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Respiratory Viruses

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KEY POINTS

- Influenza viruses are highly contagious Orthomyxoviruses that cause significant morbidity in children, especially those less than 5 years of age
- Influenza viruses demonstrate antigenic shift and antigenic drift that accounts for the yearly variation in the circulating strains
- Spread of infection is from person to person through large-particle respiratory droplet transmission
- Diagnosis by rapid diagnostic tests provides rapid results but lacks sensitivity
- Management is supportive with the use of neuraminidase inhibitors if started within first 48 hours of onset of illness
- Prevention through yearly vaccination of children (especially those at high risk) can help prevent significant morbidity

INFLUENZA

INTRODUCTION

Influenza is an important cause of fever and respiratory illness in children, and its effects are particularly severe in children less than 5 years of age. The word influenza is derived from an Italian term for influential visitation. Compared with adults aged 18–54 years, pediatric patients are at increased risk for complications, hospitalization, emergency department visits, and death from influenza infection.

Influenza viruses are negative-strand ribonucleic acid (RNA) viruses belonging to the Orthomyxoviridae family. The type A and B subtypes have eight negative-sense single-stranded linear segments of RNA, while the type C virus has seven segments. While the reservoir for influenza A viruses is in wild aquatic birds, they tend to infect several avian and mammalian (including humans) species. Influenza B viruses have been isolated only from humans and seals, and cause severe disease in humans, including lower respiratory tract infections, pneumonia, and encephalitis. Similarly, influenza C viruses, which generally cause mild upper respiratory tract infections, have been isolated only from humans and swine.¹

Two major surface proteins, hemagglutinin (HA) and neuraminidase (NA), determine the serotypes, since there are 15 types of HA and 9 types of NA that could occur in different combinations. The virus attaches to sialic acid residues on cells of the respiratory tract via HA and induces a lytic infection with loss of ciliary function, decreased mucus production, and desquamation of the epithelial layer. Mucosal immunoglobulin A appears to be protective but is very short

lasting and cannot provide protection in the face of strain variation. Influenza viruses demonstrate the phenomena of antigenic shift (major changes within a serotype) and antigenic drift (minor changes within a serotype) and this leads to yearly variation in the circulating strains. Introduction of novel strains (antigenic shift) can rapidly become a threat to human population because of lack of cross protection between strains. The most recent pandemic which started in May 2009 was due to influenza A (H1N1) 09 (pdm H1N1), and has had several waves of resurgence.

EPIDEMIOLOGY

Influenza is a highly contagious acute respiratory infection that is efficiently transmitted between humans by the inhalation of contaminated droplets or by direct contact. Potter estimated that during the last three centuries, there were 10 pandemic outbreaks that occurred on average once every 33 years.² During the 20th century, three pandemic strains emerged, H1N1 in 1918, H2N2 in 1957, and H3N2 in 1968; each viral subtype contained a novel HA. Retrospective molecular analyses indicate an avian origin for the HAs in the pandemic strains of 1957 and 1968. It is unclear how the 1918 HA originated, since its sequence is only partially related to the avian HA, so it is possible that it may have emerged from a mammalian source. It is believed that the pandemic strains originate from the reassortment of various strains that propagate in humans and birds. It is likely that these strains come together during the coinfection of a mammal, possibly swine, which then allows for the reassortment of these avian and human influenza strains. The introduction of a new influenza subtype into the human

TABLE 1: Studies related to the incidence of influenza infection in the Indian subcontinent

Study	Clinical testing	Laboratory tests	Total number of subjects tested	% of subjects with influenza infection
Misra et al. 1990 ⁴	Throat swab	Indirect immunofluorescence	230	4%
John et al. 1991 ⁵	Nasopharyngeal aspirate, throat swab	Culture and immunofluorescence	809	1.5%
Jain et al. 1991 ⁶	Nasopharyngeal aspirate	Culture and immunofluorescence	736	6%
Maitreyi et al. 2000 ⁷	Nasopharyngeal aspirate	Centrifugation enhanced cell culture	200	14.5%
Rao et al. 2005 ⁸	Throat swab, nasal swab	Nasopharyngeal aspirate culture and hemagglutinin inhibition	763	4.8%
Ramamurty et al. 2005 ⁹	Throat swab	Culture, hemagglutinin inhibition, and immunofluorescence	240	10%
Yeolekar et al. 2008 ¹⁰	Nasopharyngeal aspirate	Immunofluorescence	385	5.4%
Purakayastha et al. 2013 ¹¹	Throat and nasal swabs	Reverse transcription polymerase chain reaction	4,796	17%

population then reinitiates the pandemic/epidemic cycle, which is further propagated by human transmission, leading to the development of pandemic disease.³

There are a few studies related to the epidemiology of influenza in the Indian subcontinent, which have been summarized in table 1.

Seasonal analysis of the cases from India indicated that the highest number of isolates are generally documented during the rainy months of July, August, and September, with the maximum number in July, suggesting that temperature and humidity in the local environment can play role in transmission of infection. This suggests that the seasonal occurrence of influenza in India predominates in rainy season in contrast to the pattern seen in Western countries where majority of cases occur in winter. However, in the recent pandemic, peaks have been observed in winter months.

CLINICAL FEATURES

Influenza viruses spread from person to person primarily through large-particle respiratory droplet transmission. The typical incubation period for influenza is 1–4 days (average: 2 days). Even before the onset of acute symptoms, some young children may shed the virus for several days, and may remain infectious for 10 or more days after onset of symptoms, while immunocompromised individuals may shed the virus for weeks to months. Most cases of uncomplicated influenza infection demonstrate an abrupt onset of a combination of constitutional (e.g. fever, myalgia, headache, malaise) and respiratory signs and symptoms (nonproductive cough, sore throat, and rhinitis). The occurrence of otitis media, nausea, and vomiting are especially common among children. For the majority of cases with uncomplicated influenza infection, their illness typically resolves 3–7 days after the onset of symptoms, although in some cases, general malaise and cough can persist for more than 2 weeks. However, influenza virus infections can cause primary influenza viral pneumonia; exacerbate underlying medical conditions (e.g., pulmonary or cardiac disease); lead to secondary bacterial pneumonia, sinusitis, or otitis media; or contribute to coinfection with other viral or bacterial pathogens. Young children with influenza virus infection might have initial symptoms mimicking bacterial sepsis with high fevers, and febrile seizures have been

reported in 6–20% of children hospitalized with influenza virus infection. Rarely, myocarditis and encephalopathy have been associated with influenza infection. Severe myalgias and myoglobinuria have been associated with influenza B infection.

DIAGNOSIS

Respiratory illnesses caused by influenza virus infection are difficult to distinguish from illnesses caused by other respiratory pathogens on the basis of signs and symptoms alone, and may mimic illness caused by infectious agents including, but not limited to, other viruses such as adenovirus, respiratory syncytial virus, rhinovirus, para-influenza viruses; or bacterial infections such as *Legionella* and *Mycoplasma pneumoniae*. The diagnosis of influenza infection can be made with the help of various techniques such as rapid antigen testing, Reverse transcription-polymerase chain reaction (RT-PCR), serology, viral culture, and immunofluorescence assays. There are several factors that affect the sensitivity and specificity of any test for the diagnosis of influenza infection, and these include—the type of laboratory that performs the test, the type of test used, and the type of specimen tested. In general, nasopharyngeal specimens are more effective for the purpose of viral isolation or rapid antigen detection as compared to throat swab specimens. A number of rapid diagnostic tests can give quick results but may be plagued by lower sensitivity. Virus isolation by inoculation into the amniotic cavity of 10–12-day-old embryonated chicken eggs or tissue cultures is usually undertaken to identify the subtypes that are prevalent and this helps in epidemiologic data gathering.

MANAGEMENT

Treatment in most cases is usually supportive as the infection is self-limited in most cases. Maintenance of adequate hydration and control of fever are the most important aspects of care of children with acute infection. Salicylates should be avoided because of the risk of Reye's syndrome. Antibiotic therapy may be necessary for secondary bacterial infections, which should be suspected when there is recrudescence of fever, prolonged fever, or rapid deterioration in clinical status.

Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who is hospitalized; or has severe, complicated, or progressive illness; or is at higher risk for influenza complications. When indicated, influenza antiviral medications should be started as soon as possible after symptom onset. These medications have not been shown to be effective if administered more than 48 hours after onset.

Two classes of drugs are currently available: the adamantanes or M2 inhibitors and the NA inhibitors, which include oseltamivir, zanamivir, and peramivir.¹² The adamantanes (amantadine and rimantadine) block influx of H⁺ ions through the M2 (influenza matrix protein 2) ion channel, preventing the acid-triggered fusion reaction mediated by the influenza HA and thus interfering with viral uncoating inside the cell. These compounds are effective only against influenza A and are associated with several toxicities, particularly of the central nervous system, and with rapid emergence of drug-resistant variants (30% of treated patients shed resistant viruses within 3 days of treatment), the utility of the adamantanes (amantadine and rimantadine) has been virtually eliminated by the development of resistance. The NA inhibitors interfere with the release of progeny influenza viruses from infected host cells in the respiratory tract, preventing infection of new host cells and halting the spread of infection. Of the three licensed drugs in this class, oseltamivir is approved for treatment of people of all ages, while zanamivir is approved for treatment of people of 7 years of age or older and peramivir for individuals 18 years or older. The recommended duration of treatment with oseltamivir or zanamivir is 5 days. The dose of oseltamivir varies with age: If younger than 1 year old, the dose is 3 mg/kg/dose twice daily; if 1 year or older, dose varies by child's weight: 15 kg or less, the dose is 30 mg twice a day; >15 to 23 kg, the dose is 45 mg twice a day; >23 to 40 kg, the dose is 60 mg twice a day; >40 kg, the dose is 75 mg twice a day. The dose of zanamivir is 10 mg (two 5-mg inhalations) twice daily. In children, both zanamivir and oseltamivir shorten the duration and severity of influenza symptoms by approximately 1.5 days, if started within 48 hours after the onset of illness.

PREVENTION

With rapidly evolving and constantly changing strains of influenza virus that are in circulation in a given year, the use of influenza vaccines annually in children greater than 6 months of age has been recommended by the Advisory Committee on Immunization Practices (ACIP).¹³ For children receiving the vaccine for the first time, two doses are recommended 4 weeks apart, and then one dose is given yearly thereafter. The vaccine is updated annually as the influenza viruses change every year and it should be given as early as it becomes available depending on local prevalence patterns. The inactivated influenza vaccine is well tolerated (0.25 mL for 6–36 months of age, 0.5 mL for >3 years of age), but has an overall effectiveness of less than 50% in young children, in contrast to the live attenuated intranasal vaccine (LAIV) has been shown to be more effective but is not yet available for children <2 years of age.

In the context of Indian subcontinent, there is limited data regarding efficacy of yearly influenza vaccination in preventing significant childhood morbidity and mortality.

The Indian Academy of Pediatrics' Position Statement on influenza vaccination recommends the use of the trivalent vaccine in certain high-risk groups, but not for universal immunization.¹⁴ These high-risk categories include children older than 6 months of age who have any of the following conditions—chronic lung disorders (except asthma); chronic kidney disease (including nephrotic syndrome); chronic liver disease; heart disease; hematologic disorders; congenital or acquired immunodeficiency (including HIV/AIDS); diabetes mellitus; children on long-term aspirin therapy; and laboratory personnel as well as healthcare workers.

AVIAN FLU

KEY POINTS

- The avian flu viruses continue to remain a concern for human health, as they are still present and causing human infections in the South-Asian region
- India's first tryst with avian flu was in 2006, and since then there have been several reports of outbreaks in poultry birds
- Initial presenting symptoms include high fever and typical influenza like symptoms. Rapid progression to pneumonia and respiratory failure requiring intensive care support is common
- Diagnosis is based on positive viral culture, polymerase chain reaction assay, immunofluorescence test for antigen, or a fourfold rise in H5-specific antibody titer in paired serum samples
- Management is supportive, with use of oseltamivir (preferably within first 48 hours) in higher doses and for longer duration is being recommended
- Duration of viral shedding can be up to 21 days, so household contacts should be given prophylaxis and monitored closely

INTRODUCTION

Avian influenza A viruses can be categorized as either highly pathogenic avian influenza (HPAI) or low pathogenicity avian influenza (LPAI) based on the ability of the virus to cause significant disease or mortality among chickens and its molecular characteristics. Of all influenza A viruses that circulate in birds, the HPAI H5N1 virus was one of the first strains to cause human infections in the late 1990s.¹⁵ More recently, several other strains have emerged such as the H7N9 virus from China in 2013, followed by highly pathogenic H5N8 in 2014. The H5N1 virus has caused by far the greatest number of human cases with severe disease and the greatest number of deaths, and has the potential to become a pandemic. Several cases of human infection with avian influenza have occurred since 1997, and since November 2003, this virus has spread to more than a dozen countries in Asia, Africa, the Pacific, Europe, and the Near East. Most human cases of H5N1 virus infection are thought to have occurred as a result of direct contact with sick or dead infected poultry, although there is some evidence for possible environment-to-human, and limited, nonsustained human-to-human transmission to date.¹⁵

The current nomenclature names the virus based on the host of origin of the virus, the geography of the first

virus isolation, the number of isolates, the year that the virus was isolated, and the major type of hemagglutinin (HA) and neuraminidase (NA) glycoproteins. For example, Ty/Mass/3740/65 (H6N2) is an avian influenza virus that was isolated from a turkey in Massachusetts. The virus isolate number 3,740 and was found in 1965. The circulating H5N1 virus is officially named A/Goose/Guangdong/1/96 (H5N1). Soon after its discovery, a 3-year-old child from China became infected with the virus in May 1997 and developed a severe respiratory illness and eventually died, becoming the first human casualty of this newly discovered strain. The HA sequences of the majority of H5N1 viruses circulating in avian species are separated into a number of distinct clades; Clade 2.2 viruses have the most geographically diverse distribution and have caused outbreaks in birds in over 60 countries.

The H7N9 virus is a low pathogenic avian influenza virus that was first reported to have infected three humans in China in March 2013.¹⁶ Another case was reported from Taiwan but originated from the Chinese mainland. Containment measures, including the closure of live bird markets for several months, have impacted the agriculture sectors of affected countries and international trade. Continued surveillance for A(H7N9) will be necessary to detect and control the spread of the virus.

EPIDEMIOLOGY

Avian flu infects a wide variety of avian species, including the usual host species—ducks, geese, and chickens; but is not limited to these birds. Birds with vast migratory ranges (such as the black-headed gulls, feral pigeons, little egrets, gray herons, and peregrine falcons) and migratory shorebirds in Russia and Siberia have also been infected and can spread the virus across continents. The incubation period of avian influenza A (H5N1) may be longer than for other known human influenzas. Pathogenic influenza strains that evolve in domestic poultry have recently shown large-scale transmission into wild waterfowl populations. The ecology of this phenomenon is complex. It appears that some species, such as ducks, transmit highly pathogenic H5N1 strains without disease symptoms. This indicates that migratory aquatic birds could be responsible for the distribution of H5N1 throughout Southeast Asia and its ongoing global spread. The transmission of disease may occur via contact with excreta or secretions from an infected bird. Conditions that are favorable for transmission of infection include open-air markets, where eggs and birds are sold in crowded and unsanitary conditions; and undercooked poultry meat or eggs from infected birds. To minimize the chances of transmission, it is important to ensure that egg yolks and whites are firm and meat has achieved an internal temperature of 165°F (74°C) while cooking.

India's first tryst with bird flu was in 2006 when the virus H5N1 was detected from poultries in Surat district and it was followed by extensive culling operation in the areas of Navapur, Uchchal, and other adjoining areas. This was followed by another outbreak in poultry birds in Manipur in 2007. Another bird flu outbreak has recently been detected from several districts in West Bengal and Tripura, but so far, no human fatalities have been reported. There has been focus on sample surveys and to investigate any reported poultry deaths to prevent the spread of the virus. Once an outbreak

in poultry is notified, active culling of all birds in the area is begun, and active screening of all human cases presenting with fever and upper respiratory symptoms is initiated. The National Institute of Virology (NIV), Indian Council of Medical Research, Pune, India has now been designated as the first World Health Organization (WHO) Influenza A/H5 Reference Laboratory in the Southeast Asia region.

The WHO maintains situation updates, cumulative reports of human cases of avian influenza A (H5N1), and uses a series of six phases of pandemic alert as a system for informing the world of the seriousness of the threat and of the need to launch progressively more intense preparedness activities. World Health Organization has formulated guidelines for assisting countries in the surveillance, clinical management and treatment of cases, and for maintaining a state of preparedness for outbreaks in the future.¹⁶

The fatality rates are high among hospitalized patients and there has been a shift in the age groups that have been affected the most. The recent avian influenza A (H5N1) infections have caused high rates of death among infants and young children, in contrast to the 1997 infections, when most deaths occurred among patients older than 13 years of age. Most of the fatalities occurred an average of 9 days or 10 days after the onset of symptoms (range, 6–30) with majority of patients succumbing to respiratory failure. The case fatality rate reported from Thailand was 89% among ages less than 15 years of age. Since 2003, 650 human infections with highly pathogenic H5N1 viruses have been reported to the WHO by 15 countries. About 60% of these people died from their illness.¹⁶

Between March 31, 2013 and April 30, 2013, there were more than 126 cases of human infection with this new H7N9 virus from China.¹⁷ The eight genes of the H7N9 virus are closely related to avian influenza viruses found in domestic ducks, wild birds and domestic poultry in Asia. The virus likely emerged from reassortment, a process in which two or more influenza viruses coinfect a single host and exchange genes. This can result in the creation of a new influenza virus.

CLINICAL FEATURES¹⁵

The onset of clinical symptoms may include fever (generally >38°C), and influenza-like symptoms. Many patients report diarrhea, vomiting, abdominal pain, chest pain, and bleeding from the nose and gums in early stages of the illness. Compared to seasonal influenza infection, H5N1 virus infections may be associated with nonbloody, watery diarrhea. Majority of patients progress to the development of lower respiratory tract symptoms, and difficulty in breathing beginning around 5 days following the onset of symptoms.

Common laboratory abnormalities include leukopenia (mainly lymphopenia), mild-to-moderate thrombocytopenia, elevated aminotransferases, and some instances of disseminated intravascular coagulation. Majority of patients show radiographic changes of pneumonia and may include interstitial changes; areas of segmental or lobular consolidation with air bronchograms; or diffuse, multifocal, or patchy infiltrates, with the onset of these changes occurring a median of 7 days after the onset of fever (range 3–17 days). Pleural effusions are uncommon. Progression to respiratory failure has been associated with diffuse, bilateral, ground-glass infiltrates and manifestations of the acute respiratory distress syndrome.

Multiorgan failure with signs of renal dysfunction and, sometimes, cardiac compromise, including cardiac dilatation and supraventricular tachyarrhythmias, has been reported.

Limited postmortem analyses have documented severe pulmonary injury in fatal cases, with various patterns of histopathological changes in the lungs, including infection of type 2 pneumocytes, filling of the alveolar spaces with fibrinous exudates and red cells, vascular congestion, infiltration of lymphocytes into the interstitial areas, diffuse alveolar damage, hyaline-membrane formation, and the proliferation of reactive fibroblasts. Bone marrow changes include reactive histiocytosis with hemophagocytosis, while spleen and lymphoid tissues show lymphoid depletion with atypical lymphocytes. In cases with multiorgan failure, centrilobular hepatic necrosis and acute tubular necrosis have also been noted.

DIAGNOSIS

Laboratory confirmation of influenza A (H5N1) infection can be based on one or more of the following: a positive PCR assay for influenza A (H5N1) RNA; or a positive immunofluorescence test for antigen with the use of monoclonal antibody against H5; a positive viral culture; or at least a fourfold rise in H5-specific antibody titer in paired serum samples.^{15,16} In contrast to influenza A virus, the avian flu virus has been associated with a higher frequency of virus detection and higher viral RNA levels in pharyngeal than in nasal samples. Commercial rapid antigen tests are less sensitive in detecting influenza A (H5N1) infections than are RT-PCR assays.

MANAGEMENT

Most hospitalized patients with avian influenza A (H5N1) have required ventilatory support within 48 hours after admission, as well as intensive care for multiorgan failure and sometimes hypotension.^{15,16,18,19} In addition to empirical treatment with broad-spectrum antibiotics, antiviral agents, with or without corticosteroids, have been used in most patients, although their effects have not been rigorously assessed. Patients with suspected influenza A (H5N1) should promptly receive an NA inhibitor pending the results of diagnostic laboratory testing. The Centers for Disease Control and Prevention (CDC) recommends that all hospitalized patients should be started on treatment with an NA inhibitor even if more than 48 hours has elapsed since the onset of symptoms.¹⁹ The response to treatment with oseltamivir has been inconsistent, with disappearance of cultivable virus within 2 or 3 days after its initiation, even though some of the patients had clinical progression despite early therapy with oseltamivir, with a lack of reductions in pharyngeal viral load, and these patients eventually died. Recent murine studies indicate that as compared with an influenza A (H5N1) strain from 1997, the strain isolated in 2004 requires higher oseltamivir doses and more prolonged administration (8 days) to induce similar antiviral effects and survival rates. Therefore, CDC has recommended the use of longer treatment regimens up to 10 days in severely immunocompromised individuals. A higher dose (150 mg twice daily in adults with normal renal function) has been used in severely hospitalized and immunocompromised patients. For patients who cannot tolerate or absorb

oral or enterically-administered oseltamivir because of suspected or known gastric stasis, malabsorption, or gastrointestinal bleeding, the use of intravenous (IV) peramivir or investigational IV zanamivir should be considered. However, the use of zanamivir in combination with either oseltamivir or peramivir is not recommended as there is reported antagonism between these medications. In up to 16% of children with human influenza A (H1N1) infection, high-level antiviral resistance to oseltamivir has been detected. While the numbers of affected persons in a community are small, patients with suspected or proven influenza A (H5N1) should be hospitalized with contact and droplet isolation whenever feasible for clinical monitoring, appropriate diagnostic testing, and antiviral therapy. If patients are being discharged early, both the patients and their families should be provided education on personal hygiene and infection control measures to limit the spread of infection in the community.

PREVENTION

The duration of viral shedding in children younger than 12 years of age who have human influenza can last up to 21 days and also may be protracted in children and adults with avian influenza A (H5N1), so that infection-control precautions should be maintained for at least 7 days after the resolution of fever or possibly up to 21 days. Household contacts [within speaking distance (<1 m) of, or in the care of, a patient with confirmed or strongly suspected H5N1 infection] of persons with confirmed cases of influenza A (H5N1) should receive postexposure prophylaxis with oseltamivir (30 mg once daily for ≤15 kg, 45 mg once daily for >15–23 kg, 60 mg once daily for >23–40 kg, 75 mg once daily for >40 kg). Although the risk of secondary transmission has appeared low to date, self-quarantine for a period of 1 week after the last exposure to an infected person is appropriate.

HANTAVIRUS

KEY POINTS

- Hantaviruses cause a spectrum of vascular-leak syndromes in humans ranging from proteinuria to pulmonary edema and frank hemorrhage
- So far, *Thottapalayam virus* is the only *Hantavirus* isolated from India and there is very little epidemiologic data regarding its presence in the Indian subcontinent
- *Hantavirus* pulmonary syndrome (HPS) is more common in Americas and is characterized by three stages, with a mortality rate of 33% in children, mostly due to cardiogenic shock
- Hemorrhagic fever with renal syndrome (HFRS) is more common in Europe and Asia, and is characterized by five clinical phases
- Typical clinical features in an endemic setting with thrombocytopenia being present in the prodromal phase of illness, point towards possible diagnosis of *hantavirus* infection
- Diagnosis is based on antibodies directed to the viral nucleocapsid antigen
- Treatment involves supportive care and intensive care unit monitoring in severe cases. Ribavirin has shown some efficacy in HFRS, but not in treatment of HPS

INTRODUCTION

Hantaviruses belong to the family Bunyviridae and have a trisegmented, negative-sense, single-strand ribonucleic acid (RNA) genome enclosed within a membrane derived from the Golgi apparatus. They cause a spectrum of vascular-leak syndromes in humans ranging from proteinuria to pulmonary edema and frank hemorrhage.²⁰ Approximately half of the 20 known Old World (Europe and Asia) and New World (North and South America) *hantavirus* species are known to cause human disease. New World hantaviruses include *Andes virus* (ANDV), *Bayou virus*, *Black Creek Canal virus*, *Choclo virus*, *Juquitiba virus*, *Laguna Negra virus*, and *Sin Nombre virus* (SNV). Old World hantaviruses include *Dobrava-Belgrade*, *Saaremaa*, *Hantaan*, *Puumala*, *Seoul*, *Bat*, *Thailand*, *Thottapalayam*, *Tobetsu*, *Topografov*, and *Tula* viruses. The last six viruses of this group have not been shown to cause human disease so far.

EPIDEMIOLOGY

Hantaviruses first came to the attention of Western medicine in the early 1950s when more than 3,000 United States troops fighting in the Korean war became ill with Korean hemorrhagic fever, which later came to be known as hemorrhagic fever with renal syndrome (HFRS). The wave of HFRS cases presumably resulted from a high contact rate with rodents chronically infected with *hantaan virus* (HTNV—named after the nearby river of the same name) as soldiers lived and fought in the open fields. The second category of illness, hantavirus pulmonary syndrome (HPS), was first recognized in 1993 when an outbreak of severe respiratory disease struck in the Four Corners region of the United States of America. The *hantavirus* responsible for this disease, SNV, is harbored by the deer mouse (*Peromyscus maniculatus*).

Since the Four Corners outbreak, more than 2,000 cases of HPS have occurred in sporadic fashion throughout the Americas, leading to the discovery of many different strains of these viruses and their associated rodent reservoirs. These viruses are harbored by both Old World and New World rodents, and hence, their epidemiology reflects the geographical restriction imposed by the host range of the rodent vector.

A small pilot study²¹ was undertaken in South India looking for serological evidence of infection in the community, since no human cases have been reported from India so far. Blood samples were obtained from 152 individuals who had acute febrile illness of less than 14 days duration, associated with myalgia, headache, and hemorrhagic manifestations like petechiae and purpuric skin rash, and from voluntary blood donors as controls. Of these, 23 (14.7%) were positive for anti-hantavirus immunoglobulin M by enzyme-linked immunosorbent assays (EIA) in contrast to 5.7% of healthy blood donors, and 18 of these positive results were confirmed by immunofluorescence assay. This suggests that the virus may be present in the Indian subcontinent, although this data is from single serum samples (as opposed to paired samples) and therefore, should be interpreted with caution. So far, *Thottapalayam virus* is the only *hantavirus* isolated from India.

Hantaviruses chronically infect rodents without apparent disease, and they are spread by aerosolized excreta to humans. Most of the rodent reservoirs of human-pathogenic hantaviruses are not common in cities, making persons with rural residences, occupations, or recreational interests where there is contact with rodents the major targets of *hantavirus* diseases. More recently, person-to-person transmission has been documented in Argentina and is suggested by the observed epidemiologic patterns in Chile.

Hantaviruses enter host endothelial cells via interaction of the larger viral glycoprotein (Gn) with the host's cell surface receptor(s) $\beta 1$ and $\beta 3$ integrins. Once it infects the vascular endothelium, the immune response, mediated by lymphocytes, activated macrophages, and their products, promote vascular leakage. Soluble mediators that possibly arrive directly from the lungs finally affect the heart and result in cardiogenic shock—the end stage morbidity in most fatal cases.

CLINICAL FEATURES

There are three stages of HPS infection that have been reported. During the initial prodromic phase, most patients develop myalgias, fever, and thrombocytopenia. About 2–8 days after the prodromic phase, there are cardiopulmonary symptoms that generally start with cough and dyspnea. By this time, patients demonstrate elevated peripheral white cell count, with increased numbers of both immature granulocytes and distinctive immunoblasts that make up 10% or more of the lymphocyte series. The subsequent development of pulmonary edema is followed by rapid progression to respiratory failure, although patients can be supported through assisted ventilation. Cardiac dysfunction is notable among cases of severe disease, with a reduced cardiac index and increased systemic vascular resistance. This is the stage where most fatalities tend to occur, mostly due to cardiogenic shock and arrhythmias, and not due to respiratory failure. The final diuretic phase follows the cardiopulmonary symptoms and its onset denotes the resolution of the cardiopulmonary phase.

Sin Nombre virus infections in children have been reported with a clinical picture similar to the one seen in adults, although they reported sore throat more frequently than adults as an initial symptom. Laboratory abnormalities include elevated levels of serum liver enzymes and lactate dehydrogenase, hypoalbuminemia, and thrombocytopenia (median platelet count: 67,000/mm³). A third of patients at admission showed leukocytosis and hemoconcentration. While Hantavirus cardiopulmonary syndrome developed in all except one case, two-thirds of patients also required mechanical ventilation. The mortality in pediatric patients (33%) was similar to that reported in adults (38%). The ANDV-associated HPS in Argentina and Chile has evidenced a unique predilection for limited person-to-person transmission.²²

Hemorrhagic fever with renal syndrome starts with the febrile phase, which occurs 2–4 weeks after the initial infection, with high fever, chills, malaise, and headache, followed by onset of gastrointestinal symptoms (abdominal pain, vomiting) on second day, which can last up to 3–7 days. The occurrence of lumbar pain (usually caused by renal swelling), often heralds the onset of renal involvement in HFRS. Towards the end of this initial phase, some patients may develop

conjunctival hemorrhages and fine petechiae in conjunction with proteinuria (which is often massive). A characteristic drop of the blood platelet count marks the beginning of the second phase, the hypotensive phase, which can last from several hours to 2 days. At this stage, some patients may die of irreversible shock. This is followed by the oliguric phase of HFRS, lasting about 3–7 days, where anuria and renal failure define its severity. The beginning of the fourth, diuretic phase is a positive sign for recovery, with diuresis to the tune of 3–6 L/24 h being observed in adults. The last phase, the convalescent phase is characterized by slow normalization of the clinical markers and recovery of the patients during several weeks.

DIAGNOSIS

The clinical presentation of *hantavirus* infections can closely mimic dengue and leptospirosis, with several overlapping clinical and laboratory findings. In endemic areas, presence of thrombocytopenia in the prodromal phase is an indication for sending *hantavirus* serology. Later in the course of the disease when pulmonary edema has developed, the presence of at least four of these five findings (thrombocytopenia, leukocytosis, hemoconcentration, absence of granulations in neutrophils, and more than 10% of lymphocytes with immunoblastic morphology) has sensitivity of 96% and a specificity of 99% for diagnosis of HPS. The combination of four of these elements can guide early treatment and patient transport decisions until a definitive diagnosis is available.

Serology is the mainstay of diagnosis, with antibodies directed to the viral nucleocapsid antigen, which is uniformly recognized for all the patients with *hantavirus* infection. Immunoglobulin M and IgG EIA are available, but further identification of the virus type requires the use of nested reverse transcriptase-polymerase chain reaction (RT-PCR). Owing to the hazardous nature of hantaviruses and the dangers posed by aerosols formed during various laboratory procedures, tissues and serum specimens for serological or molecular tests are handled in biosafety cabinets in biosafety level 3 (BSL-3)-rated (or BSL-4) laboratories.

MANAGEMENT

Currently, there are no specific antiviral agents or vaccines against *hantavirus* infections and treatment includes supportive care. Close monitoring of patients with HPS should be done in an intensive care unit (ICU), with focus on maintaining normal vital signs (oxygenation, blood pressure support), and continuous cardiac output assessment. Clinical indicators that are predictive of poor outcomes include the presence of either circulatory shock, serum lactate concentration more than 4.0 mmol/L, cardiac arrhythmias (including ventricular tachycardia or fibrillation), or cardiac index less than 2.5 L/min/m².²³ Management of HFRS involves judicious fluid administration because fluid overload can lead to pulmonary edema and intracerebral hemorrhage, and both of these are important causes of mortality, especially in the oliguric stage. Subsequent massive diuresis can lead to significant and potentially fatal fluid imbalance and electrolyte abnormalities. Treatment with intravenous ribavirin provided it is administered within the first 4 days of onset of symptoms has been

shown to minimize the chances of developing renal failure, decreased incidence of bleeding manifestations, and decrease case fatality rates in a limited resource setting. Use of ribavirin for New World *hantavirus* infections has not shown any effect on mortality.

PREVENTION

For the prevention of *hantavirus* diseases, human habitations showing signs of rodent activity should be decontaminated, and steps should be taken to rid the premises of the offending animals. Decontamination can be accomplished by soaking the affected area with a 10% (v/v) solution of household bleach. Recently, an *Andes virus* M genome segment-based DNA vaccine has been tested in hamsters by inoculating them with antibody rich serum obtained from rhesus monkeys, resulting in 100% survival, even when given on day 4 or 5 after the initial viral challenge.²⁴ However, these immunotherapy techniques require rigorous testing before they can be brought into clinical use.

SARS

KEY POINTS

- Severe acute respiratory syndrome (SARS) epidemic first occurred in November 2002–July 2003 and had 8,096 probable cases, with 774 deaths and 1,706 health care workers also became infected
- Severe acute respiratory syndrome is caused by a *Coronavirus* that infects several animals but has never been known to infect man before this outbreak
- Children less than 18 years of age constituted only 5% of cases and they had milder disease and no reported mortality. Adolescents tend to have more severe disease
- Diagnosis is based on clinical criteria with evidence of seroconversion being the gold standard. Radiographic abnormalities tend to correlate with disease progression but may be absent in early stages
- Management includes supportive care, use of broad-spectrum antibiotics, ribavirin, and steroids
- Natural history and long-term effects of SARS are still largely unknown. Some short-term effects are exercise intolerance, persistence of subtle radiologic abnormalities, telogen effluvium, avascular necrosis of femoral head, and multiple foci of osteonecrosis

INTRODUCTION

Severe acute respiratory syndrome (SARS) first emerged in southern China in late 2002 and had never been reported as a human pathogen prior to the November 2002–July 2003 outbreak.²⁵ A few weeks after the outbreak began, a novel *Coronavirus* was isolated from patient samples by three separate laboratories. *Coronaviruses* (CoVs) are enveloped ribonucleic acid (RNA) viruses that had been previously classified based on antigenic and genetic studies into three groups: Group 1 (which included human CoV 229E); group 2 (which included human CoV OC43); and group 3 (which included the infectious bronchitis virus). There is some serological cross-reactivity between SARS CoV and human CoV 229E (group 1 CoV).

EPIDEMIOLOGY

The first concerns about the occurrence of a new outbreak arose when 305 cases, with 5 deaths, of atypical pneumonia were first reported in mid-February from the southern Chinese province of Guangdong, with an almost simultaneous report from Hong Kong of two confirmed cases of avian influenza A (H5N1) in family members with a recent travel history to southern China.²⁵ This was followed by an alert declared by the World Health Organization (WHO) on March 12, 2003, regarding the appearance of a severe respiratory illness of undetermined cause that had rapidly infected more than 40 staff members at hospitals in Vietnam and Hong Kong. The WHO Global Outbreak Alert and Response Network sent out a team of experts, who evaluated the first few cases admitted to the hospital and first ruled out influenza and then subsequently ruled out all other known respiratory illnesses in these patients. They also established infection control procedures and an isolation ward, but more cases continued to appear.

By March 15, 2003, more than 150 new cases of atypical pneumonia of unidentified cause had been admitted in the hospitals of six Asian countries and Canada. At that time, WHO issued a stronger global alert in the form of an emergency travel advisory and gave the new disease its name—severe acute respiratory syndrome (SARS).²⁶ A total of 8,096 probable SARS cases were reported during this epidemic worldwide, with a total of 774 deaths. An overall case fatality ratio of 9.6 was reported and 1,706 health care workers acquired the infection during this epidemic. There were three cases reported from India, all of them were males in the 25–30 year age group, and there were no deaths reported from India. The WHO finally declared that the international outbreak had been contained on July 5, 2003, when the last known probable case of SARS completed a 20-day period of isolation.

The complete 29.7 kb long genome of the SARS CoV had been sequenced by April 12, 2003, and analysis of its genome suggested that it was distinct from all other known *Coronaviruses*, and hence, was not derived through recombination between previously known animal or human *Coronaviruses*. This confirmed that SARS CoV was not a bioterrorist agent virus that was artificially generated in the laboratory and given the lack of serological reactivity in the human population, the most probable explanation for its sudden appearance was that it was a hitherto unrecognized animal virus that had recently acquired the ability for human-to-human transmission. SARS CoV is known to infect and replicate in macaques, cats, ferrets, mice, hamsters and African green monkeys, and of these animals, ferrets and cats can transmit infection to uninfected animals, while significant pathological disease is only seen in the macaque, hamster, and ferret animal models.

Children less than 18 years of age accounted for about 5% of the 8,096 patients with probable SARS, with no mortality being reported in children. In Hong Kong, a total of 121 children less than 18 years of age (6.9% of all patients notified) were clinically diagnosed with SARS, making the crude attack rate 8.9 per 1,00,000 population less than 18 years old. Of these 121 children, complete serological workup was available for 111 clinically diagnosed cases, and 89 (46 boys and 43 girls) had evidence of seroconversion to SARS CoV. The corrected

attack rate for children, based on serologic confirmation, was thus 6.6 per 1,00,000 population less than 18 years. An epidemiologic link to known cases was established in all except two (97%) of these children. There was no evidence of perinatal transmission of infection to infants born to pregnant women with SARS in Hong Kong or elsewhere.

CLINICAL FEATURES

Severe acute respiratory syndrome in children is characterized by an abrupt onset of fever in almost all cases, associated with a varying combination of constitutional symptoms like malaise, lethargy, chills, rigor, dizziness, headache, myalgia, and anorexia.^{27,28} The overall symptom profile of the 64 children from Hong Kong is listed in table 2. Respiratory symptoms comprising of cough, shortness of breath, difficulty in breathing, and sputum production (more commonly seen in adults) are not always present, even in children with radiographic evidence of moderately severe pneumonia, although coryza was noted more commonly in children (41%) than in adults.²⁷

Despite the respiratory tract being the site of major pathology in SARS, enteric involvement is clearly part of the disease process and may manifest as nausea, vomiting, abdominal pain, and diarrhea.²⁹ An epidemiologic link and the failure of clinical response to antibiotics for the presumptive treatment of community acquired pneumonia appeared to be the most important clues to clinical diagnosis during the outbreak of SARS.

Since many children received specific therapy besides supportive care, the natural history of untreated infection in children is unknown. Of the 64 hospitalized children, 11 (17%) developed respiratory distress necessitating oxygen supplementation. Five of these required ICU admission (four adolescents and one premature infant) and three of them further required assisted ventilation. There were no deaths reported in children.^{30,31}

TABLE 2: Clinical features of severe acute respiratory syndrome in children^{27,28}

Features	No. of children (n = 64)	(%)
Fever	62	(97)
Malaise	36	(56)
Cough	36	(56)
Coryza	26	(41)
Chills or rigor	21	(33)
Sputum production	19	(30)
Headache	18	(28)
Myalgia	18	(28)
Anorexia	15	(23)
Nausea and/or vomiting	13	(20)
Dizziness	12	(19)
Diarrhea	11	(17)
Sore throat	7	(11)
Dyspnea	6	(9)
Abdominal pain	4	(6)
Lethargy	3	(5)
Chest pain	1	(2)
Cyanotic attack	1	(2)

DIAGNOSIS

Shortly after the epidemic began, WHO formulated a case definition³² for surveillance of SARS that required the presence of lower respiratory symptoms of cough, shortness of breath or difficulty in breathing. Since many children do not present with these symptoms, applying this case definition to children would have resulted in many children being missed. So the pediatricians in Hong Kong adopted a more clinically oriented case definition³³ to make the diagnosis of SARS in children (Box 1). This clinical case definition was validated in the confirmed cases, with sensitivity, specificity, positive, and negative predictive values of 97.8%, 92.7%, 88%, and 98.7%, respectively, using seroconversion to SARS CoV as the gold standard.

Radiological diagnosis of SARS³⁴ depends on the presence of pneumonia, shown either on a chest radiograph or by high-resolution computed tomography (HRCT). However, many patients with suspected SARS can have a normal initial chest radiograph. In published series on SARS, 10–40% of symptomatic patients had normal chest radiographs on initial evaluation. The earliest radiographical manifestation of SARS is ground-glass opacity that rapidly progresses to focal, multifocal, or diffuse consolidation. The severity of lung abnormalities in SARS on chest radiographs reflected temporal changes in clinical and laboratory parameters such as heart rate, temperature, oxygen saturation (SaO₂) and liver transaminases, and deteriorating radiographical scores were shown to correlate with decreasing SaO₂ and increasing liver aminotransaminases.

The most common laboratory findings among children presenting with SARS infection include leukopenia (lymphopenia), thrombocytopenia, mildly prolonged activated partial thromboplastin time, and elevated lactate dehydrogenase level. Abnormalities such as elevated hepatic transaminases, creatine kinase, and D-dimer levels are more common among adults, and are less commonly seen in children. It is important to exclude various pathogens associated with community-acquired pneumonia, including atypical pneumonia as well.

Box 1

Clinical case definition of severe acute respiratory syndrome (SARS) used for children in Hong Kong

Fever (rectal temperature $\geq 38.5^{\circ}\text{C}$ or oral temperature $\geq 38^{\circ}\text{C}$)
and
Chest X-ray findings of pneumonia or acute respiratory distress syndrome
and
Suspected or probable contact with a person under investigation for or diagnosed with SARS
or
Exposure to a locality with suspected or documented community transmission of SARS, either through travel or residence, within 10 days of onset of symptoms
And one or more of the following
Chills, malaise, myalgia, muscle fatigue, cough, dyspnea, tachypnea, hypoxia, lymphopenia, falling lymphocyte count, or failure to respond to antibiotics covering the usual pathogens of community acquired pneumonia (e.g., a broad-spectrum β -lactam plus a macrolide) after 2 days of therapy in terms of fever and general well-being.

Although a reverse transcription-polymerase chain reaction (RT-PCR) assay for SARS CoV was rapidly developed, the first-generation product had a low sensitivity, with 48% of children having a positive RT-PCR result from nasopharyngeal aspirates (NPA) that were obtained at admission, generally within 1 week from onset of fever (median 5 days). Only 16% of children had a positive cell culture for SARS CoV from their NPA samples. Evidence of seroconversion 4 weeks after the onset of symptoms is still considered the gold standard for diagnosis.

MANAGEMENT

Children who were identified as probable SARS were usually started on broad-spectrum antibiotics to cover for the usual pathogens that cause community-acquired pneumonia. In addition, the treatment of SARS in children was modeled on initial reports of success in treating adult patients with a combination of ribavirin and corticosteroids. Box 2 provides the details of the treatment protocol that was used for children with SARS in Hong Kong.³³

Ribavirin is given for a total of 10–14 days. Antibiotics may be discontinued if afebrile for 5 days. The antibiotic regimen can be modified on clinical grounds if secondary or hospital-acquired infection is suspected.

OUTCOME

Follow-up studies of the Hong Kong cohort of children with SARS^{35,36} showed that 27% of children who recovered from SARS had a mild decrease in exercise tolerance lasting from 1 week to 3 months after discharge. Subtle exercise impairment was detected in some children at 6 months from disease onset which could be related to the deconditioning caused by the acute onset of severe illness. However, the most severely affected adolescents showed normal physical examination and pulmonary function test results at the 6 months follow-up.

Follow-up imaging with HRCT showed residual minor subpleural ground-glass opacification and air trapping on expiration in some cases, but no evidence of significant pulmonary fibrosis, bronchial wall thickening, bronchiectasis, or lung volume loss was present. Risk factors that predict

Box 2

Treatment protocol used for children with severe acute respiratory syndrome in Hong Kong

- Third generation cephalosporin (e.g., cefotaxime) plus macrolide (e.g., erythromycin or clarithromycin) for coverage of the usual pathogens of community-acquired pneumonia
- Commence ribavirin 40–60 mg/kg/day po divided q8h, if epidemiologic link is present and child is febrile on admission
- If fever persists, and no improvement in general well-being after 48 hours despite above regimen, commence corticosteroid: Prednisolone 1–2 mg/kg/day po div BID or hydrocortisone
- 1–2 mg/kg IV Q6h if cannot tolerate oral medication
- If the child develops hypoxemia, and progressive clinical and/or radiographic deterioration, administer methylprednisolone 10 mg/kg/dose IV Q24H for up to 3 doses, depending on clinical response plus ribavirin 20–30 mg/kg/day IV div Q8H to replace oral ribavirin
- Prednisolone 1–2 mg/kg/day or hydrocortisone 1–2 mg/kg Q6h is administered for a total of 2 weeks, and then tapered over 1–2 weeks.

abnormal HRCT findings at follow-up include the need for oxygen supplementation and lymphopenia.

About 40% of children on follow-up were noted to have increased shedding or diffuse thinning of hair, which started 2–3 months after disease onset, was self-limiting, and was followed by complete recovery within 1–3 months in all children. As ribavirin is not known to cause alopecia and glucocorticoids cause hypertrichosis or hirsutism instead, the condition is most probably secondary to the disease process itself. Telogen effluvium secondary to febrile systemic illness and severe psychological stress under life-threatening situations is characterized by a similar temporal onset and self-limiting pattern.

Both adults and about 9% of children recovering from SARS, even those without bone pain, showed evidence of avascular necrosis of the femoral head and, to a lesser extent, multifocal osteonecrosis on magnetic resonance imaging at 6-month follow-up.³⁷ The long-term effects of these changes in children recovering from SARS are not fully known.

In summary, children with SARS, especially those under 12 years of age, generally have milder disease when compared with adults. Adolescents are at higher risk of developing severe illness and should be closely monitored for clinical and radiological deterioration. Diagnosis relies on a high index of suspicion, diligent search for an epidemiologic link, and the demonstration of seroconversion. No evidence-based therapeutic approach exists to date. Children diagnosed with probable SARS require good supportive care, including oxygen and assisted ventilation, and those who recover warrant longer-term follow-up.

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