation, passive hemagglutination, and indirect immunofluorescent methods. Reinfection is com-

mon despite the presence of documented preexisting antibody.

The differential diagnosis of coronavirus infection is that of the common cold. Other viruses that cause similar illness are rhinoviruses and, less commonly, parainfluenza viruses, respiratory syncytial virus, and influenza virus. *Mycoplasma pneumoniae* infection is more often associated with lower tract disease and generally is not a consideration in the differential diagnosis of coronavirus infection in adults. The occurrence of gastrointestinal symptoms with upper respiratory disease might suggest coronavirus or adenovirus infection.

Treatment and Prevention

There is no specific treatment for coronavirus disease. Symptoms are mild, and even antipyretics are rarely indicated. Because of the frequent reinfection rate in the face of apparently adequate antibody titers, vaccines have not been developed.

Fetal Aspects

Coronavirus infections are clinically mild and are not associated with systemic viremia. Therefore, effects of coronavirus infection on the pregnant woman and fetus are not expected and have not been described.

ADENOVIRUSES

Etiology

Adenoviruses were first isolated in the winter of 1952–1953 by two groups of investigators. Rowe and his colleagues at the National Institutes of Health cultured adenoids surgically removed from young children and isolated an agent from 33 of 53 adenoids. During the same winter, an epidemic of acute respiratory illness occurred among military recruits at Fort Leonard Wood, Missouri. The throat washings from one of these patients contained a virus that caused similar cytopathic effects in tissue culture and was related by complement-fixation and neutralization tests to the agent described by Rowe et al. The recovery of these prototype adenovirus strains illustrates their ability to cause epidemic and endemic respiratory illness and also to establish latent or persistent infections in normal hosts. Adenoviruses are most commonly recovered from the respiratory and gastrointestinal tracts of infected individuals. Virus, however, can also be recovered from the conjunctiva, urine, and the central nervous system. Clinically significant adenovirus infections may involve one or more of these organ systems and body fluids.

Adenoviruses are large DNA viruses composed of an inner protein core and an outer icosahedral shell. The outer protein shell is composed of two major subunits, hexon and penton proteins. The hexon protein elicits the formation of both group-reactive complement-fixing antibodies and type-specific neutralizing antibodies. The penton base protein contains group-specific and subgroup-specific antigenic determinants and may be directly cytotoxic to cells. The penton fiber carries type-specific antigenic determinants and is associated with the hemagglutinating activity of some serotypes.

There are at present 34 recognized species of human adenoviruses and five candidate species. The 34 human adenoviruses are subdivided by their biophysical, biochemical, biologic, and immunologic characteristics into five subgenera (A–E), which are illustrated in Table 78-1. The biophysical and biological characterizations of these viruses and the clinical syndromes caused by the subgenera are remarkably parallel.

Several additional candidate adenoviruses have been isolated from patients with clinically significant illness over the past several years. They are classified as new serotypes on the basis of unique serum neutralization tests and restriction endonuclease analysis of their genomes. Adenovirus 35 was first isolated in 1972 from the lung and kidney tissues of an immunosuppressed patient who died from interstitial pneumonia following kidney transplant. It has since been frequently identified in immunosuppressed patients with a variety of clinical

TABLE 78-1. Classification of Adenoviruses

Group	Serotypes	Persistent and inapparent infection	Transformation of rodent cells	Common clinical syndromes
A	12,18,31	+	+	None
B	3,7,11,14,16, 21,34	–	–	Acute epidemic respiratory disease Severe pneumonia
C	1,2,5,6	+	–	Upper respiratory illness in childhood
D	8–10,13,15,17–19, 20,22–30,32,33	–	–	Conjunctivitis Pharyngoconjunctival fever
E	4	–	–	Severe respiratory illness Pharyngoconjunctival fever

illnesses and occasionally from nonimmunocompromised patients. Adenovirus 36 was isolated in February, 1978 in a stool specimen from a 6-year-old child with enteritis. Adenovirus 37 was first identified in May, 1976 in an eye swab from a patient with epidemic catarrhal conjunctivitis. It has also been associated with pharyngoconjunctival fever, conjunctivitis, and urethritis. Adenovirus 38 is the first of the adenoviruses to be termed "noncultivatable," "fastidious," or "enteric." Studies in the United States, England, and the Scandinavian countries have associated this adenovirus with approximately 5–15% of infantile gastroenteritis. Adenovirus 39 was recently isolated from a stool specimen obtained from a 2-year-old South American child hospitalized with severe respiratory illness.

Pathogenesis and Pathology

The pathologic lesions of adenoviral respiratory disease are secondary to viral multiplication in respiratory epithelial cells. Infected cells become necrotic and are shed into the airways, especially at the tracheal and bronchiolar levels. Alveolar necrotic lesions are also occasionally demonstrable in autopsy specimens obtained from infants dying with adenoviral pneumonia. Gross pathologic examination reveals patchy necrotizing pneumonitis and bronchiolitis obliterans.[19]

Eye findings in adenoviral keratoconjunctivitis consist of marked conjunctival edema followed by exudation of mononuclear cell, mainly lymphocytes. Later in infection a pseudomembrane consisting of degenerating epithelial cells and exfoliated lymphocytes may cover the conjunctiva.

Several children have been described with the clinical presentation of Reye's syndrome associated with adenovirus 7 disease. In these children, no evidence of active adenoviral infection (that is, recovery of infectious virus) was present at the time of their disease, but circulating adenovirus penton protein could be demonstrated. This protein is directly cytotoxic to cells in tissue culture. Severe manifestations of clinical disease associated with some adenovirus serotypes may be related to cytotoxic penton protein antigens specified by these virus strains.[20]

Epidemiology

Adenoviruses are distributed worldwide. Human adenoviruses are spread from person to person with no known animal reservoir. Approximately 5–10% of civilian respiratory disease appears to be caused by adenovirus infection. Serologic evidence of infection with one or more group C serotypes is common by age 5. Occasional outbreaks of group D conjunctival infection have been linked to swimming pools, but most have no such association.

Nasopharyngeal inoculation of volunteers with adenovirus and ingestion of the virus usually results in asymptomatic infection or mild, afebrile illness. However, inhalation of adenovirus aerosols into the lower respiratory tract causes the full range of clinical syndromes. It is thus suggested that epidemic adenovirus pneumonia seen in army recruits is the result of airborne spread facilitated by close contact within a large group of susceptibles. The fecal shedding of virus may facilitate transmission by the fecal–oral route, thus contributing to the spread of infection between young children or where personal hygiene and sanitation are poor.

Manifestations

Adenoviruses show a predilection for infection of conjunctival, respiratory, and intestinal epithelium in addition to regional lymphoid tissue. Incubation periods have been 1 to 2 weeks where discernible. Latent infections, clinically asymptomatic infections, and prolonged viral shedding following clinical illness (particularly of the intestine) have all been described.

Adenoviruses of groups B and C have been shown to cause acute respiratory illness. Group B viruses, particularly serotypes 3, 7, and 14, may cause epidemics of respiratory disease in addition to sporadic cases of illness. The group C serotypes (1, 2, 5, and 6) cause sporadic mild respiratory illness of infants and children and can also establish latent infections in tonsillar tissue. Characteristically, the patient with adenoviral respiratory infection is febrile with pharyngitis, cervical adenitis, and conjunctivitis. Coryza and cough are also frequently present.[21–23] Atypical pneumonia may occur, and adenoviruses have been recovered from the lungs of fatal cases of pneumonia. A pertussislike syndrome has also been associated with adenovirus infection. Gastrointestinal symptoms can be prominent, and occasionally adenovirus-induced lymphoid hyperplasia in the gastrointestinal tract can serve as a focus promoting intussusception.

Adenoviruses have been found to be responsible for a significant proportion of serious acute lower respiratory tract infections in children. Adenovirus infection may occur at any time of the year, but large outbreaks of pharyngoconjunctival fever tend to occur in the summer and are associated with swimming pools. Although most adenovirus infections in civilian pediatric practice are associated with undifferentiated upper respiratory disease, acute laryngitis, influenzalike syndromes, and severe and even fatal cases of bronchitis, bronchiolitis, and pneumonia are seen.

Outbreaks of severe pulmonary disease caused by adenovirus types 3, 7, and 21 have been well documented in children as well as adults in closed populations. Affected children are generally young infants or toddlers less than 3 years old. Longitudinal studies of these children show that a significant proportion will develop evidence of chronic pulmonary disease.

Adenovirus types 3, 4, 7, 14, and 21 have also been associated with epidemics of febrile respiratory illness in closed populations, particularly among military recruits. Syndromes include an influenzalike illness, febrile pharyngitis, and atypical pneumonia. The conjunctival mucosa is frequently involved, and there are occasionally gastrointestinal symptoms.

Primarily nonrespiratory clinical syndromes commonly associated with adenovirus infection are epidemic keratoconjunctivitis, gastroenteritis in small children, and cystitis. Other illnesses rarely associated with adenoviruses are myocarditis, hepatitis, renal disease, arthritis, acute and subacute meningoencephalitis, and general

exanthems. Many of the higher adenovirus serotypes have been recovered from persons with inapparent infections, and their significance in disease is uncertain. Several of the newly defined adenovirus serotypes, particularly candidate adenovirus 35, have been isolated from immunosuppressed patients and may cause life-threatening infections, primarily interstitial pneumonitis and hepatitis. These infections may represent reactivation of latent virus in a manner analogous to cytomegalovirus infection in this population.[24]

Diagnosis

Adenoviruses can be recovered in cell culture from respiratory secretions, throat swabs, conjunctival swabs, urine, feces, blood, and biopsy or autopsy tissue from infected persons. Cell culture isolation remains the most sensitive means of detecting these viruses except for the fastidious enteric adenoviruses. The specimen should be inoculated into susceptible cells of human origin such as human embryonic kidney, HeLa, HEp-2, or KB cells. Typical CPE may appear in 2–7 days but can require several weeks to be seen. Identification of the agent as an adenovirus can be accomplished using antiserum to detect the hexon group antigen by fluorescent antibody (FA) or complement-fixation (CF) tests. A monoclonal antibody specific for adenovirus hexon protein has also recently been described.

Adenoviruses or adenoviral antigens have also been detected in clinical specimens using electron microscopy, enzyme-linked immunosorbant assays (ELISAs), and radioimmunoassays. These methods of adenoviral antigen detection are of primary importance in the diagnosis of adenoviral enteric disease in which virus isolation can not be accomplished in those tissue culture cell lines used for routine clinical viral diagnosis.

Because adenoviruses can be recovered from healthy people, increases in antibody titer between acute and convalescent sera should be sought to document recent acute infection. This may be done using a complement-fixation test for the group-reactive adenovirus hexon antigen or neutralization or hemagglutination inhibition tests employing type-specific antisera.

The differential diagnosis of the clinical syndromes caused by adenoviruses includes infections with bacteria, *Chlamydia*, *Mycoplasma pneumoniae*, and several other viruses. Streptococcal and adenovirus pharyngitis often cannot be differentiated clinically, and a culture for streptococci should be obtained whenever possible. The atypical pneumonia caused by adenoviruses is very similar to that caused by *Mycoplasma*, and as many as one in five persons with adenovirus atypical pneumonia have modest elevations in cold agglutinins.

Treatment and Prevention

Treatment of adenovirus respiratory infections is symptomatic and supportive. Fever and constitutional symptoms are common in adenoviral disease, and the pregnant woman may be advised to take antipyretic medication. Interferon has been used with moderate success to treat adenoviral conjunctivitis, but no specific antiviral drugs are currently being evaluated for adenoviral disease.

Immunity following adenovirus infection is serotype specific and appears to be long lasting. Because of the problem that adenovirus infections pose in military recruit camps, vaccines have been developed and tested in these populations. Experience with subcutaneous inoculation of an inactivated polyvalent vaccine containing types 3, 4, and 7 shows that such vaccines can control infection.

More recently, vaccines of live attenuated adenovirus types 4, 7, and 21 have been developed for oral administration. The virus is encased in an enteric-coated capsule and is released in the intestine, where it causes an asymptomatic, nontransmissible infection. Good protection has been provided by these vaccines; however, the rate of seroconversion to adenovirus 7 and 21 decreases when several vaccine strains are given simultaneously.

ECHOVIRUSES AND COXSACKIEVIRUSES

The viruses of the enterovirus group of picornaviruses (echoviruses, coxsackieviruses of group A and group B, poliovirus, and hepatitis A virus) most commonly cause clinical syndromes other than respiratory infection and are described in detail elsewhere. Table 78-2 details the serotypes of enteroviruses that have been observed in association with various respiratory illness.[25]

Enteroviral infections occur or are recognized more frequently in infancy than in school-age children or adults. Retrospective review of enteroviral infections in children less than 2 months of age reported to the Centers for Disease Control classified 50% of those infections as involving the central nervous system.[26] In all, 74% of infections in children less than 2 months of age were classified as severe disease. Other severe manifestations of enteroviral illness included severe systemic illness (mimicking overwhelming bacterial sepsis), hepatitis, carditis, and known infant death. Only 26% of infections in the 338 cases reviewed were considered to represent benign disease. Other data regarding the importance of enteroviruses in the etiology of neonatal sepsis syndromes are provided by Sanders and Cramblett.[27] For a 1-year interval, all infants less than 1 month of age admitted to the hospital with suspected sepsis were cultured for viruses. Eleven of 68 infants admitted to hospital (14.9%) were found to have a viral pathogen present in the absence of bacterial disease. Furthermore, seven of those 11 positive cultures contained enteroviruses.

Recent data indicate that infants born to mothers with active enteroviral disease intrapartum may acquire fulminant infection with maternal virus leading to fatal outcomes. Nagington et al. reported three fatal cases of echovirus 11 disease occurring in a special-care nursery.[28] The index cases were twins born to a mother with acute enteroviral disease at the time of parturition. Disease in these two infants led to infection of four nursery personnel and seven additional babies, one of whom died. Of the six surviving babies with echovirus 11 infection, three were symptomatic, and three shed virus without symptoms. An additional three infants developed symptoms of echovirus disease. However, no virus could be isolated from these babies. In all, nine of 24 (38%) infants in the nursery at the time of admission of the index cases devel-

TABLE 78-2. Coxsackieviruses and Echoviruses Noted in Association with Respiratory Disease[a]

Clinical categories	Virus types		
	Coxsackieviruses A	Coxsackieviruses B	Echoviruses and Enteroviruses
Common cold	Mainly 21,24; rarely other types	Mainly 1–5; rarely 6	Mainly 2,20; rarely other types
Pharyngitis (pharyngitis, tonsillitis, tonsillopharyngitis, and nasopharyngitis)	Probably all types; mainly 9	Probably all types; mainly 1–5	Probably all types; mainly 2,4,6,9,11,16,19,25,30
Herpangina	1–10,16,22	1–5	6,9,16,17,25
Croup	9	4,5	4,11,21
Bronchitis		1,4	8,12–14
Bronchiolitis and asthmatic bronchitis	Many types	Many types	Many types
Pneumonia	9,16	1–5	6,7,9,11,12,19,20,30
Pleurodynia	1,2,4,6,9,16	1–6	1–3,6–9,11,12,14,16,18,19,23

[a]From Cherry.[25]

oped echovirus 11 infection. Subsequent to this report, Davies et al. reported an additional four cases of echovirus 11 disease occurring in another special-care nursery, and Freedman described a case of maternal echovirus 11 infection at 39 weeks of gestation leading to intrauterine death at term.[29,30]

Modlin et al. described the outcome of maternal echovirus 11 infection during an outbreak of disease caused by this virus in Boston during the summer and fall of 1979.[31] Four cases of fatal echovirus infection occurred in premature infants. The mothers of three of these infants experienced a febrile illness with abdominal pain within the last 5 days of pregnancy. In two, the illness led to a false diagnosis of abruptio placenta and interruption of pregnancy by cesearian section. Each mother ultimately developed neutralizing antibody to echovirus 11. However all four infants were born without passively acquired antibody, probably because they were delivered prior to the appearance of specific maternal IgG.

A prospective study during the same echovirus 11 outbreak documented the protective role of transplacentally acquired specific antibody.[32] Seven of 194 pregnant women (3.6%) were found to be excreting echovirus 11 at term. Each of the seven women possessed serum neutralizing echovirus 11 antibody at the time of parturition, and the cord sera of all of their infants also contained neutralizing antibodies to echovirus 11. None of the seven infants born to these seropositive mothers became clinically ill, although four of the seven babies were shedding echovirus 11 from the gastrointestinal or respiratory tract by 3 days of age. None of the infants of virus-negative mothers was documented to be infected during hospitalization or at 2 weeks of life.

Many other serotypes of enteroviruses have been reported to cause aseptic meningitis in the perinatal period and to cause the syndrome of overwhelming viral sepsis and death characterized for echovirus 11 in the preceding studies. These case reports provide further evidence for the importance of the echoviruses in the perinatal period and the need to be able to appropriately diagnose these illnesses. Modlin et al.[32] suggest that if a mother is suspected of having early enteroviral disease at the onset of labor, delivery should be delayed to allow for the development and transfer of maternal antibodies, which could protect the infant from possible fatal perinatal echovirus infection.

REFERENCES

1. Gwaltney JM Jr: Rhinoviruses, in Evans AS (ed): Viral Infections of Humans. Epidemiology and Control. New York, Plenum Press, 1978, pp 383–408
2. Gwaltney JM Jr: Rhinovirus, in Mandell GL, Douglas RG, Bennett JE (eds): Principles and Practice of Infectious Diseases. New York, John Wiley & Sons, 1979, pp 1124–1134
3. Cate TR: Rhinoviruses, in Knight V (ed): Viral and Mycoplasmal Infections of the Respiratory Tract. Philadelphia, Lea & Feiburger, 1973, pp 141–151
4. Dick EC, Chesney PJ: Rhinoviruses, in Feigin RD, Cherry JD (eds): Textbook of Pediatric Infectious Diseases. Philadelphia, WB Saunders, 1981, pp 1167–1186
5. Knight V: Common viral respiratory illnesses, in Isselbacher KJ, Adams RD, Braunwald E, et al (eds): Harrison's Principles of Internal Medicine, ed 9. New York, McGraw-Hill, 1980, pp 779–785
6. Hendley JO: Parainfluenza virus, in Mandell GL, Douglas RG, Bennett JE (eds): Principles and Practice of Infectious Diseases. New York, John Wiley & Sons, 1979, pp 1170–1176
7. Zinserling A: Pecularities of lesions in viral and mycoplasma infections of the respiratory tract. Virchows Arch [Pathol Anat] 356:259–273, 1972
8. Glezen WP, Loda FA, Denny FW: The parainfluenza viruses, in Evans AS (ed): Viral Infections of Humans. Epidemiology and Control. New York, Plenum Press, 1978, pp 337–349
9. Chanock RM, Kim HW, Brandt C, et al: Respiratory syncytial virus, in Evans AS (ed): Viral Infections of Humans. Epidemiology and Control. New York, Plenum Press, 1978, pp 365–382
10. Hall CB: Respiratory syncytial virus, in Feigin RD, Cherry JD (eds): Textbook of Pediatric Infectious Diseases. Philadelphia, WB Saunders, 1981, pp 1247–1267
11. Hall CB, Kopelman AE, Douglas RG Jr, et al: Neonatal respiratory syncytial virus infection. N Engl J Med 300:393–396, 1979
12. MacDonald NE, Hall CB, Stuffin SC, et al: Respiratory syn-

cytial viral infection in infants with congenital heart disease. N Engl J Med 307:397–400, 1982
13. Hall CB, McBride JT, Walsh EE, et al: Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. N Engl J Med 308:1443–1447, 1983
14. Taber LH, Knight V, Gilbert BE, et al: Ribavirin aerosol treatment of bronchiolitis associated with respiratory syncytial virus infection in infants. Pediatrics 72:613–618, 1983
15. McIntosh K: Coronavirus, in Mandell GL, Douglas RG, Bennett JE (eds): Principles and Practice of Infectious Diseases. New York, John Wiley & Sons, 1979, pp 1212–1217
16. Monto AS: Coronaviruses, in Evans AS (ed): Viral Infections of Humans. Epidemiology and Control. New York, Plenum Press, 1978, p 127–141
17. Knight V, Mayor HD: Coronaviruses, in Knight V (ed): Viral and Mycoplasmal Infections of the Respiratory Tract. Philadelphia, Lea & Feiburger, 1973, pp 201–208
18. Chany C, Moscovici O, Lebon P, et al: Association of coronavirus infection with neonatal necrotizing enterocolitis. Pediatrics 69:209–214, 1982
19. Ferignac B, Chany C: Adenoviruses, in Debré R, Celers J (eds): Clinical Virology. Philadelphia, WB Saunders, 1970, pp 615–626
20. Ladisch S, Lovejoy FH, Hierholzer JC, et al: Extrapulmonary manifestations of adenovirus type 7 pneumonia simulating Reye syndrome and the possible role of an adenovirus toxin. J Pediatr 95:348–355, 1979
21. Chanock RM: Impact of adenoviruses in human disease. Prev Med 3:466–472, 1974
22. Fox JP, Hall CE, Cooney MK: The Seattle virus watch. Am J Epidemiol 105:362–386, 1977
23. Spencer MJ, Cherry JD: Adenoviral infections, in Feigin RD, Cherry JD (eds): Textbook of Pediatric Infectious Diseases. Philadelphia, WB Saunders, 1981, pp 1279–1298
24. Zahradnik JM, Spencer MJ, Porter DD: Adenovirus infection in the immunocompromised patient. Am J Med 68:725–732, 1980
25. Cherry JD: Nonpolio enteroviruses: Coxsackieviruses, echoviruses and enteroviruses, in Feigin RD, Cherry JD (eds): Textbook of Pediatric Infectious Diseases. Philadelphia, WB Saunders, 1981, pp 1316–1365
26. Morens DM: Enteroviral disease in early infancy. J Pediatr 92:374–377, 1978
27. Sanders DY, Cramblett HG: Viral infections in hospitalized neonates. Am J Dis Child 116:251–256, 1968
28. Nagington J, Wrighitt TG, Gandy G, et al: Fatal echovirus 11 infections in outbreak in special-care baby unit. Lancet 2:725–728, 1978
29. Davies DP, Hughs CA, MacVicar J, et al: Echovirus 11 infection in a special-care baby unit. Lancet 1:96, 1979
30. Freedman PS: Echovirus 11 infection and intrauterine death. Lancet 1:96–97, 1979
31. Modlin JF: Fatal echovirus 11 disease in premature neonates. Pediatrics 66:775–780, 1980
32. Modlin JE, Polk BF, Horton P, et al: Perinatal echovirus infection. Risk of transmission during a community outbreak. N Engl J Med 305:368–371, 1981

79. INFLUENZA

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MATERNAL ASPECTS

Definition

Influenza is an acute, usually self-limited, febrile respiratory illness caused by infection with influenza type A or type B virus. It is classically characterized by myalgias, headache, cough, and fever but may present as any of the respiratory viral syndromes including isolated coryza, laryngitis, laryngotracheobronchitis, tracheitis, bronchitis, and pneumonia. The term "flu" should be reserved for respiratory disease directly attributable to influenza virus.

Etiology

The etiologic agent of the disease influenza is influenza virus, an orthomyxovirus containing a single-stranded, segmented RNA genome. The structure of the virus is provided by a protein capsid surrounded by a glycoprotein envelope. Influenza viruses are classified as group A, B, or C depending on the seroiogic reactivity of their capsid protein. The two major surface glycoproteins, the hemagglutinin and neuraminidase, are the antigens that determine the serotype and strain identity of an influenza virus isolate. There are five major hemagglutinin subtypes (H_0, H_1, H_2, H_3, and H_{swine}) and two neuraminidase types (N_1 and N_2) associated with influenza A disease.

Major variations in the chemical composition of the hemagglutinin and/or neuraminidase molecules in prevalent influenza viruses are termed "antigenic shifts." Changes in these glycoproteins have been associated with worldwide outbreaks of severe respiratory disease such as those indicated in Table 79-1. Minor variations in the hemagglutinin and neuraminidase molecules of influenza A viruses can be seen from year to year, presumably because of the selection pressure of antibody in an immune population. This phenomenon is termed "antigenic shift" and is responsible for smaller epidemics of influenzal illness, which occur at 2- to 3-year intervals.[1]

Pathogenesis and Pathology

Influenza is primarily an infection of the superficial cells of the respiratory mucosa. Virus replication in the ciliated columnar epithelium leads to denudation of the tracheobronchial tree. This destruction of respiratory epithelium can lead to decreased diffusion capacity, de-