injectible medication like streptomycin, or if the organism is resistant to streptomycin, then capreomycin or amikacin are chosen. If possible, at least three other oral medications should be used along with the injectable. Duration of therapy is at least 18 months; the injectable should be included in the regimen for at least the first 6 months of therapy if tolerated. For patients who have localized disease and do not have culture conversion by 2 months of therapy, consideration should be given to surgical removal of the diseased lung. Treatment regimens for patients coinfected with HIV are the same although therapy should be extended to 24 months. Patients coinfected with HIV and MDRTB have a high mortality rate.

See also: **Acute Respiratory Distress Syndrome**. **Bronchiectasis**. **Bronchoalveolar Lavage**. **Human Immunodeficiency Virus**. **Pneumonia**: Overview and Epidemiology; Atypical. **Pulmonary Fibrosis**. **Systemic Disease**: Eosinophilic Lung Diseases. **Tumor Necrosis Factor Alpha (TNF-α)**.

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Viral

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Abstract

Viral infection accounts for a substantial proportion of cases of acute pneumonia especially among young children and the elderly, the immunocompromised, and those with comorbidities. Influenza A and respiratory syncytial virus are by far the most common causes of viral pneumonia followed by adenovirus, parainfluenza virus types 1, 2 and 3, and influenza B. Other less common agents include picornaviruses, varicella-zoster virus, herpes simplex virus, cytomegalovirus, and hantavirus. The newly identified human metapneumovirus also plays a role. Zoonotic infections caused by severe acute respiratory syndrome-associated coronavirus and avian influenza A/H5N1 are examples of acute 'atypical' pneumonia with epidemic and pandemic potentials. In general, there are no reliable clinical or radiological features to distinguish viral from other causes of pneumonia. Respiratory viruses often show seasonality and a predilection for certain host groups. These epidemiological features are helpful in gauging the differential diagnoses. Confirmation of infection relies on laboratory investigations based on conventional approaches including direct viral antigen detection by specific monoclonal antibodies, virus isolation, and serology, as well as modern molecular approaches to amplify viral nucleic acid present in clinical specimens. The available spectrum of antiviral agents and the window for effective application are narrow. Treatment of viral pneumonia is primarily supportive. Vaccines for general use are only available for influenza A and B.

Introduction

Acute pneumonia is an important cause of morbidity and mortality worldwide. While the majority of cases of acute community acquired pneumonia (CAP) are due to bacteria, especially *Streptococcal pneumoniae* and less commonly the atypical organisms, respiratory tract viruses also contribute to a substantial proportion. More importantly, in general, viral pneumonia has a higher outbreak potential. A wide spectrum of viruses can cause viral pneumonia (**Table 1**, **Figure 1**). The relative importance of these viruses depends on the host's age, immune status, comorbidity, and the local epidemiological determinants such as seasonality.

Influenza

The Virus

Influenza viruses belong to the genus *Orthomyxovirus* within the family Orthomyxoviridae. This enveloped virion contains eight (influenza A and B) or seven (influenza C) segments of single, negative-stranded RNA. The pleomorphic envelope is composed of two

Table 1 Viruses associated with acute pneumonia

Children	*Adults*	*Immunocompromised*[a]
Common	Common	Cytomegalovirus
Respiratory syncytial virus	Influenza A	Human herpes simplex virus 6
Parainfluenza virus types 1, 2, 3	Influenza B	Herpes simplex virus
Influenza A	Uncommon	
Uncommon	Adenovirus	
Adenovirus	Respiratory syncytial virus	
Human metapneumovirus	Parainfluenza virus types 1, 2, 3	
Influenza B	Rhinovirus	
Measles	Enterovirus	
Rhinovirus	Human metapneumovirus	
Enterovirus	Hantavirus	
Hantavirus	Varicella-zoster virus	
	Measles	
	SARS-associated coronavirus	

[a] In addition to respiratory viruses seen for the age group.

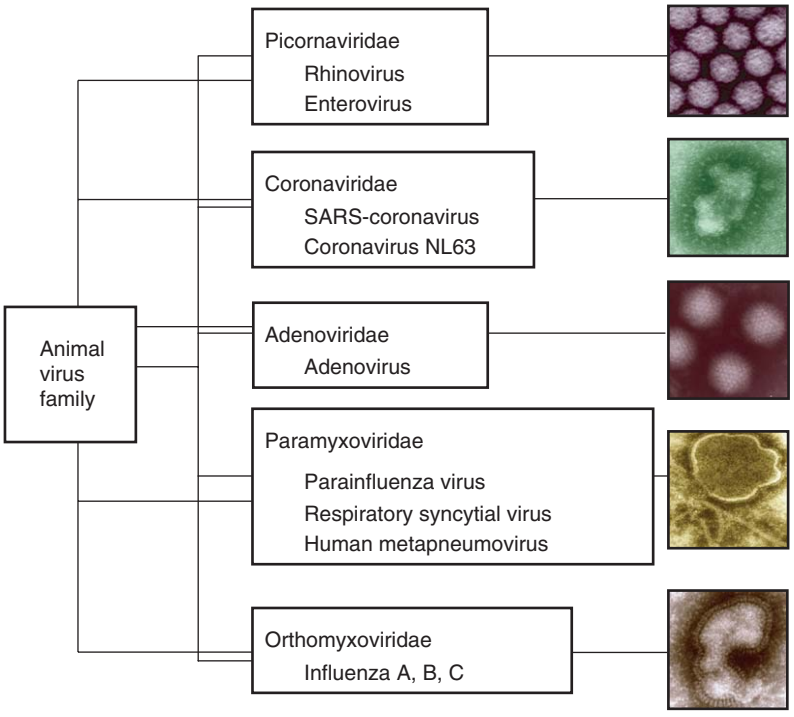

Figure 1 Electron micrographs of the major human respiratory virus families.

major antigenic glycoproteins, hemagglutinin (HA) and neuraminidase (NA). Major changes in the antigenic protein structure of HA (i.e., antigenic shift) may occur and lead to a pandemic. Minor changes involving a small number of amino acid substitutions (i.e., antigenic drift) lead to an epidemic of influenza. Antigenic shift is rare, whereas significant antigenic drift occurs once every few years. Altogether, 16 different subtypes of HA and nine different subtypes of NA have been identified from influenza A viruses from various animal species (Table 2). Currently, two subtypes of influenza A, A/H1N1 and A/H3N2, are in human circulation. Introduction of a new subtype into humans can result in a large-scale pandemic with high morbidity and mortality. This is because of the naive immunity and the absence of an effective vaccine in the initial phase of outbreak. Three influenza pandemics occurred in the twentieth century. The most severe of these was 'Spanish flu' A/H1N1, which occurred in 1918–19 with a global mortality of at least 20–25 million people. It was estimated that 50% of the global population became infected, half of which suffered clinical illnesses. The A/H2N2 pandemic that occurred between 1957 and 1958 caused about 70 000 deaths in the US. In 1968, a new type (A/H3N2) emerged and remains in circulation today.

Table 2 Hemagglutinin (HA) and neuraminidase (NA) subtypes of influenza A circulating in human and other animals

Subtype	*Host species*			
	Human	*Bird*	*Pig*	*Horse*
Hemagglutinin				
H1	√ (Major circulating subtype)	√	√	
H2	√	√		
H3	√ (Major circulating subtype)	√	√	√
H4		√		
H5	√ (No efficient human-to-human transmission)	√		
H6		√		
H7	√ (Isolated outbreaks)	√		√
H8		√		
H9	√ (Isolated cases)	√		
H10		√		
H11		√		
H12		√		
H13		√		
H14		√		
H15		√		
H16		√		
Neuraminidase				
N1	√ (Major circulating subtype)	√	√	
N2	√ (Major circulating subtype)	√	√	
N3		√		
N4		√		
N5		√		
N6				
N7	√ (Isolated outbreaks)	√		√
N8		√		√
N9		√		

Human Influenza

Influenza A viruses infect humans, pigs, birds, horses, and other species, whereas influenza types B and C only infect humans. In humans, influenza is mainly transmitted by respiratory droplets. The incubation period ranges from 1 to 4 days. The onset of illness is remarkably abrupt with fever, headache, photophobia, shivering, malaise, myalgia, nausea, dry cough, hoarseness of voice, and nasal congestion. Fever is usually continuous and lasts for about 3 days. A biphasic fever pattern may occur. Most patients recover after 1 week.

Pneumonia in patients with influenza can be a primary viral pneumonia sometimes complicated by secondary bacterial infections, often due to *Staphyloccocus aureus*, *Streptococcus pneumoniae*, or *Haemophilus influenzae*. Both forms of pneumonia are relatively uncommon for infection with usual human influenza subtypes. Pneumonia is mainly seen in immunocompromised hosts and the elderly with preexiting cardiopulmonary diseases or chronic illnesses.

Avian Influenza

Birds, particularly aquatic and migratory species, are natural hosts of all 16 HA subtypes of influenza A virus, whereas only a few subtypes have established transmissible infections in humans, pigs, and other mammals (Table 2). In 1997, 18 people in Hong Kong were infected with the avian influenza A/H5N1 virus, resulting in six deaths. Subsequent serological studies have shown that human-to-human transmission can occur although the transmission efficiency is low. In 2003, there were another two human cases of H5N1 probably imported from Fujian, mainland China, to Hong Kong. The highly pathogenic avian influenza virus H5N1 has caused further disease outbreaks in poultry in multiple East Asian countries since late 2003. The virus caused fatal human infections in Thailand, Vietnam, and Cambodia. From January 2004 to mid-June 2005, at least 107 cases of human avian H5N1 occurred in Vietnam, Thailand, and Cambodia with reported mortality rates ranging from 46% to 100%.

A series of genetic reassortment events have been demonstrated to be traceable to the precursor of the A/H5N1 virus that caused the initial human outbreak in 1997, and the subsequent avian outbreaks in 2001 and 2002 in Hong Kong. These events gave rise to a dominant A/H5N1 genotype (Z) in chickens and ducks that was responsible for the regional outbreak

in 2003–04. It appears that domestic ducks in southern China play a central role in the generation and maintenance of this virus. Wild birds may have contributed to the increasingly widespread distribution of the virus in Asia. A/H5N1 viruses with pandemic potential have become endemic in birds in the region and are not easily eradicated. The greatest concern is that there will be reassortment between the current avian A/H5N1 strain and circulating human or porcine influenza viruses, producing a novel, virulent, and readily transmissible human strain. This ecological feature of influenza poses a tremendous threat to public and veterinary health in the region and the world.

The clinical features and spectrum of human A/H5N1 cases are shown in Table 3 and Figure 2. High fever, cough, and dyspnea are the major symptoms at presentation but gastrointestinal symptoms such as diarrhea are also common. The chest radiographs of a human case are shown in Figure 3. Many patients progress to multiorgan failure involving the lungs, liver, and kidneys with evidence of hemophagocytosis. The primary lesion of experimental A/H5N1 virus in macaques was a severe necrotizing broncho-interstitial pneumonia similar in character and severity to that found in influenza viral pneumonia in humans. Recent reports have indicated that some cases may present with gastrointestinal symptoms initially without any respiratory symptoms, and with rapid progression to encephalitis or multiorgan dysfunction syndrome and subsequent death. Asymptomatic infection may occur and this is highlighted by the fact that 10% of poultry workers had positive serology to A/H5N1 and at least one worker who had participated in culling of poultry in Hong Kong in 1997 showed evidence of seroconversion without any symptoms.

Table 3 Symptoms of human influenza A/H5N1 infection

Symptoms	*Frequency (%)*
Fever	100
Cough	100
Dyspnea	100
Sore throat	75
Myalgia	42
Diarrhea	42–70
Vomiting	25
Abdominal pain	17–90
Conjunctivitis	0

Treatment

There are two classes of antiviral compounds known to be effective against influenza, namely the M2-ion channel blockers (amantadine and rimantadine) and the NA inhibitors (oseltamivir and zanamivir). Antiviral administration is recommended to reduce morbidity and mortality during a pandemic. The A/H5N1 viruses isolated from recent (2004–05) human cases are resistant to M2-ion channel blockers. This resistance may be retained in a future pandemic strain. The current World Health Organization (WHO) and the US Center for Disease Control guidelines recommend NA inhibitors as the preferred drugs for use during an influenza pandemic.

Oseltamivir, in the form of a capsule or oral suspension, is readily absorbed from the gut, and thus has a high bioavailability (at least 75%). Zanamivir, in the form of oral inhalation, has a low systemic bioavailability (<20%). NA inhibitors should ideally be administered within 48 h of the onset of symptoms. The dosage recommendations for usual human influenza strains are shown in Table 4. The future pandemic strain may require a higher dosage and a longer duration of treatment. Zanamivir has a low systemic distribution but dosage adjustment for age or renal function is not required. Oseltamivir has a better systemic distribution, which may be an advantage in case a pandemic strain causes significant extrapulmonary infection.

A trivalent influenza vaccine targeting the circulating A/H1N1, A/H3N2, and B subtypes is available. Annual vaccination 6–8 weeks before seasonal peak is recommended for those at risk and for healthcare workers.

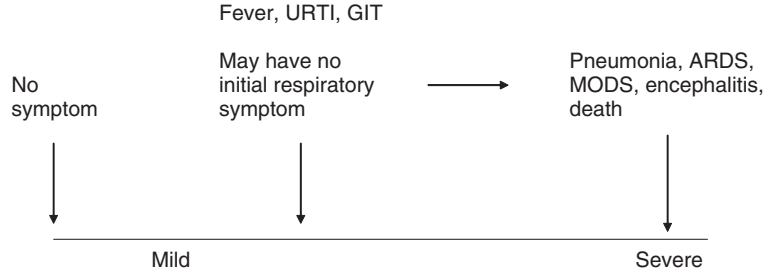

Figure 2 Human influenza A/H5N1: clinical spectrum of disease. URTI, upper respiratory tract infection; GIT, gasterointestinal tract; ARDS, acute respiratory distress syndrome; MODS, multiorgan dysfunction syndrome.

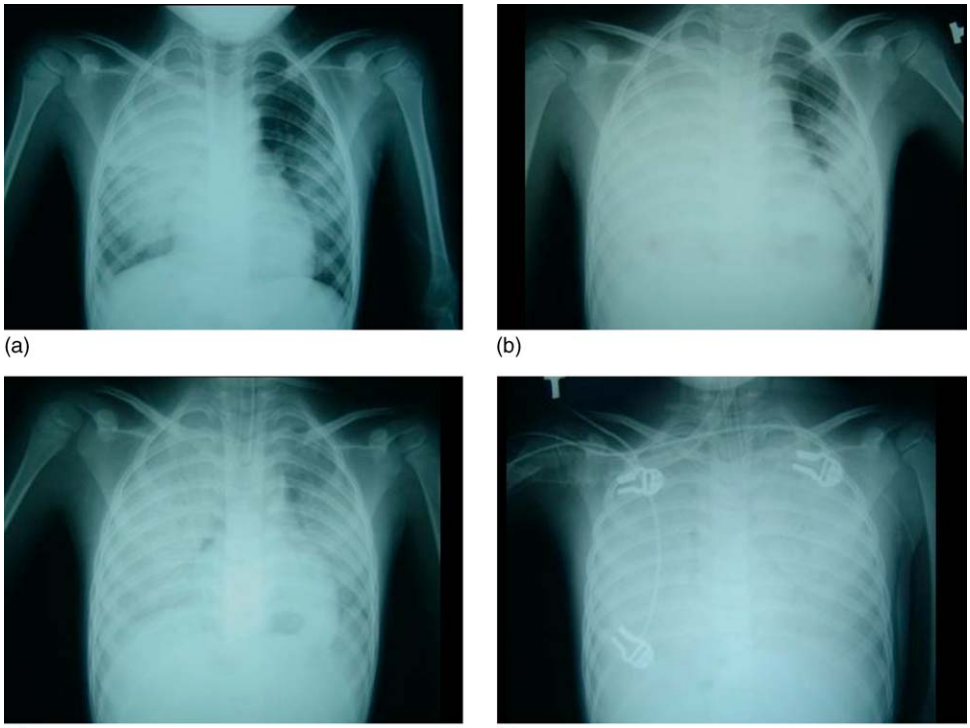

Figure 3 (a–d) Chest radiographs of a human case of A/H5N1 infection. This 6-year-old girl had previously been in contact with sick poultry. She had fever for 8 days before admission to hospital. On admission, she developed severe respiratory failure, with a total white blood cell count of $2.4 \times 10^9\,l^{-1}$, lymphocyte count of $0.5 \times 10^9\,l^{-1}$, platelet count of $127 \times 10^9\,l^{-1}$, ALT $246\,IU\,l^{-1}$, and AST $1379\,IU\,l^{-1}$. She was treated with oseltamivir on admission. She died 3 days later of multiorgan failure.

Table 4 Regimen for neuraminidase inhibitors for influenza

Treatment	
Oseltamivir	
Adults & adolescents 13 years of age or above	75 mg twice a day × 5 days
Children between 1 and 12 years of age	
15 kg	30 mg twice a day × 5 days
16–23 kg	45 mg twice a day × 5 days
24–40 kg	60 mg twice a day × 5 days
>40 kg	75 mg twice a day × 5 days
Zanamivir	
Adults & children 5 years of age or above	10 mg (2 inhalations) twice a day × 5 days
Prophylaxis	
Oseltamivir	
Adults & adolescents 13 years of age or above	
Community outbreak	75 mg once daily up to 6 weeks
Close contacts	75 mg once daily × 7 days
Children below 13 years of age[a]	
Health care and essential service workers during pandemic[b]	75 mg once daily
Zanamivir	
Healthy young adults (age not specified, not licensed for prophylaxis in some countries)	10 mg (2 inhalations) once daily, up to 1 month if exposure risk is long

[a] The safety and efficacy of oseltamivir as a prophylactic agent for children under 13 years of age have not been established. However, it may be considered for prophylactic use in this group when the benefits are expected to outweigh the risks.
[b] Duration of prophylaxis should be determined by the intensity and duration of exposure. Safety and efficacy of prophylactic administration of oseltamivir have been demonstrated for continued use of the drug for up to 6 weeks.

Respiratory Syncytial Virus

The Virus

Respiratory syncytial virus (RSV) is an enveloped, nonsegmented negative-stranded RNA virus classified as a member of the genus *Pneumovirus* within the family Paramyxoviridae. Under electron microscopy, the virions appear as pleomorphic spherical particles ranging from 150 to 300 nm in diameter. The morphology is similar to other paramyxoviruses including measles, mumps, and parainfluenza viruses (PIVs). RSV has two antigenic subgroups, A and B, with greater than 90% amino acid homology. The role of strain variation in the epidemiology, severity, and clinical impact of an RSV outbreak remains unclear.

Annual seasonal epidemics of RSV occur worldwide. A clear seasonality is seen in the temperate zone with peaks at fall, winter, or spring. In the tropical and subtropical areas, epidemics occur in rainy seasons.

Clinical Manifestations

RSV is the single most important cause of hospitalization for respiratory tract infections in babies and young children worldwide. Primary infection occurs in children aged 6 weeks to 2 years old. Rhinorrhea, sneezing, decrease in appetite, low-grade fever, and cough are common presenting symptoms. Tachypnea, diffuse rhonchi, and wheeze indicating involvement of the lower respiratory tract may follow. Bronchiolitis, pneumonia, and otitis media are common complications. Most children recover after 7–12 days. In severe cases, the chest radiograph shows features of interstitial pneumonia with hyperexpansion, segmental or lobar consolidation, and peribronchial thickening; whereas pleural effusion and bacterial superinfection are unusual. Severe illness often occurs in infants less than 9 months old, particularly in those with underlying cardiac or respiratory disease. Premature infants may present with apneic spells. Paradoxically, lower respiratory tract involvement is not common in newborns, reflecting the protective effects of maternal antibodies. Most studies reveal that a substantial proportion of children with severe RSV infection have later decreased pulmonary function, recurrent cough, and wheezing.

Repeated RSV infections in older children are usually less severe. It is now realized that RSV infection occurs commonly in healthy adults with a presentation ranging from asymptomatic to severe lower respiratory tract infection. For older persons and the immunocompromised individual, RSV can result in severe pneumonia and acute respiratory distress syndrome (ARDS).

Treatment

Supportive care is most important. Ribavirin, a synthetic nucleoside, has an antiviral effect on RSV *in vitro*. It is administered by small particle aerosol into an oxygen tent or via a ventilator. However, the clinical benefits and the indications are not entirely clear. RSV immunoglobulin administered once a month has clinical benefit in preventing severe RSV disease in high-risk children with pulmonary or cardiac disease.

Parainfluenza

The Virus

PIVs belong to the family Paramyxoviridae. There are 5 types: PIV1, PIV2, PIV3, PIV4a, and PIV4b. The pleomorphic, enveloped virion contains a nonsegmented, negative, single-stranded RNA genome. The surface glycoprotein, hemagglutinin neuraminidase (HN), is responsible for attachment to the sialic acid on the host cell to initiate the infection cycle. HN together with another enveloped protein, the fusion protein (F), mediate fusion between the viral envelope and host cell plasma membrane.

Clinical Manifestations

PIVs are the second leading cause, after RSV, of hospitalization for respiratory tract illnesses in young children. PIVs are transmitted by droplets and produce a spectrum of clinical illnesses ranging from mild upper respiratory tract infection and pharyngitis to otitis media, bronchiolitis, and severe pneumonia. In addition, a syndrome (croup) characterized by croupy cough, inspiratory stridor, hoarse voice, and difficulty in inspiration caused by acute laryngotracheobronchitis is a hallmark presentation of PIVs. Croup is mainly seen in young children, but presentation in adults has been documented. Pneumonia is uncommon in healthy children but fatal pneumonia may occur in those with severe combined immune deficiency, bronchopulmonary dysplasia, prematurity, congenital heart disease, and following bone marrow transplantation. Bronchiolitis obliterans organizing pneumonia has been reported as a long-term sequela. Extrapulmonary infection affecting the central nervous system has been documented.

Treatment

Ribavirin, a broad-spectrum antiviral agent, has inhibitory effects *in vitro*, and has been used to treat PIV pneumonia in immunosuppressed patients. Zanamivir, a sialic acid analog approved for the treatment of influenza, also has inhibitory effects on

PIVs *in vitro*. However, the clinical benefit of these agents remains to be evaluated. There are no PIV vaccines available yet.

Adenovirus

The Virus

Adenoviruses (AdVs) are nonenveloped viruses with an icosahedral capsid containing a linear double-stranded DNA genome. There are more than 40 different serotypes of human AdVs within the family Adenoviridae. Serotypes associated with lower respiratory tract infections are AdV 3, AdV 4, AdV 7, and AdV 21, and less commonly AdV 1, AdV 2, AdV 5, AdV 14, and AdV 35.

Clinical Manifestations

In addition to respiratory illnesses, AdVs also cause acute conjunctivitis and keratoconjunctivitis, gastroenteritis, hemorrhagic cystitis, meningitis, encephalitis, skin eruptions, genital tract infection, hepatitis, myocarditis, pericarditis, pancreatitis, rhabdomyolysis, and polyarthritis.

The routes of transmission for AdVs are multiple including direct contact, droplet aerosol, fecal-oral, and water-borne. AdVs being nonenveloped viruses are more resistant to the adverse environment, which allows them to be more readily spread via fomites, such as ocular instruments.

AdVs account for about 5% of all childhood respiratory illnesses requiring hospitalization. The major presenting clinical features include fever, pharyngitis, tonsillitis, and cough. Lower respiratory tract involvement with pulmonary infiltration occurs in less than half of the hospitalized children. Hilar lymphadenopathy is more commonly observed in chest radiographs compared with other respiratory viruses.

Outbreaks of acute respiratory disease due to infection with AdV 3, AdV 4, AdV 7, AdV 14, and AdV 21 in military recruits have been reported from different parts of the world. Most cases presented at the third week of training with fever, malaise, nasal congestion, headache, sore throat, and cough. Around 10% developed patchy pulmonary infiltrates. However, similar outbreaks seldom occur in other crowded situations such as dormitories.

AdVs are frequently isolated from patients with pertussis syndrome, which is primarily caused by *Bordetella pertussis*. There may be a role for AdVs in this syndrome.

AdVs may establish latency in adenoidal and tonsillar tissues following primary infections in childhood. Reactivations during immunosuppression may account for a proportion of the severe adenoviral diseases observed in immunocompromised patients. The overall fatality rate for adenoviral pneumonia, which often has multiorgan dissemination, in the immunocompromised patients is 60%.

Treatment

A few antiviral compounds have been used for treating adenoviral diseases. Successful experience has been described for ribavirin in treating pneumonia, hemorrhagic cystitis, and hepatitis in transplant recipients. Cidofovir, a broad-spectrum compound for DNA viruses, has been reported to be successful in treating adenoviral diseases in pediatric hematopoietic stem cell transplant recipients. However, effectiveness of any antiviral compounds demonstrated by randomized controlled trials is not yet available.

A live oral vaccine has been used for US military recruits, but production of the vaccine ceased in 1996. AdV vaccines are not available for the general population.

Human Metapneumovirus

The Virus

The genus *Metapneumovirus* is classified within the family Paramyxoviridae. Human metapneumovirus (hMPV) is the only known human virus in this genus. It was first recognized in 2001. hMPV shares basic properties with RSV, which belongs to the same subfamily, the Pneumovirinae.

Clinical Manifestation

The transmission of hMPV is probably similar to that of RSV, that is, mainly by droplets and fomites. hMPV is ubiquitous with infections occurring commonly in young children. Annual seasonal peaks occur in winter months in the moderate climate zones, but occur in late spring or early summer in the subtropics. Virtually all children have serological evidence of infection by the age of 5 years. Most infections are mild with cough, rhinorrhea, fever, and exacerbation of asthma. hMPV accounts for 2–12% of lower respiratory tract illnesses in children, and just a few percent in adults. Coinfection with RSV has been postulated to cause more severe disease.

In adults, hMPV predominantly causes a mild upper respiratory tract infection. Infection in the frail elderly and the immunocompromised produces more severe disease. Fatal pneumonia associated with hMPV has been reported in children and adults with leukemia, as well as in a previously healthy adult.

Hantavirus

The Virus

The genus *Hantavirus* is classified within the family Bunyaviridae. Hantaviruses are lipid-enveloped, single-stranded RNA viruses. Rodent species are the natural host and source of human infections for hantaviruses. Hantaviruses are associated with a range of nephritic and hepatic diseases in Asia and Europe. The respiratory form of disease manifestation, hantavirus pulmonary syndrome (HPS), is mainly seen in America.

Clinical Manifestations

Hantavirus infections are associated with domestic, occupational, or recreational activities that bring humans into contact with infected rodents, usually in rural settings. Transmission can occur when dried materials contaminated by rodent excreta are disturbed and inhaled, directly introduced into broken skin or conjunctivae, or, possibly, when ingested in contaminated food or water. Persons visiting laboratories where infected rodents were housed have been infected after only a few minutes of exposure to the animal holding areas.

HPS typically starts with an influenza-like illness with high fever, myalgia, and asthenia. After a prodromal period of 2–7 days, dyspnea, respiratory failure, and hemodynamic instability appear. Radiologically, HPS presents as pulmonary interstitial edema with or without rapid progression to airspace disease, which has a central or bibasal distribution. Pleural effusion is a common feature. Occasionally, pulmonary manifestations may occur during the oliguric phase of renal failure, and present as pulmonary edema and cardiomegaly with or without pleuropericardial effusion.

All hantaviruses known to cause HPS in the US are carried by the New World mice and rats (family Muridae, subfamily Sigmodontinae). The subfamily Sigmodontinae contains at least 430 species of mice and rats, which are widespread in North and South America. These wild rodents are not generally associated with urban environments. However, some species (e.g., deer mouse and white-footed mouse) may enter human habitation in rural and suburban areas. The association of hantaviruses with rodent reservoirs warrants recommendations to minimize exposure to wild rodents. The mortality for HPS treated with intravenous ribavirin (47.7%) appeared slightly lower than when treated conservatively (63.4%). The use of methylpredniso lone was associated with a dramatic decrease in mortality to 13.3%.

Severe Acute Respiratory Syndrome-Associated Coronavirus

The Virus

Severe acute respiratory syndrome (SARS) is a newly emerged disease due to infection with a novel coronavirus (SARS-CoV) that was first recognized in 2003. This was eradicated in the summer of 2004 but it is not known if it will return. SARS-CoV is a new member of the family Coronaviridae. CoVs are enveloped viruses with a large, positive, single-stranded genome. SARS-CoV appears to have originated from the wild animal reservoir in mainland China. A CoV almost identical to that in SARS patients was identified from masked palm civets (*Paguma larvata*) and the raccoon dog (*Nyctereutes procyonoides*). There was also a much higher sero-prevalence of SARS-CoV among wild animal handlers compared with controls in Guangdong, southern China.

Clinical Manifestations

The route of transmission of SARS-CoV was predominantly by close person-to-person contact via respiratory droplets. There was evidence to suggest that SARS might have spread by airborne transmission in a rapidly evolving community outbreak in a private residential complex in Hong Kong. Air samples obtained from a room occupied by a SARS patient, and swabs taken from frequently touched surfaces in rooms and in the nurses' station in a hospital in Toronto tested positive for SARS-CoV RNA by polymerase chain reaction.

The estimated mean incubation period was 4.6 days, and the mean time from symptom onset to hospitalization varied between 2 and 8 days during the outbreak in 2003. In adults, the major clinical features included persistent fever, chills/rigor, myalgia, malaise, dry cough, headache, and dyspnea. Watery, non-bloodstained diarrhea was common at presentation or developed subsequently within the first 2 weeks. Respiratory failure was the major complication of SARS. At least half of the patients required supplemental oxygen during the acute phase. About 20% of patients progressed to ARDS requiring invasive mechanical ventilatory support. The presentation of SARS in children was similar to upper respiratory infections due to other viruses but the clinical course of SARS in children was mild.

Lymphopenia, low-grade disseminated intravascular coagulation (thrombocytopenia, prolonged activated partial thromboplastin time, elevated D-Dimer), elevated lactate dehydrogenase (LDH), and creatinine phosphokinase (CPK) were common laboratory features of SARS. However, a retrospective

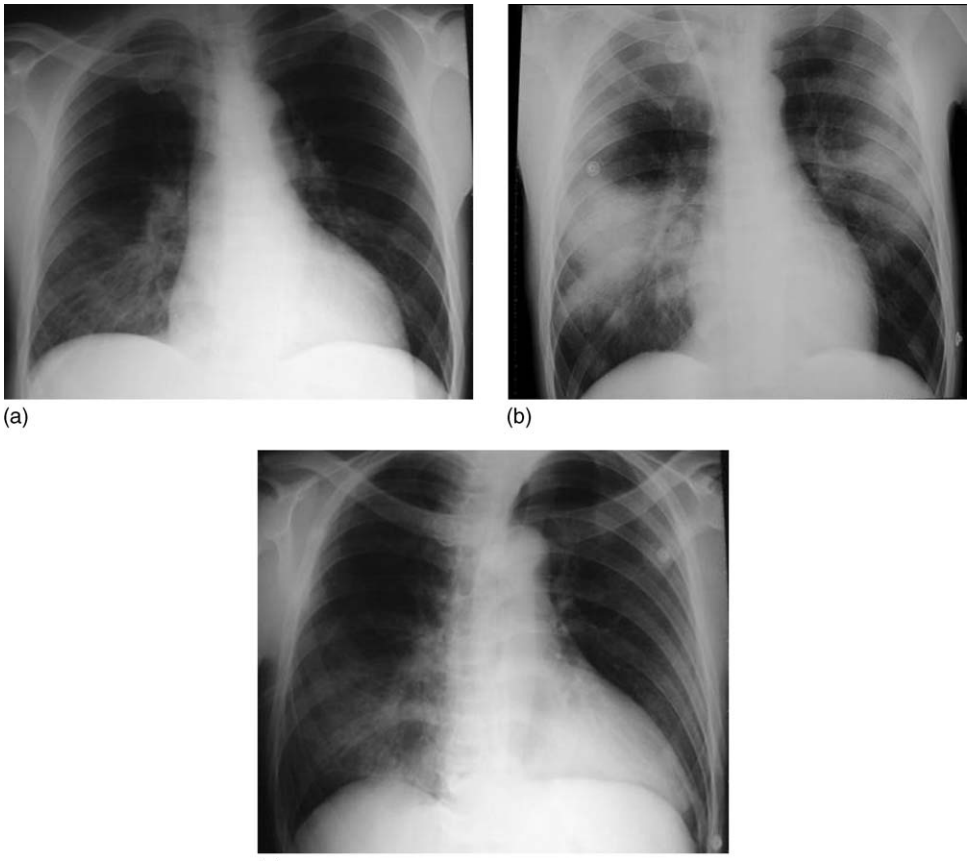

Figure 4 Serial chest radiographs of a 33-year-old male with severe acute respiratory syndrome who presented with fever, cough, and mild dyspnea. On day 2 of illness onset, there was mild right lower zone infiltrate (a). He developed acute respiratory distress syndrome (ARDS) on day 8 (b). Following pulsed steroid and intensive care support, there was marked improvement on day 14 (c).

study in Toronto has shown that all laboratory variables except the absolute neutrophil count de monstrated fair to poor discriminatory ability in distinguishing SARS from other causes of CAP. Radiographic features of SARS resembled those found in other causes of CAP (Figure 4). The more distinctive radiographic features of SARS included the predominant involvement of lung periphery and the lower zones. Cavitation, hilar lymphadenopathy, and pleural effusion were characteristically absent. Ground-glass opacification, sometimes with consolidation, and interlobular septal and intralobular interstitial thickening with predominantly a peripheral and lower lobe involvement were commonly revealed by high-resolution computed tomography.

Treatment

Owing to the limited understanding of this new disease, treatment for SARS was empirical in the 2003 outbreak. Ribavirin in combination with a protease inhibitor (lopinavir/ritonavir) as initial therapy was associated with a lower death rate than treatment with ribavirin alone. Systemic steroid may have played a role in minimizing the immune-mediated lung injury that occurs in the later phase of the disease whereas the use of interferon alfacon-1 plus corticosteroids was associated with improved oxygen saturation, more rapid resolution of radiographic lung opacities, and lower levels of CPK in SARS patients. Successful examples of using convalescent plasma with favorable outcome have been reported.

Picornaviruses

The Virus

Picornaviridae is a large virus family that includes the two genera *Rhinovirus* and *Enterovirus*, which are associated with respiratory tract infections. Both rhinoviruses and enteroviruses are small nonenveloped, single, positive-stranded RNA viruses. These viruses are more resistant to adverse environmental conditions. They are transmitted more readily by direct contact and fomites compared with other respiratory viruses.

Clinical Manifestations

Rhinovirus infection is the most important cause of acute nasopharyngitis often referred to as the 'common cold'. Repeated rhinovirus infections are common and several episodes can occur in the same individual within a year. This is because of the large number of serotypes, more than a hundred, and the type-specific immunity. Enteroviruses also contribute to respiratory tract infections.

The majority of respiratory tract infections caused by picornaviruses are self limiting. Significant morbidity occurs in a few settings. Complications include otitis media, sinusitis, and exacerbation of asthma, and other chronic respiratory disorders (e.g., chronic obstructive pulmonary disease (COPD)). Lower respiratory tract involvement with or without secondary bacterial pneumonia are more common in the elderly and those with COPDs. Other high-risk groups prone to severe, potentially fatal lower respiratory infections due to picornaviruses include infants with bronchopulmonary dysplasia, patients with cystic fibrosis, severe immunosuppression associated with bone marrow or organ transplantation, or infection with human immunodeficiency virus.

Treatment

Interferon has been investigated for treating the common cold, but its high cost and the adverse effect of local bleeding preclude its general use. Recent data suggest a potential therapeutic application for the soluble form of rhinovirus receptor intercellular adhesion molecule 1.

Measles

The Virus

The measles virus is a member of the genus *Morbillivirus* within the family Paramyxoviridae. It is an enveloped virus with a nonsegmented, negative, single-stranded RNA genome.

Clinical Manifestations

Measles was a ubiquitous common childhood febrile rash illness before the vaccine era. Typical clinical presentations include fever, conjunctivitis, malaise, sneezing, congestion, rhinitis, and cough. The pathognomonic Koplik's spots can be seen in the buccal mucosa. The distinctive maculopapular rash begins at the ears and forehead, and then spreads to face, neck, trunk, and the extremities. When the rash reaches its peak, respiratory symptoms start to subside. Complications such as otitis media and bacterial pneumonia are relatively rare.

Giant cell pneumonia is a life-threatening complication of measles seen in the immunocompromised patients. It is characterized by giant cell formation and squamous metaplasia of bronchiolar epithelia.

Atypical measles occurs in individuals who have received incomplete measles vaccination prior to the exposure to natural infection. The pattern of exanthema is different. A skin rash first develops in the extremities and then spreads, often becoming purpuric, vesicular, or urticarial. Most patients develop lobular or segmental pneumonia with pleural effusion. Recovery of respiratory symptoms is slow. Chest radiographic abnormalities remain detectable for months. The pathogenesis probably has an immune-mediated component resulting from the preexisting low-level measles antibodies.

Herpesvirus

The Virus

The virus family Herpesviridae comprises eight members that can cause infections in humans. They are herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), Epstein–Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), human herpesvirus 7 (HHV-7), and Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8). All human herpesviruses, except KSHV/HHV-8, are ubiquitous. Primary infections are followed by life-long latency with episodic reactivations.

Clinical Manifestations

The respiratory tract is not the primary site of infection for herpesviruses. Herpesviral pneumonia is rare in healthy individuals. The risk of varicella pneumonia is about 1 in 200 000 in healthy children and about 1 in 200 in healthy adults with primary VZV infection (chickenpox). In pregnant women, the incidence increases to 9% and it is more common in smokers. VZV pneumonia occurs 1–6 days after the onset of rash. Clinical features include dry cough, dyspnea, tachypnea, chest pain, hemoptysis, and cyanosis. Treatment with high-dose intravenous acyclovir is indicated. Pneumonia is the most common cause of VZV-associated death.

Most herpesviral pneumonia occurs in severely immunocompromised patients. HSV pneumonia can be part of the potentially fatal disseminated infec tion that occurs in newborns and heavily immunosuppressed transplant recipients. Treatment with acyclovir is indicated. CMV pneumonitis is a life-threatening complication seen in allograft recipients with a mortality of 80–90%. Paradoxically, acquired immunodeficiency syndrome (AIDS) patients do not

develop severe CMV pneumonitis despite the fact that other severe CMV diseases (enteritis, retinitis, adrenalitis) are common. This can be explained by the pathogenesis of CMV pneumonitis, which has an immune-mediated component. Treatment for CMV pneumonitis requires a combination of an antiviral (ganciclovir) and immunoglobulin (CMV hyperimmune globulin or human normal immunoglobulin). HHV-6 has also been associated with severe fatal pneumonitis in hemopoietic stem cell transplant recipients. HHV-6 is susceptible to ganciclovir, foscarnet, and cidofovir *in vitro*. The optimal treatment for HHV-6 pneumonitis is not clear.

See also: **Antiviral Agents**. **Pediatric Pulmonary Diseases**. **Pneumonia**: Overview and Epidemiology; Community Acquired Pneumonia, Bacterial and Other Common Pathogens. **Stem Cells**. **Surfactant**: Surfactant Protein D (SP-D). **Vaccinations**: Viral. **Viruses of the Lung**.

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The Immunocompromised Host

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Abstract

Pneumonias in the immunocompromised host can be caused by virulent organisms, which also infect normal patients, or atypical organisms not ordinarily seen in the healthy population. The type of pneumonia that develops in the immunocompromised host is determined by whether the immune defect is secondary to abnormalities in neutrophils, T lymphocytes, or B lymphocytes. Although coughing, fever, and shortness of breath develop commonly, pneumonia may be clinically silent or have unusual radiographic findings. Therefore, diagnosis often requires an open mind toward unusual organisms that may exist, as well as information acquired by sputum analysis, bronchoscopy, and/or surgical lung biopsy. Immunofluorescence and other organ-specific techniques may also be helpful in some patients. Antibiotics should be guided by cultures and other microbiology data; however, when such data are not available, they must be administered empirically.

Introduction

Immunocompromised patients are those susceptible to infectious agents of otherwise little virulence. Such patients are predisposed to develop infections from atypical organisms that do not cause disease in healthy subjects as well as from highly virulent pathogens that do. There are many ways in which patients can become immunocompromised, each associated with its own spectrum of potential pathogens.

The lung is a frequent target of opportunistic infections. This article reviews the spectrum of pulmonary diseases in the immunocompromised host, including mechanisms of immunodeficiency, types of opportunistic infections, and available diagnostic modalities.

Etiology

There exist three general mechanisms by which the immune system can be compromised. Each results from abnormalities of a different cell type, rendering the host susceptible to specific types of opportunistic infections (**Table 1**). Occasionally, more than one mechanism may be present in the same patient. They include neutrophil dysfunction or deficiency, T-cell dysfunction or deficiency, and B-cell dysfunction or deficiency.