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Epidemic Viral Pneumonia and Other Emerging Pathogens

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KEYWORDS

• Pneumonia • Virus • Influenza • Epidemic

Viral respiratory tract infections are the most common cause of symptomatic human disease, accounting for more days lost from work than any other infection.¹ Viral respiratory infections can present in myriad ways but most commonly present as two different clinical syndromes: the common cold or the flu.² With the growing immunocompromised and elderly populations, viruses are now also recognized as major contributors to lower respiratory tract infections (LRTIs), including bronchitis, bronchiolitis, and, most importantly, viral pneumonia. In the past, viral pneumonia was classified as atypical pneumonia, a residual term from the beginning of the antibiotic era used for a pneumonia in which no bacterial pathogen could be identified and response to antibiotics was minimal.³

Traditionally, the lack of focus on viral pneumonia resulted from limited antiviral treatment availability, poor diagnostic tests, and an impression that viral pathogens play a minor role in community-acquired pneumonia (CAP). Principally because of the development of nucleic acid amplification tests for diagnosis, viral pneumonia is now recognized as a major cause of CAP, causing anywhere from 18% to 28% of cases.^{4,5} CAP is a frequent and serious problem, contributing to significant morbidity and mortality in the United States. In patients on Medicare who are hospitalized with CAP, 1-year mortality may be as high as 40%.⁶ The fraction of those deaths that is actually from viral pneumonia is unclear.

PATHOGENESIS OF VIRAL PNEUMONIA

To cause pneumonia, the virus must reach the lower respiratory tract. Droplet transmission is often limited by distance.⁷ Airborne virus-containing droplets are initially deposited in the upper respiratory tract. Once the virus replicates and spreads within squamous epithelial cells, it eventually reaches the lower respiratory tract. Other viruses, including varicella and rubeola, are transmitted through aerosols deposited directly to the lower respiratory tract. Direct contact is the least common pathway of transmission.

The interferon signaling system may be one of the most critical pathways in antiviral defense.⁸ The importance of Stat1, one activator of the transcription (JAK-STAT) pathway, has been verified with both human research and experimental models. For instance, Sendai virus, simian virus 5, and measles virus encode for V and C proteins that inhibit Stat1 expression and activation. Furthermore, respiratory syncytial virus (RSV) has developed three different mechanisms to block interferon signaling. Viruses may also be able to manipulate the relationship between the airway epithelial cells and lung macrophages. For example, RSV infection may provide an antiapoptotic signal to macrophages, which leaves viral replication and subsequent inflammation unchecked. This chain of events can potentially lead to lethal outcome from an otherwise controllable infection.

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Viral infection of the lower respiratory tract can produce severe disease through triggering an inflammatory and cytokine response sufficient to cause acute lung injury, eventually developing into diffuse alveolar damage or acute respiratory distress syndrome (ARDS). Mouse models suggest that the lethal effect of viral pneumonia is more likely secondary to the host response than to a direct cytopathic result of viral replication.⁹ Although not as common, viral invasion and replication can directly cause a necrotizing bronchopneumonia with inflammatory and exudative reactions.

Immunosuppression and Viral Infections

In the past few decades, the number of patients who are immunosuppressed has increased dramatically. This growth is largely secondary to the global epidemic of HIV, the development of more aggressive and successful chemotherapy regimens, and the progress of solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT).¹⁰ Despite advances in treating infections and significant progress with new preventative techniques,¹¹ infection continues to be the leading cause of death in these populations. Patients who are immunocompromised have long been recognized as higher risk for viral pneumonia, including herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus, and measles. Over the past few decades, RSV, influenza, parainfluenza (PIV), adenovirus, picornavirus, and human metapneumovirus (hMPV) have also been recognized as causes of pneumonia in the immunocompromised population. In a study of viral infections in patient who had undergone HSCT, the incidence of influenza ranged from 14% to 52%, RSV from 14% to 48%, adenovirus from 2% to 21%, and PIV from 11% to 49% of all viral isolates.¹² The incidence and outcome of these viral pneumonias can vary significantly based on the intensity and duration of T-cell-mediated immune suppression.^{11,13} Other factors in the pathogenesis of viral infections include stem cell product, donor-recipient matching and appropriate screening in both, composition of the conditioning regimen, and graft-versus-host disease.

Bacterial Superinfection

Although influenza and other viral pneumonias can themselves be fatal, a substantial number of viral pneumonia deaths result from secondary bacterial pneumonia.^{7,14} The most common culprit is *Streptococcus pneumoniae*, followed by *Staphylococcus aureus* and *Hemophilus influenzae*.^{14,15}

This lethal combination may be partially from the viral effects on the host, such as epithelial damage within the respiratory tract and changes in airway function. Influenza A infection, the most commonly studied virus in this area of research, can also alter the inflammatory and immune response. Both influenza and bacterial infections use similar pathways, cofactors, and intermediates, and the overlap in the inflammatory mediators produced may create an interference with or augmentation of the host immune response.¹⁶ This alteration of the immune response contributes to the severity of the resulting infection either through diminishing the ability of the host to clear the bacteria or through amplification of the inflammatory cascade. The overwhelming inflammatory cascade is usually the culprit in rapidly progressive lower respiratory tract disease resulting in ARDS.^{17,18}

CLINICAL MANIFESTATIONS

The presentation of viral pneumonia varies widely. Unfortunately, no clinical predictors reliably distinguish between viral and bacterial pneumonia.⁴ Many patients with viral pneumonia present with dyspnea, cough, sputum production, and pleuritic chest pain. Other patients, especially those who are over age of 65 years old, lack any of the above symptoms and instead present with altered mental status or falls. In studies of patients who are elderly and frail, those with viral pneumonia more often present with cardiac disease, lower white blood cell and neutrophil counts, and less frequent chest pain and rigors.¹⁹

RADIOLOGIC FINDINGS

Viral pneumonia has a variety of radiographic presentations. Again, no findings reliably predict a specific pathogen or differentiate between viral and bacterial pneumonia. Despite this, two different pathologic processes are reflected in two common radiographic patterns: a slowly progressive, insidious course of pneumonia and a rapidly progressive or virulent pneumonia.²⁰ The insidious form is characterized by lymphatic infiltrates in the alveolar septa, which may extend to the areas adjacent to the terminal and respiratory bronchioles. On CT scan, well-defined nodules and patchy areas of peribronchial ground-glass opacity and air-space consolidation are seen. Because the viruses are intracellular, most of the pathologic changes tend to occur in the epithelium and adjacent interstitial tissue. In the rapidly progressive form, the underlying disease process

is often diffuse alveolar hemorrhage and the infiltrate often extends to the interstitium and alveolar space. The chest radiograph often shows a rapid presentation of patchy unilateral or bilateral consolidations and ground-glass opacities. Poorly defined centrilobular nodules may also be present.

SPECIFIC VIRUSES

Influenza

Pathogenesis

Influenza viruses are the only paramyxoviruses capable of causing disease in humans. Influenza A, the most virulent subtype, possesses eight negative-sense RNA segments that encode 11 known proteins. Of these proteins, two large viral surface glycoproteins on the outside of the viral particles, hemagglutinin (HA) and neuraminidase (NA), form the basis of multiple serologically distinct subtypes. To initiate infection, HA binds to sialic acid residues on the respiratory epithelial cell surface glycoproteins.²¹ Protease-mediated cleavage of HA results in its endocytosis, where the low pH of the endosome promotes uncoating of the virion and viral replication, eventually leading to the death of the epithelial cell.²² Once viral replication occurs, progeny virions are bound to the host cell. NA cleaves the links between the virions and host cell.²³ Recently, 16 HA and 9 NA subtypes have been identified in wild water birds, the natural host for all influenza A viruses.²⁴

Epidemiology

Influenza viruses have distinct outbreaks every year. Although both influenza A and influenza B cause infection, influenza A virus has a remarkable ability to undergo periodic changes in the antigenic characteristics of NA and HA. Influenza A viruses that infect humans are from three major subtypes of HA (H1, H2, H3) and two subtypes of NA (N1 and N2). When NA or HA undergo stepwise point mutations in the RNA gene segments as the virus replicates, antigenic drift occurs.²⁵ When two different viruses coinfect a single host, this host can act as a "mixing vessel" and a new virus is created by reassortment of the genomic segments.²⁶ Major changes such as these antigenic shifts can cause epidemics and pandemics.

Although infection can occur all year round in tropical regions, outbreaks of influenza in the northern and southern hemisphere are almost exclusively in the winter months. People at higher risk for influenza include those with known pulmonary or cardiovascular disease, diabetes, or renal disease; immunosuppressed individuals; nursing home or chronic care facility residents; or healthy individuals older than 50 years.²⁷

Recent H1N1 outbreak

In late March 2009, an outbreak of a novel H1N1 influenza A virus was detected in Mexico.²⁸ This outbreak represented a rare quadruple reassortment of two swine strains, one human strain, and one avian strain of influenza.²⁹ As a result of airline travel, the pandemic spread rapidly. Using a modeling study, the Centers for Disease Control and Prevention (CDC) estimated 61 million cases, 274,000 hospitalizations, and 12,470 deaths occurred in the United States from April 2009 to April 2010.³⁰ Even though deaths during the pandemic were fewer than the number of influenza deaths during nonpandemic years, mortality disproportionately affected younger individuals.³¹ A similar outbreak in 1957 may have provided preexisting immunity to protect the elderly people. Of those hospitalized, 70% had a known underlying high-risk condition,³² including chronic lung disease (37%), immunosuppressive conditions (17%), pregnancy (17%), cardiac disease (17%), obesity (13%), and diabetes (13%).²⁷ Asthma was also prevalent among children and adults who were hospitalized.³³

The 2009 novel H1N1 pandemic gave several important insights into influenza pneumonia. Previously, antiviral therapy was only recommended for patients with a recent onset of symptoms. Because most studies showed a significant survival benefit for early antiviral treatment,^{32,34} antivirals were also recommended for those with suspected or confirmed H1N1 influenza A infection who were severely ill or had risk factors for a complicated course. The U.S. Food and Drug Administration (FDA) authorized emergency use of a new intravenous neuraminidase inhibitor, peramivir,³⁵ for patients unable to take inhaled or oral neuraminidase inhibitors, and possibly for those who experienced no response to other neuraminidase inhibitors. Now that the outbreak has ended, peramivir is no longer approved for use in patients with influenza. Because of the H1N1 epidemic, vaccination is now recommended for all individuals older than 6 months.

Corticosteroids were also studied during the recent pandemic. Two of the most recently published studies showed that corticosteroids were associated with higher mortality, especially when given early.^{36,37} These patients tended to have longer duration of mechanical ventilation in addition to higher incidences of acquired pneumonia, including both secondary bacterial pneumonia and invasive fungal infection. These findings are consistent with the results of steroid treatment in severe acute respiratory syndrome (SARS) and avian influenza, suggesting that steroid treatment

of acute lung injury caused by viral pneumonia may be contraindicated.

Clinical findings

After an incubation period of 1 or 2 days, influenza usually presents acutely with fever, headache, malaise, and myalgias along with cough and sore throat.³⁸ Pneumonia is the most common complication of influenza, but other complications include central nervous involvement, myocarditis, myositis, and rhabdomyolysis. Primary influenza pneumonia presents with dyspnea, persistent high fever, and significant hypoxia. Secondary bacterial pneumonia is a common complication of influenza and is responsible for 25% of all influenza deaths.³⁹ These patients usually present with recurrence of fever and new respiratory symptoms after the initial viral syndrome has begun to abate. Increasingly, concomitant influenza and bacterial pneumonia is being recognized, with a significantly higher mortality, especially with *S aureus*. *S aureus* can express cytotoxins, such as Panton-Valentin leukocidin, that have the ability to cause severe necrotizing pneumonia both directly through direct toxic activity and indirectly through the upregulation of surface proteins.⁴⁰ The mortality associated from the Panton-Valentin leukocidin-associated staphylococcal infection ranges from 56% to 61%. Myositis and rhabdomyolysis often present with significant tenderness of the muscles along with elevated creatine phosphokinase levels, myoglobinuria, and renal failure.⁴¹ Central nervous involvement may include transverse myelitis,⁴¹ Guillain-Barré syndrome,⁴¹ aseptic meningitis,⁴¹ and encephalitis.⁴¹

Diagnosis

In many circumstances, influenza can be diagnosed clinically, and diagnostic testing is unnecessary. Reverse transcriptase-polymerase chain reaction (RT-PCR) is the preferred method of diagnosis.⁴¹ RT-PCR can also distinguish between different subtypes of influenza infection, which is important when different strains with different antiviral resistance patterns are both circulating. RT-PCR only takes 4 to 6 hours to run but may be delayed if not performed in-house. Although rapid antigen and immunofluorescence assays are useful if positive, the limited sensitivity of presently available tests does not warrant their use. Cultures are less sensitive and clearly delayed compared with RT-PCR.

Prevention

Vaccination is a major method of disease control during influenza season. The CDC regularly tracks influenza viral isolates throughout the world to monitor disease activity and predict components

for the annual influenza vaccine that best match the circulating viruses for the next season.⁴² As seen in the recent H1N1 pandemic, vaccine strains are chosen according to previous viral strains. Consequently, anticipating pandemics or epidemics created by large antigenic shifts can be difficult.

In 2010, new recommendations from the Advisory Committee on Immunization Practices (ACIP) included vaccination for all individuals older than 6 months,⁴³ expanding the previous recommendation of only individuals at high risk for influenza complications and people in close contact with those individuals.

The influenza vaccines licensed for use in the United States are the intramuscular trivalent inactivated influenza vaccine and an intranasal trivalent live, attenuated, cold-adapted influenza vaccine. The inactivated vaccine includes inactivated preparations of the whole virus or subviral components (also called the "split product"). Only split product vaccines are available in the United States and are preferred for use of children younger than 12 years.⁴⁴ The live, attenuated intranasal vaccine should not be administered to patients who are immunosuppressed or pregnant; have a history of Guillain-Barré syndrome; or have cardiovascular, pulmonary, or metabolic disease⁴³; or to household members or health care professionals in close contact with patients who are immunocompromised.⁴⁵ Neither vaccine should be given to individuals with history of anaphylaxis caused by eggs or other components of vaccine.⁴³

In general, vaccine and placebo recipients report similar rates of fever, myalgias, fatigue, malaise, and headaches. Concern over an association between Guillain-Barré syndrome and influenza vaccine was highlighted with the A/New Jersey (swine) influenza vaccine administered in 1976.⁴⁶ Subsequent studies show a significant decline in the association between influenza inoculation and Guillain-Barré syndrome.⁴⁷

Treatment

All patients with severe disease or high-risk status (**Box 1**) should be treated with antiviral therapy.^{41,48} People with severe disease include those with evidence of LRTI or who are hospitalized.⁴⁹ Adults younger than 65 years without chronic medical conditions and only mild illness do not require testing, but treatment within 48 hours of their illness onset may reduce duration of symptoms.

Adamantanes

The adamantanes, amantadine and rimantadine, prevent viral replication through blocking the viral

Box 1
High-risk individuals with influenza infection

Age older than 65 years

Pregnant

Resident in a chronic care facility

Chronic medical conditions (renal failure, liver failure, cardiac disease, pulmonary disease, diabetes mellitus, malignancy, hemoglobinopathies)

Chronic immunosuppression

Neurologic disease (difficulty handling respiratory secretions)

M2 protein ion channel, preventing fusion of virus and host cell membranes.⁵⁰ The ACIP recommended against the routine use of adamantanes for influenza infection in 2008.⁴⁸ Amantadines are now recommended only for patients at risk of oseltamivir-resistant influenza and who have a contraindication to zanamivir therapy. Although side effects are not common for rimantadine, amantadine has significant central nervous system side effects (eg, nervousness, anxiety, insomnia, difficulty concentrating, lightheadedness).⁵¹

Neuraminidase inhibitors

The neuraminidase inhibitors, zanamivir and oseltamivir, selectively inhibit the neuraminidase of both influenza A and B viruses.²¹ Neuraminidase inhibitors block the active sites of NA and leave uncleaved sialic acid residues on the surfaces of host cells and influenza viral envelopes. As a result, viral HA binding to the uncleaved sialic acid residues leads to viral aggregation at the host cell surface and a reduced release of virus.⁵²

When administered within 24 to 48 hours, antivirals can reduce the duration of symptoms from 1 to 3 days.^{53,54} In addition to shortening the duration of symptoms, early initiation of oseltamivir decreases overall mortality^{32,55} and length of hospitalization in cases of severe influenza.⁵⁶ Zanamivir is available for oral inhalation, but intravenous administration is still being evaluated in clinical trials.⁵⁷ Because zanamivir induced bronchospasm and decreased lung function in some patients, it is contraindicated in patients with underlying asthma or other chronic respiratory conditions. Before 2007, resistance to oseltamivir occurred in 1% to 5% of patients.^{58,59} Since 2007, several different outbreaks of oseltamivir-resistant influenza have occurred.^{60,61} Patients who are immunocompromised seem to have a higher incidence of resistance, which is thought to result from prolonged viral shedding.⁶²

PIV

PIVs are important respiratory viral pathogens with presentations ranging from mild upper respiratory tract infections in adults who are immunocompetent to life-threatening LRTIs in those who are immunocompromised. PIV-3, representing 52% of all PIV infections, and is endemic year-round.⁶³ PIV-1 and PIV-2 (representing 26% and 12% of all the PIV infections) tend to peak during the fall months. Although pneumonia is rare, infection usually recurs throughout adulthood and accounts for 1% to 15% of acute febrile respiratory illnesses. In a prospective study of the role of viruses in CAP since the advent of nucleic amplification tests, 3 of 75 (4%) of patients who had a pathogen identified were found to have PIV.¹⁹ Despite the low incidence of pneumonia in the general adult population, PIV pneumonia commonly afflicts elderly people, especially nursing home residents.⁶⁴

Among patients who are immunocompromised, PIV infection is known to cause significant morbidity and mortality.⁶⁵ For example, in a study of more than 1000 patients who underwent bone marrow transplants, although only 5.2% tested positive for PIV, 44% of these developed pneumonia, with a mortality of 37% (10 of 27 patients).⁶⁶ Glucocorticoids were associated with an increased risk of progression from upper to lower tract disease and mortality in patients who had undergone HSCT.⁶⁷ Lung transplant recipients are also prone to PIV infection, with an estimated incidence of 5.3 per every 100 patients,⁶⁸ with LRTIs in 10% to 66% of cases. Patients who have undergone lung transplants and acquire PIV have worse short- and long-term pulmonary dysfunction, along with more acute rejection episodes⁶⁸ and bronchiolitis obliterans.⁶⁹

Because most of these studies involve inpatients, the incidence of PIV infection may be underestimated and severity may therefore be overestimated. However, outbreaks have been discovered among HSCT units, and asymptomatic shedding of HSCT recipients is common.^{70,71} Therefore, nosocomial acquisition is a major concern.

Polymerase chain reaction (PCR), specifically multiplex PCR, is now the preferred method of testing, especially in the immunocompromised population. Compared with culture, RT-PCR enzyme hybridization assay shows 100% sensitivity (95% CI, 0.66–1.00) and 95% specificity (95% CI, 0.88–0.99).^{72–74}

No treatment has proven efficacy for PIV infection. In patients who are immunosuppressed, the most common treatment is reduction of

immunosuppression.⁶⁵ Aerosolized ribavirin with or without intravenous immunoglobulin in HSCT recipients did not change mortality or viral shedding from the nasopharynx with either treatment group.⁶⁷ An inhibitor of HA and NA and a recombinant sialidase fusion protein with potent *in vitro* and *in vivo* activity against PIV are being studied.^{75,76}

RSV

Epidemiology

Although widely known to be the leading cause of LRTI among infants and children, RSV also causes significant LRTI among older children and adults, especially people who are elderly and immunocompromised.^{61,77} Although mortality from RSV in children has declined, the number of hospitalizations climbs yearly; recent estimates are approximately 120,000 hospitalizations each year.⁷⁸ RSV infections are responsible for approximately 2700 deaths in adults and children every year.⁷⁷

Direct contact is the most common form of transmission, but RSV can also be transmitted through large aerosol droplets.⁷⁹ In temperate climates, RSV typically peaks in winter months, whereas in tropical and semitropical climates, the outbreaks usually occur throughout the rainy season. Patients at risk for more severe infections include infants, children with comorbid conditions, institutionalized adults, and people who are immunosuppressed.^{80–82}

Clinical findings

The clinical presentation of RSV infection varies significantly. Typically, younger children and infants with RSV infection develop LRTI symptoms, including pneumonia, bronchiolitis, or severe respiratory failure. Although LRTI is common with an individual's first RSV infection, it decreases with subsequent infections.⁸³ RSV infection can also alter the sensitivity of the laryngeal chemoreceptors and cause apnea in infants.⁸⁴ Almost 20% of infants who present with apnea are found to have RSV infection.⁸⁵ Upper respiratory tract infections are also common in children and adults,⁸⁶ with wheezing the most common presenting symptom.⁶¹ Adults who are immunocompetent rarely develop pneumonia with RSV infection. Patients who are immunocompromised often present with pneumonia that may progress to respiratory failure. Although RSV infection can cause substantial mortality in patients who have undergone a bone marrow transplant, no long-term sequelae to RSV infection are found and pulmonary function returns to normal.⁸⁷

Radiographic findings

In children, the radiographic appearance of RSV infection also varies. Controlling for several factors, including bacterial superinfection and age of child, the most common findings on chest radiograph are normal (30%), central pneumonia (32%), or peribronchitis (26%).⁸⁸ Less common findings are emphysema (11%), pleural effusion (6%), lobar- or broncho-pneumonia (each 6%), atelectasis (5%), or pneumothorax. In immunocompromised patients, radiographic findings vary from ground-glass attenuation to tree-in-bud opacities to consolidation.

Diagnosis

In mild cases of RSV infection, the diagnosis can be made clinically. If hospitalization and treatment are necessary, diagnosis should be confirmed. In children, nasopharyngeal wash is preferred, although nasopharyngeal swab or throat culture is often adequate.⁸⁹ In patients who are intubated or immunocompromised, bronchoalveolar lavage provides the highest diagnostic yield.⁹⁰ Because the definitive diagnosis through isolation of the virus in HEp-2 cells can take weeks, multiplex PCR assay is preferred, especially in the immunocompromised population.⁹¹

Treatment

The primary management of significant RSV infection is supportive care. If lower airway obstruction is present, a trial of β -agonist or aerosolized racemic epinephrine is recommended but should not be continued if no significant clinical improvement results. Although racemic epinephrine did not shorten hospital stay nor improve other comorbid conditions associated with bronchiolitis after hospital discharge, the medication improved respiratory distress.⁹² Despite the potential benefit of decreased bronchiolar swelling and airway obstruction, corticosteroids have not been shown to benefit patients with bronchiolitis and are not recommended for infants with RSV bronchiolitis or pneumonia.^{93,94} If RSV causes an asthma exacerbation in older children or adults, corticosteroid treatment is reasonable.

The FDA has approved ribavirin, a synthetic nucleoside analog administered through continuous aerosol, for the treatment of RSV infection. Although FDA-approved, routine use of nebulized ribavirin in infants and children with RSV is not recommended by the American Academy of Pediatrics (AAP). A beneficial effect of this therapy has not been proven and several studies show conflicting results.^{95–97} Concerns for toxicity limit use, and ribavirin should never be administered to pregnant patients, and supportive staff working

with the patient should not be pregnant. Intravenous immunoglobulin with high neutralizing activity against RSV or monoclonal antibody for infants or young children has no proven benefit with RSV infection.⁷⁴ Ribavirin and immunotherapy also have shown no substantial benefit in patients who are immunocompromised and severely ill with RSV infection.^{84,98,99} Ribavirin may have the greatest potential benefit in preventing the progression of upper respiratory tract infection to LRTI.

Prevention

Intravenous immunoglobulin has been shown to be safe and effective in decreasing the severity of RSV infections.^{100,101} The AAP now recommends that palivizumab, a humanized monoclonal antibody against the RSV F glycoprotein, be considered for infants and children at risk for severe RSV infection, including those with bronchopulmonary dysplasia, prematurity, and hemodynamically significant congenital heart disease.¹⁰² Multiple factors have limited the development of more effective live, attenuated RSV vaccines, including potentiation of disease in people who have been vaccinated and subsequently become infected with wild-type virus.¹⁰³

Adenovirus

Epidemiology

Adenovirus is the most common cause of pharyngitis and coryza in young children,¹⁰⁴ and causes 5% to 10% of all febrile illnesses in infants and young children.¹⁰⁵ Of all young children who contract adenovirus, 10% will develop pneumonia, most commonly with serotype 14.¹⁰⁶ Although most infections are self-limiting and mild, adenovirus also causes potentially fatal pneumonia in patients who are immunocompromised.¹⁰⁷ In a study of more than 200 of bone marrow transplant recipients, 20.9% had evidence of adenovirus infection and 6.2% developed invasive disease. The high incidence of adenovirus infection in this particular study may be secondary to more intensive immunosuppressive regimens.¹⁰⁸ Nonpneumonic disease, such as colitis, hepatitis, hemorrhagic cystitis, tubulointerstitial nephritis, encephalitis, or disseminated disease, can also be seen in patients who have undergone HSCT.^{109,110} For patients who have undergone solid organ transplants, the most common presenting symptom for adenovirus infection is strongly associated with the transplanted organ (eg, liver transplant recipients present with hepatitis, lung transplant recipients with pneumonia).¹¹¹

In the early 1950s to 1960s, almost 10% of all military recruits were infected with adenovirus,

representing 90% of the pneumonia hospitalizations in that population.¹¹² As a result, all military recruits received oral, live enteric-coated vaccines starting in 1971. In 1996, the manufacturer of the vaccine ceased production and outbreaks of adenoviral respiratory illness reemerged, with approximately 10% of all recruits again ill with adenovirus infection. Efforts to contain the virus have not been successful.^{112,113} Therefore, interest in vaccination has again increased. A double-blind placebo-controlled study of new live, oral, type 4 and type 7 adenovirus vaccines in adult military recruits found the vaccines to be safe and to induce an appropriate immune response. Further trials are in progress.¹¹⁴

Once again, PCR has become the diagnostic method of choice, replacing viral culture of a nasopharyngeal aspirate or swab, throat swab, or sputum.¹¹⁵ Since adenoviral infection is usually self-limited, treatment is mostly supportive. Antiviral treatments are usually reserved for immunocompromised patients and those individuals with severe disease. Cidofovir, an acyclic nucleoside phosphonate with broad-spectrum activity against a wide variety of DNA viruses, has been tried.¹¹⁶ Small studies have shown mixed results,^{99,117} particularly with adenoviral pneumonia.¹¹⁸ Combination with pooled intravenous immunoglobulin (IVIg) may be more effective.¹¹⁹ Mortality was only 19% in patients who are severely immunocompromised with adenovirus infection treated with cidofovir and IVIg,¹¹⁹ compared with the historical control mortality of 26% overall, with 73% mortality in patients with pneumonia.¹²⁰

Rhinovirus

Rhinovirus is responsible for 30% of all upper respiratory tract infections, including a third to half of all colds in adults.^{121,122} Rhinovirus is responsible for one to three respiratory illnesses per year in adults and four to eight per year in healthy children.¹²¹ Although most often self-limited, rhinovirus can cause LRTIs, particularly in patients who are immunocompromised,¹²³ and can trigger asthma exacerbations.¹²⁴ Although aerosol transmission is possible, the most common mode of transmission is self-inoculation through the nose or conjunctival surfaces.¹²⁵

Rhinovirus usually presents as the common cold, including cough, nasal discharge, and nasal obstruction.¹²⁶ In contrast to adults, children may have fever early in the illness. Symptoms in adults usually resolve within a week, whereas children often continue to report symptoms for at least 7 to 10 days.¹²⁷ Rhinovirus may significantly contribute to asthma exacerbations and wheezing in

both children and young adults.¹²⁴ The virus is responsible for 15% of pneumonias within the first month of life¹²⁸ and is also very common in patients who are immunosuppressed.^{123,129} Mortality as high as 32% has been reported in bone marrow transplant recipients.

In most cases, diagnosis is not necessary and patients are given supportive care. If diagnosis is necessary, PCR is the gold standard.¹³⁰ Viral culture is time-consuming and has poor sensitivity and specificity. Because of the multiplicity of serotypes, rapid antigen detection and serologic tests do not exist for rhinovirus infections.¹³¹

Treatment

Rhinovirus is usually self-limited and the mainstay of therapy usually includes rest, hydration, and nasal decongestants. In a double-blind, randomized, placebo-controlled trial of oral pleconaril for treatment of colds caused by picornaviruses in adults,¹³² median time to alleviation of symptoms was found to be 1 day shorter compared with placebo. Prednisolone was also found to be promising for the treatment of rhinovirus infection. During a 2-month period after the first episodes of wheezing, prednisolone was found to reduce rhinovirus relapses.¹³³ A randomized double-blind study of a recombinant soluble intercellular adhesion molecule-1 (ICAM-1) administered intranasally six times per day, beginning either 7 hours before or 12 hours after rhinovirus challenge,¹³⁴ showed no effect on the incidence of infection, although clinical colds, total symptoms score, and nasal secretion weight decreased. A virally encoded enzyme, 3C protease, which cleaves viral proteins from precursor polyproteins essential for the viral replication and virion assembly, is currently in phase II trials.¹³⁵ Although some of these treatments show promise, more studies must be completed, and standard treatment for rhinovirus remains supportive care.

hMPV

Although in retrospect hMPV has caused infection for the past 50 years, it was only recently discovered after successful isolation from symptomatic children in the Netherlands.¹³⁶ Because hMPV is only newly recognized, detailed data are limited. Although hMPV can cause upper respiratory tract infection and LRTIs in all age groups, symptomatic infection is most common in young children and older adults. In individuals with LRTIs, bronchiolitis (59%), croup (18%), asthma exacerbation (14%), and pneumonia (8%) are the most common presentations.^{137,138} For adults, the most common presentations include cough (100%), nasal congestion (85%), rhinorrhea (75%), dyspnea (69%),

hoarseness (67%), and wheezing (62%). Despite usually being self-limiting, hMPV infection may account for the hospitalization of a significant portion of persons with respiratory infections.

Similar to the other viral infections, hMPV has more severe consequences in the immunocompromised population. In a prospective study of 251 patients with hematologic malignancies presenting with upper respiratory tract infections and LRTIs, 9% of the infections were associated with hMPV.¹³⁹ Of these, 16 of 22 occurred in patients who underwent HSCT. Only 9 of 251 (3.6%) had hMPV pneumonia but 3 died. Another retrospective study of HSCT patients found hMPV in the bronchoalveolar lavage of 5 of 163 patients (3%), and 4 of 5 patients died from overwhelming respiratory failure and shock. This study emphasized the importance of waiting for mild upper respiratory tract infections to clear before transplantation.¹⁴⁰

hMPV can be isolated from viral culture but grows slowly and inefficiently. RT-PCR is the most sensitive method for diagnosing hMPV infection. Serology is another method of detection.¹⁴¹

Treatment of hMPV is supportive. Ribavirin has been shown to be active against hMPV *in vitro*¹⁴² and in animal studies,¹⁴³ but efficacy in human subjects is unknown.

SARS Coronavirus

Epidemiology

The SARS coronavirus was discovered during the near-pandemic that infected 8096 individuals with 774 confirmed deaths between November 2002 and July 2003.¹⁴⁴ SARS is a highly contagious, severe, atypical pneumonia first noted in Guangdong Province in Southern China. The index case for the epidemic was a physician who traveled to Hong Kong 5 days after the onset of his symptoms.¹⁴⁵ The virus spread rapidly from southern China and Hong Kong to Vietnam, Thailand, and Singapore, eventually spreading to Europe, Canada, and the United States. The virus was not identified as a new viral strain from the coronavirus family until February/March 2003.¹⁴⁶ After extraordinary efforts at containment, no new cases were identified after July 2003. Most of the patients were adults; health care workers accounted for nearly 23% of these cases, testifying to the high infectivity.¹⁴⁷ Since then, smaller outbreaks have occurred because of laboratory transmission and contact with animal sources.^{148,149}

This SARS epidemic case-fatality rate was 9.6%.¹⁴⁴ Mortality was strongly associated with age: the estimated case fatality rate was 13.2% for patients younger than 60 years and 43.3% for

patients aged 60 years or older.¹⁵⁰ Younger children (<12 years) had milder disease with no mortality.¹⁵¹

Because of the rapid and extensive spread of SARS, multiple modes of transmission, including droplet, airborne, and close contact, were suspected.¹⁵² Environmental sampling showed that both air samples and swab samples from surfaces of a room containing a patient with SARS were PCR-positive.¹⁵³ Even the medication refrigerator door in the nursing station was PCR-positive. These findings stressed the need for adequate respiratory protection along with strict surface hygiene practices.

Clinical presentation

SARS is a respiratory viral disease with an atypical prolonged prodrome, most commonly presenting with fever, cough, chills, rigors, myalgias, dyspnea, and headache.^{145,154} As the disease progresses, respiratory symptoms become more severe, often necessitating admission to the intensive care unit (ICU) and mechanical ventilation (approximately 26% of patients).¹⁵⁵ Death is most commonly attributable to ARDS and multiorgan failure.^{145,156} Laboratory findings include lymphopenia, thrombocytopenia, elevated alanine aminotransferase, elevated C-reactive protein, and elevated lactate dehydrogenase.^{147,154} Elevated lactate dehydrogenase is associated with poor outcome. Although chest radiographs often vary in appearance, the most common presentation is focal peripheral air-space disease with gradual resolution.¹⁵⁷ Even when initial chest radiographs are normal, CT scan usually shows parenchymal abnormalities.¹⁵⁸

Diagnosis

Because of both limited sensitivity and specificity, positive RT-PCR from two separate samples (either two different sites or the same site on two different occasions) is recommended for diagnosis. The alternative is culture of the virus from any clinical specimen or detection of antibody by enzyme-linked immunosorbent assay or immunofluorescent assay. When SARS is suspected, initially negative RT-PCR should be repeated, because the sensitivity can be poor in the early stages of disease.¹⁵⁹ Although serologic testing is the most sensitive test available, several weeks are required before antibodies develop: the mean time to seroconversion is 19 to 20 days.^{156,160} Because these tests can cross-react with other human coronaviruses, false-positive results are also seen.¹⁶¹

Treatment

Although several different treatments were tried during the recent epidemic, none were proven to have beneficial effect, including high-dose glucocorticoids and ribavirin.¹⁶² Since the outbreak, lopinavir-ritonavir, interferon- α , and convalescent plasma have been tried in a smaller number of patients or in animal models without proven clinical efficacy.^{163–165} Aggressive infection control standards were the key to control of the most recent epidemic. Vaccination and monoclonal antibodies are currently not ready for human subjects.^{166–169} Concern that subsequent exposure to the SARS coronavirus after vaccination could lead to paradoxically severe disease may limit vaccination trials.

Varicella Pneumonia

Epidemiology

Varicella pneumonia is a rare complication in immunocompetent children. In adults, the reported incidence of varicella pneumonia is approximately 1 in every 400 cases.¹⁷⁰ Although the incidence of varicella pneumonia has decreased significantly since the introduction of the vaccine, most morbidity and mortality seen from varicella infection in adults are from pneumonia. The decrease in adult pneumonia is likely secondary to herd immunity from child immunization rather than adult immunization.¹⁷¹ Despite the lower incidence, mortality from varicella pneumonia in immunocompetent individuals is staggering (up to 25%).¹⁷² Risk factors for the development of varicella pneumonia include cigarette smoking, immunocompromised state, and pregnancy.^{173–175} Overall, the severity of varicella pneumonia is highest in immunosuppressed individuals (mortality, 15%–18%) and in pregnant women in the second and third trimesters (mortality, 41%). Although only 0.1% of varicella infections develop in patients who are immunosuppressed, they accounted for approximately 25% of varicella-related deaths before the development of the vaccine.¹⁷⁶ The incidence and complication rates have decreased because of early initiation of acyclovir for high-risk individuals and vaccination of those in close contact with people who are immunosuppressed and were not candidates for varicella vaccination.¹⁷⁷

Pathogenesis

VZV is a human herpesvirus that infects nearly all humans and causes chickenpox (varicella). Once a patient contracts chickenpox, VZV becomes latent in cranial nerve, dorsal root, and autonomic nervous system ganglia. Reactivation of the virus can produce shingles (herpes zoster), which is characterized by pain and rash.¹⁷⁸

Clinical presentation

The varicella rash usually starts with fever along with a pruritic, vesicular rash commonly involving the mucosa.¹⁷⁹ Typically, varicella pneumonia develops 1 to 6 days after the appearance of the rash. Symptoms include progressive tachypnea, dry cough, and dyspnea. Patients often have progressive hypoxia with diffuse bilateral infiltrates.¹⁸⁰ In one of the rare times that radiographic pattern is diagnostic of the cause of pneumonia, nodular infiltrates can become calcified, especially in the early stages of disease.¹⁸¹

Although not more frequent, varicella pneumonia in pregnancy is considerably more severe than in nonpregnant women. Varicella in people who are immunocompromised is also similar to that in people who are immunocompetent, except in the severity of the infection. These patients are at increased risk for dissemination throughout their organs, disseminated intravascular coagulation, persistent development of new skin lesions for weeks, more severe vesicles becoming large and hemorrhagic, and, of course, increased risk of pneumonia.¹⁸²

Diagnosis

Most cases of varicella infection (chicken pox and varicella zoster) are diagnosed clinically through the appearance of the typical vesicular rash at different stages. For varicella zoster, a painful, unilateral vesicular eruption usually occurs in a restricted dermatomal distribution. Further diagnostic testing is needed for an atypical rash or concern for disseminated disease in an immunocompromised host without typical cutaneous lesions. In these cases, PCR provides rapid and sensitive confirmation of VZV from clinical specimens obtained from skin lesions and body fluids, such as bronchoalveolar lavage.¹⁸³ The bronchoalveolar lavage may be most helpful in patients with pneumonia-like symptoms in whom the diagnosis of varicella has not been confirmed. Performing direct immunofluorescent test on the scrapings from active vesicular lesions is also a rapid helpful test to diagnose varicella.¹⁸⁴ Viral culture and serologic testing have not been found to be very helpful for diagnosis.

Treatment

Immediate treatment with intravenous acyclovir has been associated with improved outcomes.^{180,185} Steroids have also been used for treatment but are controversial. In an uncontrolled study of patients in the ICU already on antiviral and antibiotic therapy,¹⁸⁶ those given steroids had shorter hospitalization (median difference, 10 days) and

shorter ICU stay (median difference, 8 days) than historical controls.

Cytomegalovirus

Cytomegalovirus pneumonia is the most common viral pathogen in transplant recipients, acquired through either transfer of virus with the allograft or reactivation of the latent virus in the recipient, typically 1 to 3 months after transplantation. Incidence ranges from 1% to 9% of autologous HSCT recipients, 10% to 30% of allogeneic HSCT recipients,¹⁸⁷ and 15% to 55% of lung transplant recipients. Mortality is high, at 31% to 100% in HSCT recipients and 54% to 100% in solid organ transplant recipients. Patients who have undergone HSCT usually present after engraftment but can also present much later in disease. In patients who have undergone lung transplant, cytomegalovirus pneumonia develops 15 to 60 days posttransplant. In cases of cytomegalovirus donor-positive/recipient-negative patients, the progression of the infection is rapid.

Cytomegalovirus is also among the most frequent viruses detected among patients in the ICU who are not immunosuppressed. This occurrence was first documented in 1996 when autopsies and lung biopsies performed on patients with acute respiratory failure and possible ventilator-associated pneumonia showed that 25 of 86 of patients who were not immunocompromised had histologic findings compatible with cytomegalovirus lung disease.¹⁸⁸ Of course, viral detection does not necessarily correlate with viral disease, and this topic is still under much scrutiny.¹⁸⁹ Regardless, subsequent studies have shown enough evidence that an interventional randomized trial using anticytomegalovirus drugs would be warranted.

Although patients can be asymptomatic, common presenting symptoms usually include fever, dyspnea, nonproductive cough, and hypoxia. The most common chest CT scan findings of cytomegalovirus pneumonia are multiple, small centrilobular nodules, patchy ground-glass opacities, and small bilateral/asymmetric foci of consolidation.¹⁹⁰

Cytomegalovirus pneumonia is established through the presence of viral inclusions on a cytologic or histologic specimen. Because the yield of these findings can be low, bronchoalveolar lavage fluid is often sent for rapid shell vial culture.

The primary treatment for acute cytomegalovirus pneumonia is ganciclovir (5 mg/kg intravenously every 12 hours for 14 to 21 days) followed by valganciclovir, 900 mg, orally daily for suppression.¹⁹¹ An alternative agent is foscarnet.

Although evidence is lacking, high-dose intravenous immunoglobulin has been used successfully in conjunction with ganciclovir to treat cytomegalovirus pneumonia.¹⁹²

Bocavirus

Bocavirus, a linear nonenveloped DNA virus, was newly discovered by Swedish scientists in 2005. Although the pathogenesis of the virus is unknown, bocavirus has been implicated in respiratory tract infections in adults, along with acute gastroenteritis in children and adults. Human bocavirus was detected through PCR in 4 of 273 respiratory samples of hospitalized adults.¹⁹³ Another study performed in children showed that 36 of 1539 respiratory specimens were positive for bocavirus. Although described in immunocompromised individuals, the incidence is not known.¹⁹⁴ In children, symptoms of bocavirus include cough, dyspnea, wheezing, rhinitis, fever, and diarrhea.¹⁹⁵ In adults, symptoms are similar to atypical pneumonia or acute bronchitis. Although limited by availability, most diagnoses are PCR-based.¹⁹⁶ Treatment is supportive care.

SUMMARY

Viruses cause a high percentage of community-acquired pneumonias. The advent of PCR and other molecular techniques has been associated with the detection of a higher prevalence of common respiratory viruses than previously suspected. Better diagnostics have shown new viral pathogens regularly in epidemics, immunocompromised patients, and occasionally children. Despite better diagnostics, treatment for all but influenza is still very limited.

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