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Human Respiratory Viruses

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Glossary

Bronchiolitis A disease condition characterized by trapping of air in the lungs with difficulty expiring (i.e., wheezing), caused by inflammation or infection of the bronchioles, the smallest and highest-resistance airways.
Croup A disease condition characterized by a difficulty in inspiration, associated with a barky cough, caused by inflammation or infection of the larynx, trachea, and bronchi.
Lower respiratory tract The anatomical region below the vocal cords, including the trachea, bronchi, bronchioles, and lung.
Pneumonia Infection of the alveolar space of the lungs.

Introduction

Respiratory virus infections of humans are the most common and frequent infections of man. Hundreds of different viruses can be considered respiratory viruses. Viruses that enter through the respiratory tract include viruses that replicate and cause disease that is restricted to the respiratory epithelium, and other viruses that enter through the mucosa but also spread by viremia causing systemic disease. An example of the latter is measles virus. SARS coronavirus is another. In general, viruses that do not cause viremia are capable of reinfecting the same host multiple times throughout life. In contrast, infections with systemic viruses induce lifelong immunity. Probably, the high rate of reinfection of mucosally restricted viruses reflects the difficulty and metabolic cost of maintaining a high level of immunity at the vast surface area of the mucosa. Virus-specific IgA levels are maintained at high levels generally only for several weeks or months after infection.

The Human Respiratory Tract

The anatomy and the cell types of the respiratory tract dictate to a large degree the type of disease observed during respiratory virus infection. The demarcation between the upper and lower respiratory tracts is the vocal cords. The structures of the upper respiratory tract, which are all interconnected, include the nasopharynx, the larynx, the Eustachian tube and middle ear space, and the sinuses. Significant collections of lymphoid tissue reside in the upper respiratory tract, the tonsils and the adenoids. The lower respiratory tract structures include the trachea, bronchi, bronchioles, alveoli, and lung tissue. The cell types that line the respiratory tract are complex, and exhibit different susceptibilities to virus infection. The predominant cell types are ciliated and nonciliated epithelial cells, goblet cells, and Clara cells. Smooth muscle cells are prominent features of the airways down to the level of the bronchioles, and the lung possesses type I and II pneumocytes.

Disease Syndromes

The disease syndromes that are associated with respiratory viruses generally follow the anatomy of the respiratory tract. Different viruses appear to have tropisms for different cells or regions of the respiratory tract; therefore, there are particular associations of viruses with clinical syndromes. The clinical diagnoses for infections with disease manifestations in the respiratory tract are rhinitis and the common cold, sinusitis, otitis media, conjunctivitis, pharyngitis, laryngitis, tracheitis, acute bronchitis, bronchiolitis, pneumonia, and exacerbations of reactive airway disease or asthma. Clinical syndromes with more systemic illness due to respiratory viruses include the influenza syndrome, measles, severe acute respiratory syndrome (SARS), and hantavirus pulmonary syndrome (HPS).

Viruses That Cause Respiratory Illness in Immunocompetent Humans

The principal causes of acute viral respiratory infections in children became apparent through large epidemiologic studies conducted soon after cell culture techniques became available. The landmark studies of association of viruses with clinical syndromes were performed in the 1960s and 1970s. Recent studies have increased our understanding of the causes of viral respiratory infection in infants, especially because of the advent of molecular tests such as the polymerase chain reaction (PCR), which is more sensitive than cell culture. Respiratory syncytial virus (RSV), parainfluenza viruses (PIVs), adenoviruses, and influenza viruses were identified initially as the most common causes of serious lower respiratory tract disease in infants and children. More recently, human metapneumovirus (hMPV) was identified as a major cause of serious illness. In the last 10 years, a number of additional viruses have been associated with respiratory illness, as discussed

below. However, still, infectious agents are not identified in 30–50% of clinical illnesses in large surveillance studies, even using sensitive diagnostic techniques such as viral culture on multiple cell lines, antigen detection assays, and RT-PCR based methods. It is not known if these illnesses are due to identified pathogens that are simply not detected due to low titers of virus in patient samples or if there are novel agents that are yet to be identified.

Immunocompromised Hosts

Reactivation of latent viruses, such as the herpesviruses HSV and CMV, and adenoviruses occurs in immunocompromised humans, particularly subjects with late-stage HIV infection, those with organ transplantation, and patients with leukopenia and neutropenia caused by chemotherapy. CMV is the most frequently recovered virus from diagnostic procedures such as bronchoalveolar lavage in immunosuppressed patients with pneumonia. These patients also suffer more frequent and more severe disease including mortality with common respiratory viruses, including RSV, hMPV, PIV, influenza viruses, rhinoviruses, and adenoviruses. Nosocomial transmission including large unit outbreaks is not uncommon, and can result in high frequency of transmission.

Specific Viral Causes of Respiratory Disease

Picornaviridae

A wide variety of picornaviruses cause respiratory disease, including rhinoviruses, the enteroviruses A to D including coxsackieviruses A/B, echoviruses, non-polio enteroviruses, and parechoviruses 1–3. Enterovirus infections occur most commonly in the summer months in temperate areas, which differs from the season of many of the other most common respiratory viruses such as paramyxoviruses and influenza virus. Rhinovirus infections occur year-round.

Rhinoviruses

Rhinovirus is a genus of the family *Picornaviridae* of viruses. Rhinoviruses are the most common viral infective agents in humans, and a causative agent of the common cold. There are over 105 serologic virus types that cause cold symptoms, and rhinoviruses are responsible for approximately half of all cases of the common cold. Rhinoviruses have single-stranded positive-sense RNA genomes. The viral particles are icosahedral in structure, and they are nonenveloped. Rhinovirus-induced common colds may be complicated in children by otitis media and in adults by sinusitis. Most adults, in fact, have radiographic evidence of sinusitis during the common cold, which resolves without therapy. Therefore the primary disease is probably best termed rhinosinusitis. Rhinovirus infection is associated with exacerbations of reactive airway disease in children and asthma in adults. It is not clear whether rhinovirus is restricted to the upper respiratory tract and induces inflammatory responses that affect the lower respiratory tract indirectly, or whether the viruses spread to the lower respiratory tract. In the past, it was thought that these viruses did not often replicate or cause disease in the lower respiratory tract. However, recent studies discern strong epidemiological associations of RVs with wheezing and asthma exacerbations, including episodes severe enough to require hospitalization. Likely, rhinoviruses can infect the lower airways to some degree, inducing a local inflammatory response. Another possibility is that significant local infection of the upper respiratory tract might induce regional elaboration of mediators that causes lower airways disease. Association of rhinovirus infection with lower respiratory tract illness is difficult to study because cell diagnosis by cell culture is not sensitive. RT-PCR diagnostic tests are difficult to interpret because they are often positive for prolonged periods of time and even asymptomatic individuals may have a positive test. Comprehensive serologies to confirm infection are difficult because of the large number of serotypes. Nevertheless, most experts believe rhinoviruses are a common cause of lower respiratory tract illness.

Coxsackieviruses

These viruses cause oral lesions and often are associated in children with a disease syndrome termed 'hand-foot-and-mouth disease'. The pharyngitis associated with this infection often is marked by the very characteristic findings of herpangina, a clinical syndrome of ulcers or small vesicles on the palate and often involving the tonsillar fossa associated with the symptoms of fever, difficulty swallowing, and throat pain. Outbreaks commonly occur in young children, in the summer.

Enteroviruses

Non-polio enteroviruses are common and distributed worldwide. Although infection often is asymptomatic, these viruses cause outbreaks of clinical respiratory disease, sometimes with fatal consequences. Studies have associated particular types with clinical syndromes, as enterovirus 68 with wheezing and enterovirus 71 with pneumonia.

Echoviruses

The term 'echo' in the name of the virus is an acronym for enteric cytopathic human orphan, although this may be an archaic notion since most echoviruses are associated with human diseases, most commonly in children. There are at least 33 echovirus serotypes. Echoviruses can be isolated from many children with upper respiratory tract

infections during the summer months. Echovirus 11 has been associated with laryngotracheitis or croup. Epidemiology studies also have associated echoviruses with epidemic pleurodynia, an acute illness characterized by sharp chest pain and fever.

Parechoviruses

These viruses have been assigned a new genus of the family *Picornaviridae* because of distinctive laboratory-based molecular properties. The most common member of the genus *Parechovirus*, human parechovirus 1 (formerly echovirus 22) is a frequent human pathogen. The genus also includes the closely related virus, human parechovirus 2 (formerly echovirus 23). Human parechoviruses usually cause mild respiratory or gastrointestinal illness. Most infections occur in young children. There is a high seroprevalence for parechoviruses 1 and 2 in adults, and a few clear descriptions of neonatal cases of severe disease.

Paramyxoviridae

Respiratory syncytial virus

RSV is a single-stranded negative-sense nonsegmented RNA genome virus of the family *Paramyxoviridae*, genus *Pneumovirus*. It is one of the most infectious viruses of humans and infects infants at a very young age, often in the first weeks or months of life. It is the most common viral cause of severe lower respiratory tract illness in children and one of the most important causes of hospitalization in infants and children throughout the world. There is one serotype, but circulating viruses exhibit an antigenic dimorphism such that there are two antigenic subgroups designated A and B. Reciprocal cross-neutralization studies using human sera showed that the antigenic groups are about 25% related. Reinfection is common and can be caused by viruses of the same subgroup. Yearly, epidemics of disease often peak between January and March in temperate regions. RSV infection causes mild upper respiratory tract infection in most infants and young children, but results in hospitalization in 0.5–1% of infants. Most children have been infected by the age of 2 years. There is an association of RSV infection early in life and subsequent asthma, although a causal relationship is controversial. Most hospitalized infants are otherwise healthy, but some groups are considered high risk for severe disease such as premature infants especially those with chronic lung disease and infants born with congenital heart disease. Immunocompromised patients of any age are at risk of severe disease.

Human parainfluenza viruses

These viruses constitute a group of four distinct serotypes (types 1–4) of single-stranded RNA viruses belonging to the family *Paramyxoviridae*. When considered as a group, they are the second most common cause of lower respiratory tract infection in young children. PIV3 is the most common cause of severe disease. Repeated infection throughout life is common. First infections are more commonly associated with lower respiratory tract disease, especially croup, while subsequent infections typically are limited to the upper respiratory tract. PIVs are detected using cell culture with hemadsorption or immunofluorescent microscopy, and RT-PCR.

Human metapneumovirus

In 2001, investigators in the Netherlands described a new human respiratory virus, hMPV. Evidence of near universal seroconversion was found in the general population by 5 years of age, suggesting ubiquitous infection in early childhood. This virus, a member of the genus *Pneumovirus* with RSV, differs from RSV in that it lacks the NS1 and NS2 nonstructural genes that counteract host interferons and it possesses a slightly different gene order. Studies of the role of hMPV in pediatric lower respiratory tracts infection (LRI) in otherwise healthy children in the United States, using a prospectively collected 25-year database and sample archive representing about 2000 children, revealed that nearly 12% of LRI in children was associated with a positive hMPV test. This and similar studies suggested that the virus is one of the major respiratory pathogens of early childhood. The clinical features of hMPV LRI were similar to those of other paramyxoviruses, most often resulting in cough, coryza, and a syndrome of bronchiolitis or croup. Interestingly, hMPV seemed to be clinically intermediate between RSV and PIV in that it tended to cause bronchiolitis with similar frequency to RSV but more frequently than PIV, while causing croup less often than the latter. Studies in subjects with conditions predisposing to increased risk of respiratory illness suggest that hMPV plays a significant role in exacerbations of asthma in children and adults, LRI in immunocompromised subjects, and in the frail and elderly.

Measles virus

Measles virus, a paramyxovirus of the genus *Morbillivirus* causes infection with systemic disease, also known as rubeola. The virus is spread both by direct contact/fomite transmission and by aerosol transmission, and therefore is one of the most highly contagious infections of man. The classical symptoms of measles include 3 or more days of fever that is often quite high and a clinical constellation of symptoms termed 'the three Cs': cough, coryza, and conjunctivitis. A characteristic disseminated maculopapular rash appears soon after onset of fever. Transient mucosal lesions in the mouth of a characteristic appearance (Koplik's spots) are considered diagnostic when identified by an experienced clinician. The virus causes a number

of systemic effects and can be complicated by severe pneumonia, especially when primary infection occurs in an unvaccinated adult or immunocompromised person of any age. Mortality in developing countries is high, especially when infection occurs in the setting of malnutrition.

Hendra and Nipah viruses

These emerging pathogens that are grouped in their own new genus *Henipaviruses* may not be respiratory pathogens in a conventional sense, but they are paramyxoviruses that probably infect humans by the respiratory route. Nipah virus is a newly recognized zoonotic virus, named after the location in Malaysia where it was first identified in 1999. It has caused disease in humans with contact with infectious animals. Hendra virus (formerly called equine morbillivirus) is another closely related zoonotic paramyxovirus that was first isolated in Australia in 1994. The viruses have caused only a few localized outbreaks, but their wide host range and ability to cause high mortality raise concerns for the future. The natural host of these viruses is thought to be a certain species of fruit bats present in Australia and the Pacific. Pigs may be an intermediate host for transmission to humans in Nipah infection, and horses in the case of Hendra. Although the mode of transmission from animals to humans is not defined, it is likely that inoculation of infected materials onto the respiratory tract plays a role. The clinical presentation usually appears to be an influenza-like syndrome, progressing to encephalitis, may include respiratory illness, and causes death in about half of identified cases.

Orthomyxoviridae

Influenza viruses

Influenza is a single-stranded segmented negative-sense RNA genome virus of the family *Orthomyxoviridae*. There are three types of influenza viruses: influenza virus A, influenza virus B, and influenza virus C. Influenza A and C infect multiple species, while influenza B infects humans almost exclusively. The type A viruses are the most virulent human pathogens among the three influenza types, and cause the most severe disease. The influenza A virus can be subdivided into different subtypes based on the antibody response to these viruses. The subtypes that have been confirmed in humans in seasonal influenza, ordered by the number of known human pandemic deaths, are: H1N1 which caused the 1918 pandemic, and H2N2 which caused the 1957 pandemic of avian influenza that originated in China, H3N2 which caused the pandemic of 1968. Currently, H3N2, H1N1, and B viruses cause annual seasonal epidemics. In addition, H5N1 virus infection of humans occurred during an epizootic of H5N1 influenza in Hong Kong's poultry population in 1997. The disease affected animals of many species and exhibited a high rate of mortality in humans. The virus is spreading throughout Asia, carried by wild birds. Human-to-human transmission does not occur efficiently at this time; however, there is widespread current concern about the potential for an H5N1 pandemic if the virus acquired transmissibility among humans. The H7N7 avian virus also has unusual zoonotic potential. In 2003 this virus caused an outbreak in humans in the Netherlands associated with an outbreak in commercial poultry on several farms. One death occurred and 89 people were confirmed to have H7N7 influenza virus infection. H1N2 virus appears to endemic in pigs and humans. H9N2, H7N2, H7N3, and H10N7 human infections have been reported. Influenza B virus is almost exclusively a human pathogen, and is less common than influenza A. It mutates less rapidly than influenza A, and there is only one influenza B subtype. In humans, common symptoms of influenza infection and syndrome are fever, sore throat, myalgias, headache, cough, and fatigue. In more serious cases, influenza causes pneumonia, which can be fatal, particularly in young children and the elderly. Influenza pneumonia has an unusually high rate of complication by bacterial superinfection with staphylococcal and streptococcal bacterial pneumonia occurring in as many as 10% of cases in some clinical series.

Adenoviridae

Viruses of the family *Adenoviridae* infect both humans and animals. Adenoviruses were first isolated in human lymphoid tissues from surgically removed adenoids, hence the name of the virus. In fact, some serotypes establish persistent asymptomatic infections in tonsil and adenoid tissues, and virus shedding can occur for months or years. These double-stranded DNA viruses are less than 100 nm in size, and have nonenveloped icosahedral morphology. The large dsDNA genome is linear and nonsegmented. There are six major human adenovirus species (designated A through F) that can be placed into 51 immunologically distinct serotypes. Human respiratory tract infections are mainly caused by the B and C species. Adenovirus infections can occur throughout the year. Sporadic outbreaks occur with many of the serotypes, while others appear to be endemic in particular locations. Respiratory illnesses include mild disease such as the common cold and lower respiratory tract illness, including croup, bronchiolitis, and pneumonia. Conjunctivitis is associated with infection by species B and D. There is a particular constellation of symptoms called 'pharyngoconjunctival fever' which is very frequently associated with acute adenovirus infection. In contrast, gastroenteritis has been associated most frequently with the serotype 40 and 41 virus of species F. Immunocompromised subjects are highly susceptible to severe disease during infection with respiratory adenoviruses. The syndrome of acute

respiratory disease (ARD), especially common during stressful or crowded living conditions, was first recognized among military recruits during World War II and continues to be a problem for the military following suspension of vaccination. ARD is most often associated with adenovirus types 4 and 7.

Coronaviridae

Members of the genus *Coronavirus* also contribute to respiratory illness including severe disease. There are dozens of coronaviruses that affect animals. Until recently, only two representative strains of human coronaviruses were known to cause disease, human coronavirus 229E (HCoV-229E) and HCoV-OC43. A recent outbreak of SARS-associated coronavirus (SARS-CoV) showed that animal coronaviruses have the potential to cross species to humans with devastating effects. There has been one major epidemic to date, between November 2002 and July 2003, with over 8000 cases of the disease, and mortality rates approaching 10%. SARS-CoV causes a systemic illness with a respiratory route of entry. SARS is a unique form of viral pneumonia. In contrast to most other viral pneumonias, upper respiratory symptoms are usually absent in SARS, although cough and dyspnea occur in most patients. Typically, patients present with a nonspecific illness manifesting fever, myalgia, malaise, and chills or rigors; watery diarrhea may occur as well. Recently, investigators reported the identification of a fourth human coronavirus, HCoV-NL63, a new group 1 coronavirus. Evidence is emerging that HCoV-NL63 is a common respiratory pathogen of humans, causing both upper and lower respiratory tract illness. Human coronavirus (HCoV) HKU1 was first described in January 2005 following detection in a patient with pneumonia. Several cases of respiratory illness have been associated with the virus, but the infrequent identification suggests to date that this putative group 2 coronavirus causes a low incidence of illness.

Herpesviridae

Several herpes viruses cause upper respiratory infections, especially infection of the oral cavity. Herpes simplex pharyngitis is associated with characteristic clinical findings, such as acute ulcerative stomatitis and ulcerative pharyngitis. Herpes simplex virus 1 (HSV-1) and herpes simplex virus 2 (HSV-2), also called human herpesvirus 1 (HHV-1) and human herpesvirus 2 (HHV-2), respectively, cause oral lesions, although over 90% of oral infections are caused by HSV-1. Primary oral disease can be severe, especially in young children, who sometimes are admitted for rehydration therapy due to poor oral intake. A significant proportion of individuals suffer recurrences of symptomatic disease consisting of vesicles on the lips. Epstein–Barr virus (EBV) mononucleosis syndrome is often marked by acute or subacute exudative pharyngitis; in some cases, the swelling of the tonsils in EBV pharyngitis is so severe that airway occlusion appears imminent. Most of the viruses of the family *Herpesviridae* can cause severe disease in immunocompromised patients (especially hematopoietic stem cell transplant patients), including cytomegalovirus (CMV), EBV, varicella-zoster virus, herpesvirus 6, herpesvirus 7, and herpesvirus 8.

Parvoviridae

Human bocavirus

A new virus was identified recently in respiratory samples from children with lower respiratory tract disease in Sweden. Sequence analysis of the viral genome revealed that the virus is highly related to canine minute virus and bovine parvovirus and is a member of the genus *Bocavirus*, subfamily *Parvovirinae*, family *Parvoviridae*. This virus was tentatively named human bocavirus (HBoV). HBoV has been identified as the sole agent in a limited number of respiratory samples from children hospitalized with respiratory tract disease. It remains to be seen whether the virus is causative of or merely associated with disease in these preliminary studies.

Bunyaviridae

Hantavirus

Over 400 cases of HPS have been reported in the United States. The disease was first recognized during an outbreak in 1993. About a third of recognized cases end in death. The Four Corners area outbreak is well known; however, cases now have been reported in 30 states. Patients with HPS usually present with a febrile illness beginning with symptoms of a flu-like illness. Physical examination is not specific, often only with findings of fever, and increased heart and respiratory rates. In addition to the respiratory symptoms, abdominal pain and fever are common. Diagnosis is often delayed until a severe illness occurs requiring mechanical ventilation.

Reoviridae

Rotavirus

Rotaviruses are dsRNA enteric viruses that are the most common cause of severe viral infectious gastroenteritis in children. Clinical series suggest that some children with gastroenteritis suffer upper respiratory symptoms during the prodrome of disease manifestation, and virus can be recovered from respiratory secretions. Some reports suggest

that rotavirus infection is associated with lower respiratory tract illness, although this association is unclear.

Reovirus

These dsRNA viruses (named using an acronym for respiratory enteric orphan virus) are not clearly associated with respiratory disease, but seroconversion rate is high in the first few years of life, and they probably cause minor or subclinical illness.

Retroviridae

Human immunodeficiency virus

Pharyngitis occurs with primary HIV infection and may be associated with mucosal erosions and lymphadenopathy.

Papovaviridae

Polyomaviruses

Polyomaviruses are small dsDNA genome nonenveloped icosahedral viruses that may be oncogenic. There are two polyomaviruses known to infect humans, JC and BK viruses. Eighty percent or more of adult US subjects are seropositive for these viruses. JC virus can infect the respiratory system, kidneys, or brain. BK virus infection causes a mild respiratory infection or pneumonia and can involve the kidneys of immunosuppressed transplant patients.

Co-Infections

Given the overlap in the winter season of these viruses in temperate areas, it is not surprising that co-infections with two or more viruses occur. In general, when careful studies using cell culture techniques were used for virus isolation, more than one virus was isolated from respiratory secretions of otherwise healthy subjects with acute respiratory illness in about 5–10% of cases in adults and 10–15% in children. There is little evidence that more severe disease occurs during co-infections, although there is insufficient evidence on this point to be definitive. The incidence of two molecular diagnostic tests being positive (generally RT-PCR, for these RNA viruses) is expected to be higher than that of culture, because molecular tests can remain positive for an extended period of time after virus shedding has ended.

Transmission

Respiratory viruses generally have two main modes of transmission, large particle aerosols of respiratory droplets transmitted directly from person-to-person by coughing or sneezing, or by fomites. Fomite transmission occurs indirectly when infected respiratory droplets are deposited on hands or on inanimate objects and surfaces with subsequent transfer of secretions to a susceptible subject's nose or conjunctiva. Most respiratory viruses, unlike measles virus or varicella zoster virus, do not spread by small particle aerosols across rooms or down halls. Therefore, contact and droplet precautions are sufficient to prevent transmission in most settings; handwashing is critical in healthcare settings during the winter season.

Antiviral Drugs for Respiratory Viruses

Ribavirin is a nucleoside antimetabolite pro-drug that is activated by kinases in the cell, resulting in a 5′ triphosphate nucleotide form that inhibits RNA replication. The drug was licensed in an aerosol form in the US in 1986 for treatment of children with severe RSV lower respiratory tract infection. The efficacy of aerosolized ribavirin therapy remains uncertain despite a number of clinical trials. Most centers use it infrequently, if ever, in otherwise healthy infants with severe RSV disease. Intravenous ribavirin has been used for adenovirus, hantavirus, measles virus, PIV, and influenza virus infections, although a good risk/benefit profile has not been established clearly for any of these uses.

A humanized mouse monoclonal antibody directed to the F protein of RSV, 'palivizumab', is licensed for prevention of RSV hospitalization in high-risk infants. It is efficacious in half or more of high-risk subjects. A more potent second-generation antibody is being studied in clinical trials. Experimental treatment of both immunocompetent and immunocompromised RSV-infected subjects has been reported but the efficacy of this approach is not established.

There are four licensed drugs in the US for treatment or prophylaxis of influenza. 'Amantadine' and 'rimantadine' are two of the drugs that interfere with the ion channel activity caused by the viral M2 protein of influenza A viruses, which is needed for viral particle uncoating following endocytosis. The other two drugs, 'oseltamivir' and 'zanamivir', are neuraminidase inhibitors that act on both influenza A and B viruses by serving as transition state analogs of the viral neuraminidase that is needed to release newly budded virion progeny from the surface of infected cells. The cell surface normally is coated heavily with the viral receptor sialic acid. Resistance to the ion channel inhibitors arises rapidly during prophylaxis or treatment, and in 2006 resistance levels became so common in circulating viruses that the CDC no longer recommends use of these drugs.

'Interferon-α' has been shown to protect against rhinovirus infections when used intranasally. This biological drug causes some side effects, such as nasal bleeding, and resistance to the drug developed during experimental use, so the molecule is no longer being developed for this

purpose. 'Pleconaril' has been tested for treatment of rhinovirus infection, as it is an oral drug with good bioavailability for treating infections caused by picornaviruses. This drug acts by binding to a hydrophobic pocket in the VP1 protein and stabilizing the protein capsid, preventing release of viral RNA into the cell. The drug reduced mucus secretions and other symptoms and is being further examined.

'Acyclovir' and related compounds are guanine analog antiviral drugs used in treatment of herpes virus infections. HSV stomatitis in immunocompromised patients is treated with 'famciclovir', or 'valacyclovir', and immunocompetent subjects with severe oral disease compromising oral intake are sometimes treated. These compounds have also been used prophylactically to prevent recurrences of outbreaks, with mixed results. Intravenous acyclovir is effective in HSV or varicella zoster virus pneumonia in immunocompromised subjects. 'Ganciclovir' with human immunoglobulin may reduce the mortality associated with CMV pneumonia in hematopoietic stem cell transplant recipients and has been used as monotherapy in other patient groups.

'Cidofivir' is a nucleotide analog with activity against a large number of viruses, including adenoviruses. Intravenous cidofovir has been effective in the management of severe adenoviral infection in immunocompromised patients but may cause serious nephrotoxicity.

Vaccines

There are licensed vaccines for influenza viruses. In the US, both a trivalent (H3N2, H1N1, and B) inactivated intramuscular vaccine and a live attenuated trivalent vaccine for intranasal administration is available. The efficacy of these vaccines is good when the vaccine strains chosen are highly related antigenically to the epidemic strain. Antigenic drift caused by point mutations in the HA and NA molecules leads to antigenic divergence, requiring new vaccines to be made each year. The influenza genome is segmented, which allows reassortment of two viruses to occur during co-infection, which sometimes leads to a major antigenic shift resulting in a pandemic. Pandemics occur every 20–30 years on average. There is current concern about the potential for an H5N1 pandemic, and experimental vaccines are being tested for this virus. To date, H5N1 vaccines have been poorly immunogenic compared to comparable seasonal influenza vaccines. Vaccines were developed for adenovirus serotypes 4 and 7, and these were approved for preventing epidemic respiratory illness among military recruits. Essentially, these were unmodified viruses given by the enteric route in capsules, instead of the respiratory route, which is the natural route of infection leading to disease. Inoculation by the altered route resulted in an immunizing asymptomatic infection. All US military recruits were vaccinated against adenovirus from 1971 to 1999 with near complete prevention of the disease in this population, but the sole manufacturer of the vaccine halted production in 1996 and supplies ran out 3 years later. Since 1999, adenovirus infection has reemerged as a significant problem in the military with approximately 10% of all recruits suffering illness due to adenovirus infection during basic training; some deaths have occurred. Live attenuated vaccine candidates are under development and being tested in phase I and II clinical trials for RSV and the PIVs. Mutant strains with reduced pathogenicity were isolated in the laboratory, tested, and sequenced. Now, vaccine candidates are being optimized by combining mutations from separate biologically derived viruses into single strains using recombinant techniques for generating RNA viruses from cDNA copies, a process called reverse genetics. Subunit vaccines have been developed for RSV, but there are safety concerns about their use in young infants because formalin inactivated vaccine induced a more severe disease response to infection in the 1960s. There are no vaccines against rhinoviruses as there is little or no cross-protection between serotypes, and it is not feasible to develop a vaccine for over 100 serotypes. Efforts to develop coronavirus vaccines are in the preclinical stage.

Summary

Viruses are the leading causes of acute lower respiratory tract infection in infancy. RSV is the most common pathogen, with hMPV, PIV-3, influenza viruses, and rhinoviruses accounting for the majority of the remainder of acute viral respiratory infections. Humans generally do not develop lifelong immunity to reinfection with these viruses; rather, specific immunity protects against severe and lower respiratory tract disease.

See also: Human Respiratory Syncytial Virus.

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Human T-Cell Leukemia Viruses: General Features

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Glossary

pX region HTLV sequence between the env and 3′ LTR, encoding Tax, Rex and other small regulatory proteins.

Rex Trans-modulator of viral RNA splicing and transport.

Tax Pleiotropic regulator activating viral and cellular replication interacting with cellular transcription factors, tumor suppressor proteins, and cell cycle checkpoints.

Introduction

Human T-cell leukemia virus 1 (HTLV-1) is the first established tumorigenic retrovirus of humans; exogenous to humans this virus is classified as the species *Human T-cell leukemia virus*, in *Deltaretroviridae*, within the family *Retroviridae*. HTLV-1 infection is associated with leukemia and neural disease, adult T-cell leukemia (ATL) and HTLV-1-associated myelopathy/tropical spastic parapasis (HAM/TSP), respectively. The genomic structure of the virus with genes for nonstructural proteins established a distinct viral genus that includes *Bovine leukemia virus*. HTLV-1 has no oncogene, but nevertheless transforms T cells rather efficiently and is identified as the etiologic agent of ATL. HTLV-1 has unique regulatory proteins, Tax and Rex, and Tax has been identified as a critical molecule not only in regulation of viral replication but also in induction of ATL.

History and Classification

After long and enormous efforts to identify a retrovirus in human tumors, HTLV was described in T-cell lines as a convincing human retrovirus. The first report of the virus (HTLV) was from a patient with Mycosis (MF) in the US, and another (adult T-cell leukemia virus (ATLV)) was from a patient with ATL in Japan. Subsequently, the MF case was characterized as ATL and the two isolates were established to be the same following a comparison of their genomes.

A prototypical retroviral genome contains the *gag*, *pol*, and *env* genes encoding the virion proteins including core proteins, reverse transcriptase, and surface glycoprotein, respectively. Acute leukemia viruses generally have an oncogene acquired from cellular genes that substitutes a part of the *gag*, *pol*, and *env* sequences. In contrast to these genomes, HTLV has additional genes in an extra pX region between *env* and the 3′ LTR (LTR – long terminal repeat). This unique genomic structure classified HTLV as a member of a distinct genus of the *Retroviridae*, which includes HTLV-1, and-2, bovine leukemia virus (BLV), and simian T-cell leukemia viruses (STLV-1, -2, and -3). HTLV-2 was isolated from a patient with hairy T-cell leukemia and its genome similarity to the type 1 is about 60%.

STLVs have been isolated from various species of Old World nonhuman primates, including the Japanese macaque, African green monkey, pig-tailed macaque, gorilla, and chimpanzee. Their genomes share 90–95% homology.

BLV infects and replicates in B cells of cows and sheep and induces B-cell lymphoma.