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Viral Pneumonias

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Viral pneumonia is a diagnosis which is usually considered when a specific bacterial etiology for a pulmonary infection cannot be established by routine laboratory procedures. However, in the individual case this diagnosis is seldom confirmed by specific viral diagnostic techniques. Viral pneumonia is a common disease in early childhood, but when large scale etiologic investigations of adult pneumonia have been performed, viruses do not appear as common pathogens.[18,29,32,91,121] Moreover, a significant number of "non-bacterial" pneumonias are caused by mycoplasma, chlamydia, rickettsia, fungi, and unusual bacteria. Recent work has extended this list to include several previously unrecognized microorganisms which may cause serious pulmonary infection in normal as well as immunocompromised patients.[60,92,108,125]

Thus, referring to an undiagnosed lung infection as "viral" may only serve to provide a false sense of security for the physician. On the other hand, a specific viral diagnosis aids the physician in designing further diagnostic and therapeutic measures, and may provide helpful prognostic information. A specific viral diagnosis could also have important public health implications. Specific viral diagnoses in cases of pneumonia will also permit the accumulation of clinical and epidemiologic information which will form the basis for appropriate evaluation of new methods of therapy for serious viral respiratory disease.

The etiologic diagnosis of any infectious disease requires specific microbiologic and/or immunologic techniques. A definitive diagnosis cannot be determined on the basis of clinical or radiologic criteria, or by the use of nonspecific laboratory tests. The microbiologic diagnosis of infectious pneumonia usually requires isolation of the causative organism from appropriate specimens. The reliability of a specific microbiologic diagnosis is often enhanced by the simultaneous demonstration of a four-fold rise in serum antibody directed against the putative pathogen.

These general principles also apply to the diagnosis of viral pneumonia. However, because modern methods of diagnostic virology have not been widely available until recently, the diagnosis of viral pneumonia has often been made on the basis of serologic evidence of infection in the presence of a compatible illness.

There are many different sources of error inherent in this practice, and

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although this method has been helpful in epidemiologic studies of known respiratory pathogens, it can be misleading in an individual case. For example, during an outbreak of enteroviral disease a large segment of a susceptible population will become infected with the circulating enterovirus and manifest a four-fold rise in antibody which is directed against that agent. Any individual within that population who develops pneumonia, of any etiology, is likely, therefore, to demonstrate serologic evidence of infection with the circulating enterovirus. However, enteroviruses very rarely cause pneumonia, and thus serologic evidence alone might be misleading in this situation.

It is therefore desirable, when making a specific viral diagnosis, to recover the virus in cultures of appropriately obtained clinical specimens. However, even positive viral cultures can be misleading because some viruses may be excreted for prolonged periods after an initial infection occurs, and because some viruses produce latent infections with periodic shedding of virus which is etiologically unrelated to the acute illness. Thus, it is frequently necessary to confirm viral diagnoses with appropriate serologic methods and/or histopathologic techniques. These concepts are particularly important to remember when a common clinical syndrome is attributed to an unusual viral pathogen, and when a traditional respiratory virus is associated with unusual clinical manifestations.

Although many studies have been performed without strict adherence to the principles discussed above, currently available knowledge allows us to make several generalizations about viral pneumonias. Viruses are generally considered to be common etiologic agents in early childhood pneumonias.[72] Lung infections in older children and young adults are most frequently caused by *Mycoplasma pneumoniae*,[12] whereas most radiographically demonstrated parenchymal lung infections in older adults are caused by pyogenic bacteria, of which *Streptococcus pneumoniae* is the most common.[17] Several different viruses frequently cause lower respiratory tract disease in children, whereas in adults only influenza is well established as a common cause of viral pneumonia in civilian populations.

The clinical manifestations of viral pneumonia are highly variable, and these infections often present diagnostic difficulties. As with many infectious diseases, epidemiologic considerations may provide helpful clues. Thus, factors such as geographic location, time of year, and socioeconomic status are important parameters to consider when evaluating individuals with serious respiratory disease. The onset and course of the disease may be gradual and indolent, or abrupt and rapidly progressive. With certain exceptions, such as chickenpox and measles, there is nothing about the physical examination which is distinctive about viral pneumonia.

Although sputum associated with viral pneumonia is usually scant or watery, respiratory secretions may be grossly purulent and contain mostly polymorphonuclear leukocytes.[9,17,77] The sputum gram stain shows either no bacteria or a mixed flora which is suggestive of oral contamination.[9,22] The white blood cell count is frequently suggested as a means to distinguish between viral and bacterial pneumonias. However, it is well recognized that grossly elevated white counts may be seen in viral pneumonia,[9,77] and this measurement cannot be relied upon to determine the microbiologic etiology of a lower respiratory tract infection. Viral pneumonias often produce interstitial or reticular patterns on chest x-ray films, but both viruses and bacteria can produce a wide spectrum of radiologic manifestations.[98,111] One recent study demonstrated the inability of six

radiologists to distinguish reliably between bacterial and nonbacterial pneumonia on the basis of chest radiographs of 31 patients in whom a specific microbiologic diagnosis had been established.[124] In summary, although the history, physical examination, initial laboratory work and chest x-ray examination are helpful aids in the approach to a patient with infectious pneumonia, the microbiologic diagnosis must be made by specific laboratory techniques.

The remainder of this paper will consist of five separate sections. In the first, we will discuss the viral pneumonias associated with early childhood. In this age group, several different viruses are capable of causing severe lower respiratory tract disease. Second, we will discuss the viral pneumonias which occur in adults. A third section will consider systemic viral infections in which pneumonia occurs but is not the dominant clinical feature of the disease. Next we will discuss viral pneumonias in the special setting of the immunocompromised patient. Lastly, we will briefly consider the control measures which are presently available for this group of diseases.

VIRAL PNEUMONIA IN CHILDREN

Respiratory Syncytial Virus

First isolated by Morris, Blount, and Savage in 1956,[90] respiratory syncytial virus (RSV) is now recognized as the major cause of serious lower respiratory tract disease in young children.[49] Most serious cases occur in children less than 6 months of age,[16] and the peak incidence of respiratory syncytial virus-associated bronchiolitis and penumonia occurs at ages 2 to 3 months.[100] Epidemics of respiratory syncytial virus infections occur annually in the winter and the spring.[6] Unusually severe and widespread respiratory syncytial virus infection has been described in certain isolated populations,[89] and the occurrence of severe neonatal disease has recently been appreciated.[50] Although infections are usually acquired in the community, recent data have shown that the virus can cause serious nosocomial illness as well.[51] In a 4 year study of serious lower respiratory tract disease in preschool children reported by Foy et al., where the annual incidence of pneumonia was 30 per thousand, the highest rates of lower respiratory tract illness occurred during the yearly respiratory syncytial virus epidemics.[35] Virus isolation and serologic data showed respiratory syncytial virus infection to be the most common cause of pneumonia and bronchiolitis in these young children. Other studies have given similar results.[6,7,46,79] There is evidence which suggests that these diseases are somewhat more common in boys, although the rates of infection are about equal in both sexes.[16,45] Antibody to respiratory syncytial virus is present in about 35 percent of infants 3 to 12 months of age, and in 95 percent of children 5 years of age or older.[49] The virus is shed in large quantities in the respiratory secretions of infected infants, and the virus can be recovered for prolonged periods after the acute illness has resolved.[52,53]

Respiratory syncytial virus produces several different clinical syndromes in children, the most serious of which are the lower respiratory tract diseases, bronchiolitis and pneumonia. Bronchiolitis is classically manifested by shortness of breath, wheezing, and a clear chest x-ray which often shows hyperinflated lungs. Some children go on to develop pneumonia with rales and signs of con-

solidation which are confirmed radiographically. Often the distinction between bronchiolitis and pneumonia is difficult to make.[19]

In one radiographic study of 65 patients with lower respiratory tract disease caused by respiratory syncytial virus, the dominant findings were bronchial wall thickening, peribronchial shadowing, and perihilar linearity, which were present in 60 cases.[98] Findings suggestive of sublobular or lobular consolidation were seen in 39 cases, whereas more homogeneous shadowing was present in only 10. It was common to have multiple areas involved, and air-trapping was evident in 41 cases.

In fatal cases, purulent bronchitis and hemorrhagic pneumonia can be demonstrated at postmortem examination, as well as necrosis and obstruction of bronchial epithelium, peribronchial mononuclear infiltration, and cytoplasmic inclusion bodies in epithelial cells which are characteristic of respiratory syncytial virus.[2]

Parainfluenza Virus

Parainfluenza virus infections are very common, and usually occur in a slightly older age group than those caused by respiratory syncytial virus. In the absence of significant influenza activity in the community, these viruses are the second most common cause of serious lower respiratory tract disease in young children.[35] The epidemiology and clinical manifestations of parainfluenza infection vary with respect to the type of virus. Type 3 infection occurs very early in life, and 50 per cent of children will have antibody to it by the age of 12 months. This percentage increases to 90 per cent by the age of 5 years. In contrast, less than 10 per cent of infants under 1 year of age have antibody against types 1 and 2, and only about 60 per cent will have serum neutralizing activity against these types by age 5.[19] Parainfluenza virus type 3 is endemic and infections caused by this agent do not have a seasonal pattern of incidence. Types 1 and 2, on the other hand, have demonstrated a marked tendency to produce periodic outbreaks, which appear during late fall, winter, or early spring months.[56] The principal lower respiratory tract disease associated with the parainfluenza viruses is acute laryngotracheobronchitis, or croup.[19,56] Types 1 and 2 are the most common causes of croup, whereas type 3 tends to produce more bronchitis, bronchiolitis, and pneumonia.[76] These latter syndromes tend to be less severe than similar illness caused by respiratory syncytial virus. Parainfluenza viruses types 4A and 4B require prolonged incubation for isolation, and the spectrum of diseases associated with these agents is not well established, although it is known that large numbers of young children possess antibody to them.[41]

Influenza Virus

Attack rates of influenza are higher in children than in adults, but in children the disease tends to be milder and the incidence of pulmonary complications lower.[20] Nevertheless, a number of studies have demonstrated that these viruses are an important cause of morbidity and mortality in young children, and that they can produce the entire spectrum of respiratory disease which is seen in that age group.[47,139] Thus, the incidence of croup, bronchiolitis, and pneumonia may increase during epidemics of influenza. A wide range of manifestations of influenza both in and out of the respiratory tract was recently described in a retrospective review of 83 children hospitalized with influenza in Denver.[99]

Twenty-nine per cent of this selected population had pneumonitis and 3 patients died from severe viral pneumonia. Recent studies of influenza in children have stressed the frequency and severity of the croup syndrome caused by these viruses.[68,99] Influenza A virus has also been shown to precipitate childhood asthma,[85] and to produce serious nosocomial infections in pediatric patients.[110]

Adenoviruses

Adenoviruses are common respiratory pathogens, and may cause severe, fatal pneumonia in young children.[57,94,112] Of the more than 30 types which can infect humans, types 1, 3, and 7 have been most frequently associated with severe childhood pneumonia.[70] Epidemiologic studies have shown that infections with low numbered serotypes occur before 6 months of age, peak in preschool years, remain common in children from 5 to 9 years of age, and then decrease in frequency.[34] Severe illness generally occurs in the very young, and may be epidemic or sporadic.[57,94,112,122] Chest x-rays generally show patchy or mottled infiltrates, but unusual presentations, including large pleural effusions, have been described.[118]

Rhinoviruses

Rhinoviruses are among the most common respiratory pathogens of man, but they do not have an established role as important pathogens in the lower respiratory tract. Although some investigators have suggested that these viruses do cause pneumonia and other serious respiratory disease,[101,120] other studies have failed to document such an association.[104] There are probably occasional pediatric pneumonias caused by rhinovirus, but the bulk of evidence suggests that members of this genus are not important causes of childhood pneumonia.

Enteroviruses

Like rhinoviruses, members of the other genus within the family picornaviridae, enterovirus, are not common causes of pneumonia, even in small children. Of the three groups within this genus, only Coxsackie virus and echovirus contain members which occasionally infect the lung. Despite the devastating consequences which polio can have on respiratory function, the virus itself does not appear to infect pulmonary tissue. Pneumonia caused by enteroviruses has been documented with only a few serotypes.[141,142] Whether this is a reflection of the rarity of the disease, or whether particular enteroviruses are more "pneumotropic" than others is not known. Although uncommon, enteroviral pneumonia can be severe and lead to death.[11]

Coronaviruses

Coronaviruses probably produce serious lower respiratory tract disease in infants on occasion, but such infections appear to be uncommon.[81]

VIRAL PNEUMONIA IN ADULTS

Influenza

We have seen that a broad variety of viruses causes pneumonia in young children. In adults, however, only influenza virus has been well established as

a common cause of viral pneumonia in civilian populations.[19] Influenza is usually an acute, self-limited disease which may be caused by either type A or type B virus. Outbreaks occur virtually every winter and result in a variety of respiratory tract illnesses, the most serious of which is pneumonia.[20] The various syndromes of pneumonia associated with influenza infection were well described by Louria et al. in their detailed study of 30 patients who were hospitalized with pneumonia at the New York Hospital during the pandemic of 1957–1958.[77] Three syndromes were recognized: (1) influenza virus infection followed by secondary bacterial pneumonia; (2) an acute, rapidly progressive pneumonia apparently produced by influenza virus infection alone; and (3) concomitant viral and bacterial pneumonia. Twenty-four of the 30 patients fell into groups 1 and 3. *Streptococcus pneumoniae, Staphylococcus aureus,* and *Hemophilus influenzae* were the most commonly isolated bacteria. Four of these 24 patients died. Five of the 6 patients with influenza virus infection alone died. Patients with viral lung infections tended to have more significant underlying cardiopulmonary disease than did those with primarily bacterial disease. Subsequent studies of pneumonia associated with influenza have confirmed and extended these findings.[5,38,67,114] These later investigations have found a lower incidence of pure viral pneumonia and have also shown that the disease has a broader clinical spectrum than was originally described. Primary influenza viral pneumonia can be a mild segmental disease. The frequency of pneumonia in influenza infection varies considerably, but tends to increase with underlying cardiopulmonary disease and with increasing age.

Adenoviruses

Aside from influenza, the only virus which has frequently produced pneumonia in normal human adults is adenovirus. However, adenoviruses commonly produce pneumonia only in military recruits, and adenoviral pneumonia in civilian adults occurs rarely and sporadically.[19] The original association between adenoviruses and pneumonia in military recruits was made by Hilleman and Werner in 1954.[58] Subsequent studies established these viruses as major pulmonary pathogens in this particular population and eventually led to the development of effective live vaccines.[4,132] Types 3, 4, 7, and 21 are responsible for most serious respiratory infection caused by these viruses in adults.[70] The disease is generally mild and self-limited, but it can be severe and result in death.[23,74,140] Although adenovirus infections are usually community-acquired, a recent report suggests that these viruses may cause nosocomial disease as well.[103]

Miscellaneous

There are scattered reports of other viruses producing pneumonia in adults. These include cases associated with infections caused by rhinoviruses,[42] enteroviruses,[13,63] parainfluenza viruses,[133] coronaviruses,[134] and respiratory syncytial virus.[107] In addition, there have been reports of virus infections which appear to affect small pulmonary airway function adversely in the absence of radiographic evidence of pneumonia.[37,54,75] Whether such infections represent viral replication in the lower respiratory tract is not known. Nevertheless, it is important to reemphasize that at the present time, only influenza is established as a common cause of viral pneumonia in non-immunocompromised, civilian adults.

PNEUMONIA AS A PART OF SYSTEMIC VIRAL DISEASES

Measles

At one time a common pediatric disease in the United States, measles has decreased dramatically in incidence since the introduction of effective vaccines in 1963.[43] These vaccines also led to a change in the age group in which measles occurs. Once an almost exclusively pediatric infection, the incidence of measles is now increasing in adults.[106] Respiratory tract involvement is an integral part of measles and radiographic evidence of pneumonia can occur during uncomplicated disease.[28] In addition to asymptomatic radiographic findings, however, pulmonary infections associated with measles can represent major, life-threatening complications of the disease.

Severe pneumonia may be caused by the measles virus itself, or by common bacterial pathogens.[43] Pulmonary disease is also a common part of "atypical measles." This disease is seen in individuals who received killed measles vaccine and subsequently were infected with wild-type measles virus.[39] Killed vaccine has not been available in the United States since 1968, and thus atypical measles should no longer be seen in individuals less than 12 years of age. This syndrome is characterized by a rash, which unlike classical measles, begins peripherally and may be urticarial, maculopapular, hemorrhagic, and/or vesicular. The patient usually has a high fever and interstitial pulmonary infiltrates. The disease tends to be quite severe, with a prolonged course. The pulmonary infiltrates may coalesce into nodules which can persist for some time after resolution of the acute illness, and may be mistaken for pseudotumors or metastatic cancer.[73]

Herpes Varicella-Zoster Virus

Primary infection with herpes varicella-zoster virus, or chickenpox, remains an almost universal disease experience of early childhood, and major outbreaks continue to occur regularly.[130] Pneumonia associated with chickenpox may be either viral or due to bacterial superinfection. Varicella pneumonia is rarely observed in normal children, and is generally felt to be more common and severe when chickenpox occurs in adulthood.[8,126] Prospective studies in young male military recruits demonstrated abnormal chest x-ray films in 16 per cent of patients with varicella, although only 2 per cent of the patients were short of breath.[129] The disease in both adults and children is generally benign and resolves without specific therapy, although several severe cases which resulted in death have been reported.[126] A peculiar radiographic feature of varicella pneumonia is that the lesions may calcify, producing multiple calcifications throughout both lung fields.[126]

Miscellaneous

Several viral diseases may involve the lung as part of overwhelming infection. Such pneumonias are not uncommonly seen as part of congenital or neonatal infections. Infection of the fetus with either rubella virus[71,102] or cytomegalovirus[55] may, for example, produce viral pneumonia in the newborn. Lung involvement is not uncommonly seen as part of disseminated herpes simplex infections in neonates.[95]

Less severe systemic viral diseases may also involve the lung as a minor

part of the illness. For example, lung involvement has been described as part of the infectious mononucleosis syndrome, although it is not clear that these infiltrates were related to Epstein-Barr virus infection.[113]

VIRAL PNEUMONIAS IN IMMUNOCOMPROMISED HOSTS

Despite the large number of human respiratory viruses, the great frequency with which normal individuals suffer from viral respiratory infections, and the importance of the lung as a site of infection in the compromised host, viruses have not been recognized as major pulmonary pathogens in this population with the possible exceptions of the subgroups which have undergone bone marrow or kidney transplantation.[84,116,138] Occasionally, however, viruses do produce significant pulmonary disease in these patients, and we will briefly review these infections here.

Cytomegalovirus

Probably the single most important virus associated with pulmonary infections in immunocompromised patients is cytomegalovirus.[138] Although usually isolated in association with other recognized pathogens, there is good evidence that cytomegalovirus alone can produce serious lung disease in this patient population.[1] Cytomegalovirus, like other herpesviruses, gives rise to a latent infection, and reactivation with shedding of infectious virus commonly occurs in asymptomatic persons. Such shedding probably occurs more commonly in immunocompromised patients, and is particularly common in renal transplant recipients.[78,131] Because virus can be recovered from patients in the absence of demonstrable disease, the presence of positive viral cultures in association with disease is often difficult to interpret. Serology can also be misleading in the diagnosis of diseases caused by latent viruses. Thus optimal diagnosis of cytomegalovirus pneumonia requires histological demonstration of typical cytomegalic cells combined with viral culture.[1] Cytomegalovirus pneumonia can be a mild disease in immunocompromised patients, or it can be fulminant and produce pulmonary insufficiency and death. Radiographically, it typically presents with interstitial infiltrates, but other manifestations have been described.[59]

Herpes Varicella-Zoster Virus

Herpes varicella-zoster virus has already been discussed as a cause of pneumonia in normal children and adults. Primary herpes varicella-zoster infection, or chickenpox, can be devastating in immunosuppressed patients.[8] A severe form of "progressive varicella" is seen in about one third of such patients. Skin lesions are more prominent than those seen in normals, fever is higher, and visceral involvement (predominantly pneumonia, meningoencephalitis, and hepatitis) is common. The overall mortality of varicella in children with leukemia is about 7 per cent. Reactivation of herpes varicella-zoster virus produces herpes zoster, or shingles. Dissemination of herpes varicella-zoster in immunocompromised patients who develop zoster is not an uncommon event, particularly in patients with Hodgkin's disease or other lymphomas.[80] However, this dissemination is usually limited to the skin and does not often produce visceral involvement.

Nevertheless, an occasional patient develops life-threatening herpes varicella-zoster pneumonia associated with disseminated zoster.[10]

Herpes Simplex Virus

Herpes simplex virus rarely causes pneumonia, although tracheitis is not uncommon in immunosuppressed patients.[21,64,96] Herpes simplex virus pneumonia usually occurs in association with evidence of herpes simplex virus disease in the upper airway, and thus probably results from contiguous spread or aspiration of oropharyngeal contents. Alternatively, the virus may arrive in the lungs from centrifugal spread down multiple efferent nerves.

Measles

Severe measles virus infections may occur in immunocompromised patients. Common, often fatal, complications of the disease in these patients are giant cell pneumonia and encephalitis.[43,115] These infections can be caused by either wild-type or vaccine virus strains, may occur in the absence of any rash, and have been described in both children and adults.[27,39,86]

Miscellaneous

Adenovirus has occasionally caused fulminant disease in immunocompromised patients. Fatal cases have been described in an immunodeficient infant and in a renal transplant recipient.[93,137] There is a case report of rhinovirus type 13 which produced pneumonia in a patient with advanced multiple myeloma.[14] Whether immunocompromised patients are more susceptible to severe influenza than are normal individuals is not clear. In one retrospective review of influenza in 20 children with cancer, patients had a more prolonged course of influenza than normals, but the disease was not unusually severe.[30] Influenza has caused severe pneumonia after renal transplantation.[66]

METHODS OF CONTROL

Active Immunization

Only a few effective vaccines are currently available for prevention of the diseases which we have discussed in this review. As previously noted, vaccination has dramatically reduced the incidence of measles and its complications. Live, attenuated measles vaccine is safe and effective and is recommended as part of routine childhood immunization programs. In addition, all susceptible persons, regardless of age, should be vaccinated when identified. Guidelines for the use of measles vaccine as well as contraindications to its use may be found in a number of standard reference sources.[82,83] Oral administration of live adenovirus vaccines has reduced the incidence of respiratory disease caused by types 4 and 7 in military recruits.[24] The rarity of severe disease caused by these viruses in the general civilian population, along with concern about the potential oncogenicity of these preparations has limited their use to certain high risk military groups.

Several clinical trials in a variety of patient populations have demonstrated that inactivated influenza vaccines reduce the incidence of infection and un-

complicated influenzal illness in vaccine recipients.[25,36,87,109,119] However, the effectiveness of vaccination as a public health measure has been reduced by inadequate utilization of these preparations. In addition, the inherent antigenic variability of the influenza virus contributes to incomplete vaccine-induced protection. Nevertheless, these preparations continue as the mainstay of prevention against this disease and are recommended annually for use in individuals who are considered to be at high risk of serious influenza. Each year, the Public Health Advisory Committee on Immunization Practices updates its recommendations concerning the composition of vaccines.[22]

Attempts to develop effective vaccines against respiratory syncytial virus and parainfluenza viruses have so far been unsuccessful. Inactivated respiratory syncytial virus vaccine appeared to potentiate rather than to protect against disease, and live respiratory syncytial virus vaccines have, thus far, been insufficiently attenuated.[65,69] Inactivated parenteral parainfluenza virus vaccines have not provided protection, and live, attenuated parainfluenza virus vaccines administered intranasally have produced unacceptable degrees of illness in recipients.[48,127] Vaccines designed to prevent diseases associated with herpes varicella-zoster and cytomegalovirus infections are in early stages of development.[3,44,61]

Passive Immunization

Passive immunization, the administration of immunoglobulin preparations to prevent disease, has a limited role as a control measure for viral pneumonias. Because of the potentially severe disease which may occur in immunosuppressed children who are exposed to herpes varicella-zoster infections, these individuals should be given varicella-zoster immune globulin (VZIG) after exposure to either chickenpox or herpes zoster.[8] The availability of this preparation has varied in recent years. At this writing, varicella-zoster immune globulin may be obtained through the Division of Clinical Microbiology at the Sidney Farber Cancer Institute in Boston, Massachusetts.[128] Immune serum globulin can be used to prevent or modify measles in a susceptible person if given within 6 days of exposure to an infectious case.[83] Immune serum globulin is currently felt to be indicated for susceptible household contacts of measles patients, particularly those who are under one year of age. Immune serum globulin is also recommended for protection of exposed susceptible persons for whom the live vaccine is contraindicated, such as pregnant women and individuals who are immunocompromised. However, although immune serum globulin will usually prevent measles in normal susceptibles, it may not be effective in those with depressed immune function.[83]

Chemoprophylaxis

Amantadine hydrochloride may be used effectively as a chemoprophylactic agent against influenza A virus infections. Although it is reasonable to assume that prevention of a sufficient number of such infections might result in a decrease in the number of influenza-related pneumonias, there are no currently available data which demonstrate that amantadine prophylaxis can decrease the risk of influenza-associated pulmonary infections. Numerous studies in different populations, in experimental as well as naturally occurring disease, have docu-

mented the effectiveness of amantadine as a prophylactic agent.[33,40,62,88,97,105,117] The drug generally reduces the incidence of disease by 60 to 75 per cent, which is similar to the level of disease reduction produced by vaccination. Administration of amantadine does not interfere with serologic responses to simultaneously administered inactivated vaccine. Side-effects of amantadine are uncommon and consist primarily of minor central nervous system effects which resolve promptly when the drug is discontinued. However, because amantadine must be given orally on a daily basis throughout the entire period of influenza exposure in order to be effective, it is not a practical alternative to vaccination for the protection of large numbers of people over long periods of time. Nevertheless, there are specific situations in which the use of amantadine appears to be appropriate. Individuals who are considered to be at high risk of severe influenza who have not received vaccine at the onset of an outbreak should be given both drug and vaccine simultaneously. If vaccine cannot be obtained, such persons should receive amantadine and then vaccine when the appropriate preparation becomes available. In either situation, amantadine should be continued for 10 to 14 days after vaccine is administered. Household contacts of index cases during the early stages of an influenza epidemic may also be considered as potential candidates for chemoprophylaxis, as may individuals who provide essential services.

Chemotherapy

At the present time, there is no chemotherapeutic agent with well-documented efficacy in the therapy of any viral pneumonia. However, the balance of evidence suggests that amantadine is effective in the treatment of uncomplicated influenza, and there are encouraging anecdotal reports of its use in complicated disease.[22] Adenine arabinoside (ARA-A) favorably alters the course of herpes varicella-zoster infections in immunocompromised patients, and may have a role in the therapy of chickenpox pneumonia when it occurs in those individuals.[135,136]

Treatment

In the absence of effective antiviral drugs, the treatment of viral pneumonias, at the present time, should be directed toward the provision of optimal supportive care. The use of prophylactic antibiotics in the absence of established bacterial infection is not effective, may induce colonization and subsequent infection with more resistant organisms, and exposes the patient to unnecessary risks of drug toxicity.[22,26] However, bacterial superinfection of the lung must be carefully watched for and treated aggressively, if it does occur, with specific antimicrobials in optimal dosages.[22] Severe viral pneumonia may progress to the adult respiratory distress syndrome. The treatment of adult respiratory distress syndrome is controversial and a discussion of this entity is beyond the scope of this review. However, it should be mentioned that although corticosteroids are not indicated in the therapy of uncomplicated viral pneumonias and may actually be harmful in those diseases,[15,126] some physicians recommend the use of these drugs in adult respiratory distress syndrome.[31] Recent reports of successful outcomes in cases of severe viral pneumonia which were managed with modern methods of intensive care emphasize the need for aggressive support of these patients.[31,123]

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