Influenza and Viral Pneumonia

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KEYWORDS

• Influenza • Virus • Pneumonia • Epidemiology • Antiviral • Symptoms • Polymerase chain reaction

KEY POINTS

- Most community-acquired respiratory viruses are RNA viruses except for adenovirus and human bocavirus, which are DNA viruses.
- Using molecular techniques, respiratory viruses are identified in approximately 25% of patients with community-acquired pneumonia.
- In addition to the community-acquired respiratory viruses, immunocompromised patients are particularly susceptible to viruses of the Herpesviridae family.
- It is difficult to diagnose influenza or other viral infection on clinical grounds.
- Patients with influenza pneumonia should be treated with a neuraminidase inhibitor. For other viruses, treatment options are limited.

INTRODUCTION

Respiratory viral infections cause substantial burden. They are prevalent and tend to affect those who are more vulnerable, such as children, elderly, and people living in developing areas, such as sub-Saharan Africa and Southeast Asia.[1] The advent of molecular techniques has facilitated the identification of respiratory viruses in patients with pneumonia and has shed a light on how commonly these viruses occur in patients with pneumonia. With the currently available diagnostic tools, viral pathogens are more often identified than bacterial pathogens in community-acquired pneumonia.[2] A large amount of effort is currently being dedicated to elucidate the pathogenicity of respiratory viruses and the interaction between viruses and bacteria in the setting of pneumonia. Since the last century, a number of devastating pandemics and outbreaks related to respiratory viruses have occurred.[3,4] Recently, there has been a growing interest in the development of new antiviral medications for respiratory infection. In this article, we provide an overview of pneumonia caused by influenza and other respiratory viruses from the practicing clinician perspective and with a focus on the adult population.

MICROBIOLOGY OVERVIEW

Human influenza is an RNA virus that belongs to the Orthomyxoviridae family and is categorized into types A, B, and C based on its nucleoprotein and matrix protein. Influenza A virus is subcategorized into subtypes such as H1N1, H1N2, and H3N2 based on hemagglutinin and neuraminidase.

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Influenza B is subcategorized into the B/Yamagata and the B/Victoria lineages.[3,5,6] Most influenza infections are caused by types A and B.[7] The gene mutation that influenza undergoes every year is called antigenic drift and is responsible for seasonal outbreaks. Conversely, influenza pandemics are caused by antigenic shift, which occurs when new hemagglutinin or neuraminidase subtypes are acquired.[7]

Most community-acquired respiratory viruses are RNA viruses except for adenovirus and human bocavirus, which are DNA viruses.[8–15] The Paramyxoviridae family includes respiratory syncytial virus, parainfluenza, and human metapneumovirus. A distinctive feature of the Paramyxoviridae family viruses is the presence of a fusion protein.[9,12,14] The fusion protein, which enables the integration of the virus with the cell membrane, allowing the introduction of the viral genome into the cell cytoplasm, is a potential target for vaccines and antivirals.[16] The Picornaviridae family of virus, which includes enterovirus and human rhinovirus, are characterized by a capsid that contains the viral genome. The capsid has a large cleft (or canyon) that binds to adhesion molecules on the cell surface, leading to the eventual entry of the viral genome into the cell. The capsid and the adhesion molecules are potential targets of antivirals[17,18] (Table 1).

INCIDENCE AND EPIDEMIOLOGY

Epidemiology of Viral Respiratory Infection in Community-Acquired Pneumonia

A systematic review included 31 observational studies that enrolled patients with community-acquired pneumonia who underwent viral polymerase chain reaction testing. The pooled proportion of patients with viral infection was 24.5% (95% confidence interval [CI] 21.5%–27.5%; I^2 = 92.9%).[19] Most of these studies were performed in the inpatient setting and viral polymerase chain reaction was obtained mostly from nasal or oropharyngeal swab. In the only study that was performed in the outpatient setting, the proportion of viral infection was 12.1% (95% CI 7.7%–16.5%; I^2 = 0.0%).[20] The pooled proportion of viral infection was 44.2% (95% CI 35.1%–53.3%; I^2 = 0%) from studies in which a lower respiratory sample was obtained in more than half of the patients.[21,22] The proportion of dual bacterial and viral infection was 10% (95% CI 8%–11%; I^2 = 93.1%). Although the presence of a viral infection did not significantly increase the risk of short-term death, patients with dual bacterial-viral infection had twice the risk of death as compared with patients without dual infection.[19] It is important to note that the identification of a viral pathogen in a patient with pneumonia does not necessarily mean that the virus has a pathogenic effect, particularly if the identification is via nasopharyngeal swab (Fig. 1, Table 2).

Epidemiology of Viral Respiratory Infection in Immunocompromised Patients

In immunocompromised patients with pneumonia, infection by respiratory viruses is exceedingly common. Surveillance studies show that a respiratory viral pathogen is identified in close to a third of hospitalized patients with leukemia or hematopoietic stem cell transplantation and respiratory symptoms. Pneumonia occurs in most immunosuppressed patients infected with a respiratory viral pathogen.[23] Immunocompromised patients are commonly infected by the same respiratory viruses that cause infection in immunocompetent patients. However, viruses of the Herpesviridae family also tend to cause infection in immunocompromised patients. As an example, in an early series of patients who underwent allogeneic bone marrow transplantation, cytomegalovirus was the most common viral pathogen.[24] Varicella zoster virus reactivation can occur in patients after hematopoietic stem cell transplantation with early series reporting incidences ranging from 22% to 41%.[25,26] It is not unusual for the infection to present in a disseminated form in these patients, and pneumonia is one of the complications.[25–27]

Epidemiology of Hospital-Acquired Viral Respiratory Infection

Traditionally, hospital-acquired respiratory viral infection has been thought to be limited to immunocompromised patients. However, it is now known that this can also commonly occur in immunocompetent patients. This was highlighted by a prospective cohort study that included 262 patients with hospital-acquired pneumonia. The proportion of viral infection was 36.1% in immunocompromised patients and 11.2% in non-immunocompromised patients. The identified viruses were respiratory syncytial virus (6.1%), parainfluenza virus (6.1%), influenza virus (3.8%), cytomegalovirus (1.9%), human coronavirus (1.5%), bocavirus (0.8%), human metapneumovirus (0.8%), and adenovirus (0.4%).[28] These data underscore the importance of infection control measures in patients with pneumonia.

Pandemics and Outbreaks

Since the past century, there have been 5 influenza pandemics: 1918 to 1919 Spanish influenza, 1957 H2N2 Asian influenza, 1968 H3N2 Hong Kong

Table 1
Characteristics and taxonomy of commonly identified respiratory viruses in patients with community-acquired pneumonia

Virus	Genome	Family	Important Antigenic Structures
Influenza	RNA	Orthomyxoviridae	Surface glycoproteins hemagglutinin (HA) and the neuraminidase (NA).[8]
Respiratory syncytial virus	RNA	Paramyxoviridae	Attachment glycoprotein (G) and fusion (F) glycoprotein.[9]
Human rhinovirus	RNA	Picornaviridae	Viral capsid proteins VP1, VP2, VP3, and VP4.[10]
Adenovirus	DNA	Adenoviridae	Capsid major structures: hexon (the building block of the capsid), penton base, and polypetides.[11]
Parainfluenza	RNA	Paramyxoviridae	Surface glycoproteins hemagglutinin-neuraminidase and fusion protein. Membrane protein.[12]
Coronavirus	RNA	Coronaviridae	Membrane glycoprotein and spike protein.[13]
Human metapneumovirus	RNA	Paramyxoviridae	Virus fusion (F) glycoprotein.[14]
Human bocavirus	DNA	Parvoviridae	Capsid viral proteins (VPs), VP1, and VP2.[15]

influenza, 1977 H1N1 Russian influenza, and the 2009 H1N1 pandemic.[3,4] It is estimated that the 2009 H1N1 pandemic caused 201,200 respiratory deaths and 83,000 cardiovascular deaths. Most of these deaths occurred in patients younger than 65 years old.[29] In 2003, a major outbreak of atypical pneumonia was reported. The cases initially clustered in China but were subsequently reported worldwide. The pneumonia often resulted in acute respiratory failure and was named severe acute respiratory syndrome.[30] Subsequently, the etiologic agent of this disease was identified as a novel coronavirus,[31,32] which was named the Urbani strain of severe acute respiratory syndrome–associated coronavirus.[31] In 2012, another novel coronavirus was isolated from a patient with pneumonia in Saudi Arabia.[33] The virus was subsequently named Middle East respiratory syndrome coronavirus.[34] Infection by this virus causes an illness that is clinically similar to that caused by severe acute respiratory syndrome–associated coronavirus but with higher mortality.[35] Cases of Middle East respiratory syndrome coronavirus were initially reported in Saudi Arabia but were subsequently reported in other countries, including the United States, typically in persons who had traveled from the Arabian Peninsula.[36–38]

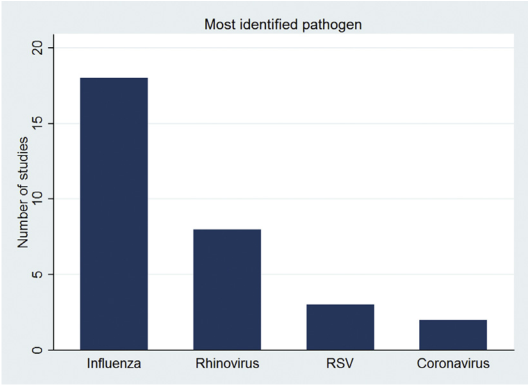

Fig. 1. Number of studies according to most commonly identified viral pathogen. RSV, respiratory syncytial virus. (*Data from* Burk M, El-Kersh K, Saad M, et al. Viral infection in community-acquired pneumonia: a systematic review and meta-analysis. Eur Respir Rev 2016;25(140):178–88.)

Influenza

The incidence of influenza can vary substantially in different seasons. As an example, using online surveillance data, it was estimated that the influenza attack rate for adults aged 20 to 64 years old was 30.5% (95% CI 4.4–49.3) in the 2012 to 2013 season and 7.1 (95% CI −5.1 to 32.5) in the 2013 to 2014 season.[39] The rates of influenza-associated hospitalization per 100,000 persons varied from 4.8 to 18.7 in 3 different seasons in the United States.[40]

Different studies showed that approximately one-third of hospitalized patients with laboratory-confirmed influenza have pneumonia.[41–43] In a study that included 4765 patients hospitalized with influenza, those with pneumonia were older

Table 2
Different scenarios for the effect of an identified viral pathogen in the setting of pneumonia

Virus is a "bystander" and does not have a pathogenic effect.	Although uncommon in adults, asymptomatic carriage of respiratory viruses occurs.[126]
Virus has a pathogenic effect and is causing pneumonia in isolation.	Potential mechanisms include dysregulation of cytokines and chemokines, infection of epithelial cells in the lungs, and apoptosis.[127]
Virus has a pathogenic effect and is causing pneumonia along with a bacterial pathogen.	A study showed that the mortality for patients with community-acquired pneumonia and bacterial and viral coinfection is higher.[19]
Virus caused a recent infection that prompted a secondary bacterial infection.	This occurs particularly with *Streptococcus pneumoniae* or *Staphylococcus aureus* infection following influenza infection.[128] Lag time of 2–4 wk between the viral and bacterial infection.[129] Polymerase chain reaction test may remain positive for up to 5 wk after a viral infection.[130]

than those without pneumonia (median age of 74 years vs 69 years; $P < .01$). In a multivariate analyses, the following factors were significant predictors of pneumonia in hospitalized patients with influenza: age older than 75 years (odds ratio [OR] 1.27; 95% CI 1.10–1.46), white race (OR 1.24; 95% CI 1.03–1.49), nursing home residence (OR 1.37; 95% CI 1.14–1.66), chronic lung disease (OR 1.37; 95% CI 1.18–1.59), and immunosuppression (OR 1.45; 95% CI 1.19–1.78). Asthma was associated with lower odds of pneumonia (OR 0.76; 95% CI 0.62–0.92).[42] In another study of 579 adult patients hospitalized with laboratory-confirmed influenza, a multivariate analyses showed that the following factors were significantly associated with pneumonia: older age (OR 1.026; 95% CI 1.013–1.04), higher C-reactive protein, mg/dL (OR 1.128; 95% CI 1.088–1.17), smoking (OR 1.818; 95% CI 1.115–2.965), low albumin level (OR 2.518; 95% CI 1.283–4.9), acute respiratory failure (OR 4.525; 95% CI 2.964–6.907), and productive cough (OR 8.173; 95% CI 3.674–18.182).[43]

During an influenza season, the attributed mortality to pneumonia and influenza in the United States ranges from 5.6% to 11.1%.[44] In a cohort study that included laboratory-confirmed cases of influenza admitted to the hospital, those with pneumonia, as compared with those without pneumonia, were more likely to require intensive care unit (ICU) admission (27% vs 10%) and mechanical ventilation (18% vs 5%), and to die (9% vs 2%)[42] (**Fig. 2**).

Respiratory Syncytial Virus

In older subjects, the burden of respiratory syncytial virus infection is similar to that of influenza. A study prospectively followed 2 outpatient cohorts during 4 seasons: 608 heathy elderly patients and 540 high-risk adults. High-risk status was defined as the presence of congestive heart failure or chronic pulmonary disease. Respiratory syncytial virus infection was diagnosed in 3% to 7% of healthy elderly subjects and 4% to 10% of high-risk subjects. This accounted for 1.5 respiratory syncytial virus infections per 100 person-months in high-risk adults and 0.9 in healthy elderly subjects.[45] In an analysis of hospitalization and viral surveillance data that encompassed several years, it was estimated that the respiratory syncytial virus–associated hospitalization rate per 100,000 person-years in the United States was 12.8 (95% CI 2.4–73.9) for patients age 50 to 64 years old and 86.1 (95% CI 37.3–326.2) for patients aged $\geq$65 years old. In contrast to influenza-associated hospitalizations, the rates of respiratory syncytial virus–associated hospitalizations were relatively similar across the years.[46] In a cohort of 1388 hospitalized adults older than 65 years or with underlying cardiopulmonary diseases, respiratory syncytial virus infection was diagnosed in 8% to 13% of these patients depending on the year. Of the 132 hospitalized patients with respiratory syncytial virus infection, 41 (31%) had an infiltrate on chest radiograph, 20 (15%) required ICU admission, 17 (13%) required mechanical ventilation, and 10 (8%) died.[45]

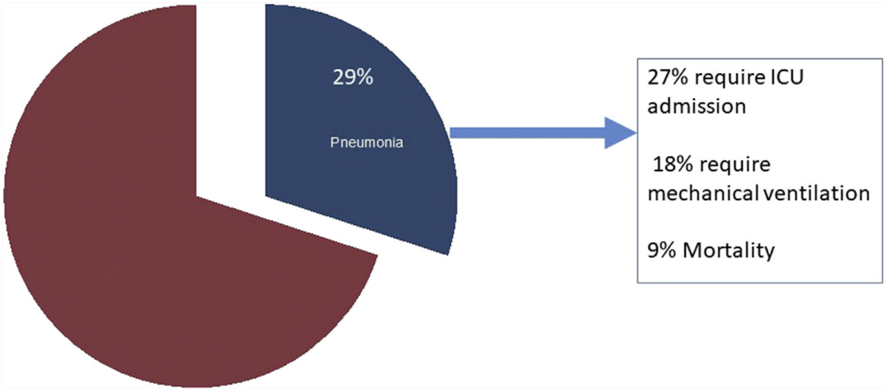

Fig. 2. Proportion of pneumonia and associated outcomes in patients admitted to the hospital with influenza infection. (*Data from* Garg S, Jain S, Dawood FS, et al. Pneumonia among adults hospitalized with laboratory-confirmed seasonal influenza virus infection-United States, 2005-2008. BMC Infect Dis 2015;15:369.)

Epidemiology of Other Respiratory Viruses

Rhinovirus

- Most common cause of common cold, a self-limited acute illness that occurs 2 to 4 times per year in adults.
- This infection is characterized by sneezing, nasal discharge, sore throat, and low-grade fever.[47]
- Rhinovirus tends to occur more often in the early fall or spring.[48]
- Rhinovirus is commonly identified in the upper respiratory tract of patients with community-acquired pneumonia via molecular techniques. In fact, rhinovirus was the most commonly identified pathogen in a large cohort of adult patients hospitalized with community-acquired pneumonia conducted in the United States.[2]

Coronavirus

- Occurs more commonly in the winter and follows a seasonal pattern that resembles that of influenza.[49]
- Coronaviruses HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 have ubiquitous circulation and are a usual etiology of common cold.[35]
- Coronaviruses have also been commonly associated with lower respiratory tract symptoms.[49]
- Adult hospitalized patients with coronavirus infection are often immunocompromised, and pneumonia is a common occurrence.[50]
- Severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus caused outbreaks and pandemics of an acute respiratory illness, often leading to respiratory failure.[35]

Adenovirus

- Adenovirus is a common cause of upper respiratory tract symptoms and conjunctivitis.[51]
- Adult patients with adenovirus pneumonia are relatively young.
- Different studies have reported that patients with community-acquired pneumonia and adenovirus infection have mean age that ranges from 30 to 38 years old.[52,53]
- Adenovirus also causes serious infection in immunocompromised patients. The adenovirus species found in immunocompromised patients are not typically found in the community, which indicates endogenous viral reactivation in these patients.[54]
- No clear seasonality, although cases may spike in some months.[55]
- A number of outbreaks caused by adenovirus have been reported. Some examples include reports of outbreaks in military personnel,[56] psychiatric care facility,[57] and ICU.[58]

Parainfluenza

- Most infections are caused by parainfluenza 1 and 3.[59] Parainfluenza 2 is less commonly identified, and parainfluenza 4 is a rare cause of respiratory infection.
- In adults, influenzalike symptoms are a common manifestation of parainfluenza infection.[60] In children, common presentations are croup and bronchiolitis.[59]
- In a population-based study of adults hospitalized for lower respiratory tract infection in 2 counties in Ohio, parainflueza-1 and parainfluenza-3 were detected in 2.5% to 3.1% of tested patients. Parainfluenza-1 epidemic season spanned the summer-autumn. Parainfluenza-3 epidemic season

spanned the spring-summer. Median age was 61.5 years for parainfluenza-1–infected patients and 77.5 years for parainfluenza-3–infected patients. Of those infected by parainfluenza-3, 59% had an infiltrate on chest radiograph, 23% required ICU stay, and none died.[61]

Metapneumovirus

- It has been identified in 4.5% of acute respiratory illnesses of adults prospectively followed as outpatients.[62]
- It has been identified in 4% of patients with community-acquired pneumonia.[63]
- Among outpatient adults, those of younger age tend to be more commonly infected by metapneumovirus, which has been presumably attributed to their closer contact with children; however, hospitalized patients with metapneumovirus infection are older.[62]
- Mean age in a series of community-acquired pneumonia and metapneumovirus infection: 62 years.[63]
- In the outpatient setting, cough and nasal congestion are the most common symptoms.[62]
- In patients with metapneumovirus infection and pneumonia, common symptoms are cough with sputum production, dyspnea, and fatigue.[63]

Human bocavirus

- Commonly identified in symptomatic and asymptomatic children but it seems to be a less common cause of respiratory symptoms in adults.[64]
- Human bocavirus infection is more common in the winter.[65]
- Common clinical presentations include upper respiratory tract symptoms, bronchiolitis. and pneumonia.[66] Cases of encephalitis have been reported.[67,68]
- It has been detected in acute respiratory illness of adults with immunosuppression and chronic lung disease.[69,70]
- A study showed that it can be often identified in the sinus tissue specimens of adult patients with chronic sinusitis.[71]

CLINICAL PRESENTATION

Clinical Manifestations

Patients with influenza infection in general (not just pneumonia) commonly present with cough, fever, fatigue, myalgia, runny nose, and sweating. Wheezing as a symptom can occur in close to half of the patients.[72] Patients with influenza pneumonia tend to have the same symptoms as patients with nonpneumonic influenza infection but an important distinction is that patients with pneumonia more often have dyspnea.[73] Perhaps the greatest clinical clue for influenza in a patient with acute respiratory symptoms (or pneumonia) is whether the patient is presenting during an influenza epidemic. As an example, the absence of coughing and temperature higher than 37.8°C make influenza very unlikely in patients presenting with influenzalike illness outside an influenza epidemic but has a lesser impact on the likelihood of influenza if the same patient presenting during an epidemic. On the other hand, the presence of these symptoms during an epidemic substantially increases the probability of influenza but has a lesser impact outside of an epidemic.[74]

Studies have assessed the accuracy of clinical manifestations for the diagnosis of influenza in patients with acute respiratory symptoms. Some of the earlier studies were limited by retrospective design, leading to potential classification bias, or by the reliance on clinical manifestations for the final diagnosis of influenza, leading to incorporation bias.[75] More recent studies used a prospective design and viral polymerase chain reaction test as the reference standard. A prospective study enrolled 100 patients with influenzalike illness who presented to 3 different clinics. Viral polymerase chain reaction test was used for the diagnosis of influenza. The accuracy of a number of symptoms was tested. On multivariate analysis, only cough and temperature remained significant predictors of influenza.[76] In a prospective study of 258 patients who presented to the emergency department with acute respiratory symptoms, a symptom inventory and influenza polymerase chain reaction test was applied to the patients. Using polymerase chain reaction test as the reference standard, the accuracy of clinical judgment, decision rule, and rapid influenza test was provided. The presence of cough and fever had a positive likelihood ratio of 5.1 and a negative likelihood ratio of 0.7.[72] In a prospective study of 270 high-risk patients who presented to an emergency department with acute respiratory illness, clinicians were asked whether they thought the patient had influenza. Viral polymerase chain reaction was the reference standard. A clinician diagnosis of influenza had a positive likelihood ratio of 1.63 and negative likelihood ratio of 0.82.[77] Likelihood ratios are an interesting way of providing the accuracy of symptoms or clinical diagnosis because they allow for the estimate of the probability of a disease after taking into account the pre-test probability[78] (**Fig. 3**). See **Table 3** for a summary of these studies.

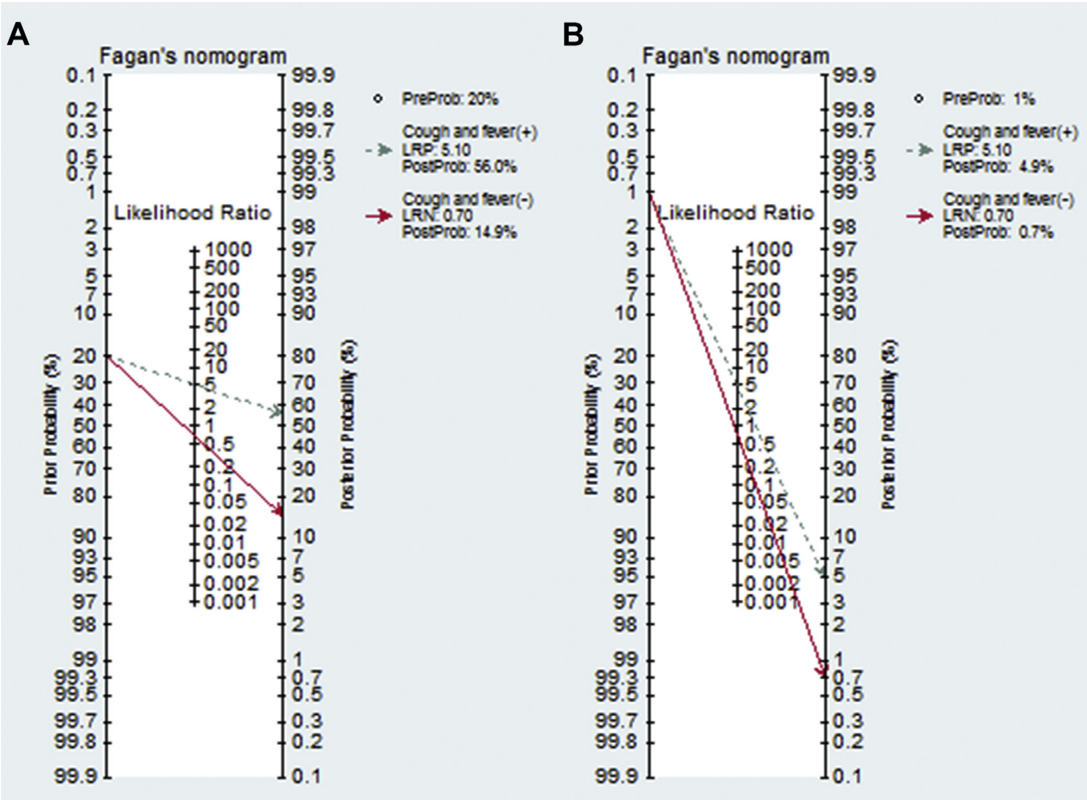

Fig. 3. Probability of influenza according to presence of combined cough and fever in patients presenting during influenza season (*A*) and outside the influenza season (*B*). (*Data for likelihood ratios from* Stein J, Louie J, Flanders S, et al. Performance characteristics of clinical diagnosis, a clinical decision rule, and a rapid influenza test in the detection of influenza infection in a community sample of adults. Ann Emerg Med 2005;46(5):412–9.)

Overall, the previously described studies indicate that the predictive value of symptoms, combination of symptoms, or clinical impression for the diagnosis of influenza is only modest for patients presenting with acute illness. Symptoms or clinical impression are not enough to rule in or rule out influenza. In fact, clinicians failed to clinically diagnose influenza in approximately two-thirds of influenza-confirmed patients in a prospective series.[77] Ultimately, clinicians need to pay close attention to surveillance data, and if there is evidence of influenza activity in the area where they practice, any acute febrile respiratory illness should place influenza as a high possibility in the differential diagnosis. In the United States, the Centers for Disease Control and Prevention provide weekly data on influenza activity according to regions in the country. This is available at https://www.cdc.gov/flu/weekly/index.htm. Other important aspects of clinical history include close contact with persons with acute febrile illness, and recent travel. Additionally, it is important to realize that in some tropical countries, influenza circulates throughout the year.[79]

A hallmark of respiratory syncytial virus infection is the presence of wheezing, which occurs in a higher frequency as compared with patients with influenza. Hospitalized patients with respiratory syncytial virus infection may present with clinical-radiological dissociation, in which patients may appear toxemic despite mild radiological abnormalities. In a cohort of 118 hospitalized patients with respiratory syncytial virus infection, the most common symptoms were cough (97%), dyspnea (95%), wheezing (73%), and nasal congestion (68%). On physical examination, wheezing was present in 82% of the patients. A temperature higher than 39°C was present in only 13% of the patients. It should be noted, however, that these percentages are for all hospitalized patients with respiratory syncytial virus infection. When assessing only those hospitalized patients with respiratory syncytial virus infection and pneumonia, wheezing and nasal congestion were less common.[80] In another study of 57 patients with respiratory syncytial virus infection and clinical diagnosis of pneumonia, the most common symptoms were cough (88%), dyspnea (82%), wheezing (79%),

Table 3
Characteristics of studies that prospectively assessed the accuracy of symptoms for the diagnosis of influenza infection

Author, Year	Design	Setting	Sample	Inclusion Criteria	Reference	Results
Boivin et al,[76] 2000	Prospective cohort	Patients presenting to 3 outpatient clinics	100	Flulike illness of <72 h duration	PCR and culture from nasopharyngeal swab	Cough and fever (>38°C): Sens of 77.6% Spec of 55.0% PPV of 86.8% NPV of 39.3%
Stein et al,[72] 2005	Prospective cohort	Adult patients presenting to the emergency department	258	New illness within the past 3 wk associated with cough, fever, or upper respiratory tract symptoms		Clinician judgment: Sens of 29% (95% CI 18%–43%) Spec of 92% (95% CI 87%–95%) PLR of 3.8 (95% CI 1.9–7.5) NLR of 0.8 (95% CI 0.6–0.9) Decision rule (cough and fever): Sens of 40% (95% CI 27%–54%) Spec of 92% (95% CI 87%–95%) PLR of 5.1 (95% CI 2.7–9.6) NLR of 0.7 (95% CI 0.5–0.8)

Dugas et al,[77] 2015	Prospective cohort	Adult patients presenting to the emergency department	270	Fever or any respiratory-related symptom	PCR from nasopharyngeal swab	Clinical judgment: Sens of 36% (95% CI 22%–52%) Spec of 78% (95% CI 72%–83%) PLR of 1.63 (95% CI 1.01–2.62) NLR of 0.82 (95% CI 0.65–1.04) Influenzalike illness (fever ≥37.8°C with either cough or sore throat): Sens of 31% (95% CI 18%–47%) Spec of 88% (95% CI 83%–92%) PLR of 2.61 (95% CI 1.47–4.64) NLR of 0.78 (95% CI 0.64–0.96)

Abbreviations: CI, confidence interval; NLR, negative likelihood ratio; NPV, negative predictive value; PCR, polymerase chain reaction; PLR, positive likelihood ratio; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

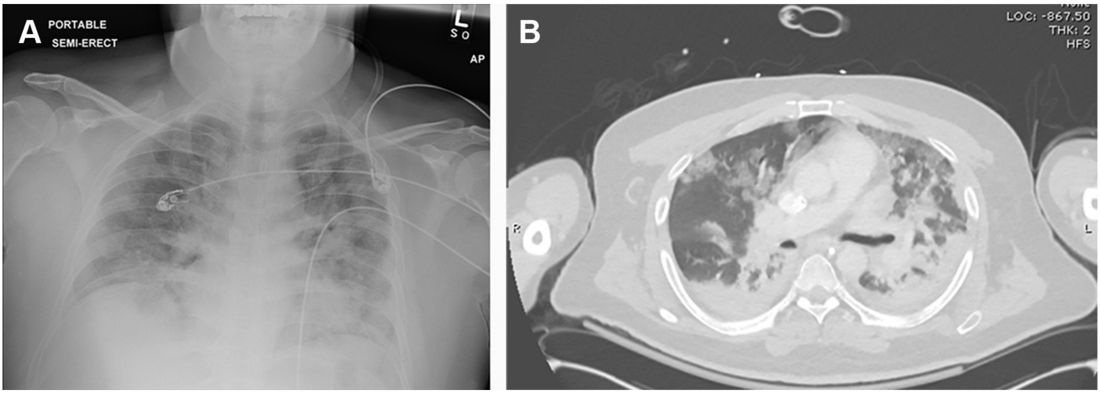

Fig. 4. Chest radiograph and computed tomography of the chest of a 42-year-old male patient admitted with pneumonia and 2009 H1N1 influenza infection leading to acute respiratory failure. Chest radiograph (*A*) reveals diffuse consolidation, and the computed tomography of the chest (*B*) reveals bilateral patchy ground-glass opacities and dense consolidation in the dorsal areas.

fever (61%), and runny nose (58%). On physical examination, the most common findings were wheezing (53%), rhonchi (46%), and crackles (40%).[81]

Just as in pneumonia caused by influenza or respiratory syncytial virus, there are no specific clinical manifestations of pneumonia caused by other respiratory viruses. In fact, symptoms and signs are not specific enough to differentiate viral from bacterial pneumonia.[82] The usual clinical manifestations of pneumonia, including fever higher than 37.8°C, heart rate faster than 100 beats per minute, crackles, and decreased breath sounds,[83] are to be expected in pneumonia caused by any of the respiratory viruses. In the end, the diagnosis of viral infection in patients with pneumonia relies on the recognition that respiratory viruses are a common etiology of pneumonia, and on the systematic performance of viral microbiology studies on these patients.

Radiological Manifestations

The chest radiograph of patients with viral pneumonia can show different patterns, including ground-glass opacities, consolidation, and nodular opacities. In general, patients present with faint opacities, commonly described as a ground-glass pattern. The second most commonly reported pattern is consolidation. Nodular opacities are less common but can occur. The opacities are often patchy in distribution.[80,84–87] Bilateral involvement is fairly common, and some series in influenza pneumonia show that bilateral involvement is slightly more common than unilateral involvement.[84] On the other hand, other series in respiratory syncytial virus or coronavirus pneumonia show that unilateral involvement is more common.[80,85] Pleural effusions are not usual but have been reported.[87] On computed tomography of the chest, the most common pattern, ground-glass opacity, becomes even more noticeable, often in a patchy and bilateral distribution. Other patterns, such as consolidation, nodular opacities, and interlobular thickening, also can be present[86] (**Figs. 4** and **5**).

Similar to the clinical manifestations, the radiological findings are not specific and do not allow for the differentiation of viral from bacterial infection in patients with pneumonia, let alone the identification of a specific virus. The radiological findings, however, can help corroborate the diagnosis of viral pneumonia. For instance, in a patient in whom a viral pathogen has been identified by oropharyngeal swab, the demonstration of patchy ground-glass opacities in the lung are suggestive of a viral pneumonic infiltrate.

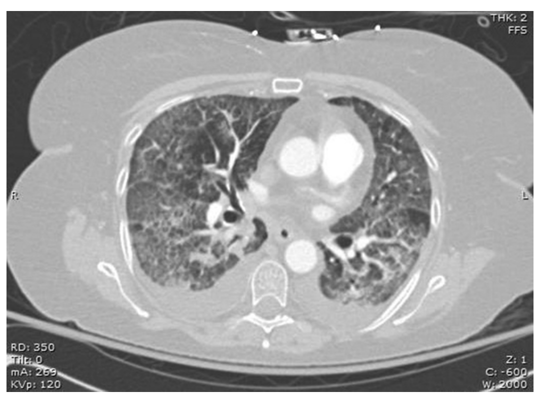

Fig. 5. Computed tomography of the chest revealing diffuse ground-glass opacities and small bilateral pleural effusion in a 62-year-old female patient with respiratory syncytial virus infection who developed pneumonia and acute respiratory distress syndrome.

PATHOGEN-DIRECTED THERAPY

Influenza

The 2 main classes of antiviral drugs for treatment of influenza include neuraminidase inhibitors and adamantanes.[7] Influenza viruses infect cells through the binding of its surface glycoprotein hemagglutinin to the sialic acid receptor. The attached virus is then released into the cells by another surface glycoprotein, neuraminidase, which is the target of neuraminidase inhibitors.[88] The adamantanes, which include amantadine and rimantadine, block the M2 protein, a membrane protein with ion channel activity.[89] They exhibit activity against influenza A but not against influenza B. The antiviral drugs currently approved by the US Food and Drug Administration are the neuraminidase inhibitors oral oseltamivir, inhaled zanamivir, and intravenous peramivir.[90] The adamantanes are not recommended for the treatment of influenza because of high resistance of influenza A against these drugs.[90]

There are a number of clinical trials that assessed the effect of oseltamivir for influenza. A comprehensive systematic review summarized the effect of oseltamivir for prophylaxis and treatment in adults and children. For the assessment of time to alleviation of symptoms in adults with influenza, 8 studies were pooled, totaling 2208 patients in the oseltamivir group and 1746 in the placebo group. Oseltamivir led to earlier relief of symptoms (16.8 hours; 95% CI 8.4–25.1 hours; $P < .001$). For the assessment of pneumonia prevention in adults with influenza, 8 studies were pooled, which included 2694 patients in the oseltamivir group and 1758 in the placebo group. Oseltamivir led to a reduction in pneumonia (risk difference of 1% [0.22%–1.49%]). For the assessment of hospitalization prevention in adults with influenza, 7 studies were pooled that included 2663 patients in the oseltamivir group and 1731 in the placebo group. There was no difference in need for hospitalization (risk ratio 0.92; 95% CI 0.57–1.5; $P = .73$). The pooling of 8 studies in adults, which included 2694 patients in the oseltamivir group and 1758 in the control group, showed that oseltamivir led to more nausea (risk ratio 1.57; 95% CI 1.14–2.15; $P = .005$) and more vomiting (risk ratio 2.43; 95% CI 1.75–3.38; $P<.001$]).[91] In aggregate, these meta-analyses indicate that influenza-infected patients treated with oseltamivir have a modest benefit in relief of symptoms and prevention of pneumonia. This comes at the expense of more nausea and vomiting. It should be noted, however, that the patients included in these trials did not appear ill. For instance, studies that enrolled patients with immunosuppressive conditions such as human immunodeficiency virus infection or malignancy were not included in the meta-analyses. The inclusion criteria for the pooled studies were the presence of influenzalike illness rather than pneumonia. Additionally, only 1 death was reported among all trials that included the adult population.

An earlier systematic review included observational studies that evaluated antiviral therapy versus no therapy or other antiviral therapy in patients with laboratory-confirmed or a clinical diagnosis of influenza. This review of observational studies had important distinctions from the review of randomized clinical trials. First, here the investigators pooled studies that included hospitalized patients, a high-risk population. The pooling of 3 studies (total of 681 patients) that adjusted for confounders showed that oseltamivir, as compared with no antiviral therapy, was associated with a reduction in mortality (OR 0.23; CI 0.13–0.43).[92] The quality of the evidence generated by this review was generally low because it relied on observational studies, which are at risk of confounding despite adjustment in the analyses. However, these observational studies and their meta-analyses fill in important knowledge gaps that were not and likely will not be addressed by clinical trials.

The Centers for Disease Control and Prevention recommends that treatment be initiated as soon as possible for those hospitalized; patients with severe, complicated, or progressive disease; and those at higher risk for influenza complications.[90] We agree with the Centers for Disease Control and Prevention recommendations and as such we submit that all influenza-infected patients with pneumonia, a complication from influenza, should receive antiviral therapy, which currently should be a neuraminidase inhibitor. In the absence of a sensitive point-of-care polymerase chain reaction, clinicians have to decide whether to initiate empiric treatment for influenza pneumonia. Strong consideration should be given to surveillance data and risk factors for influenza. It is important to note that not only an influenza diagnosis is often missed but also clinicians often fail to prescribe antiviral influenza treatment when a clinical diagnosis of influenza is made and there is indication for treatment.[93,94] The benefit from treatment is greatest when it is started early but a survival benefit has been demonstrated with treatment up to 5 days after symptom initiation[95] (**Fig. 6**).

Other Respiratory Viruses

For the treatment of pneumonia caused by respiratory viruses other than influenza, defining whether the patient is immunocompetent or

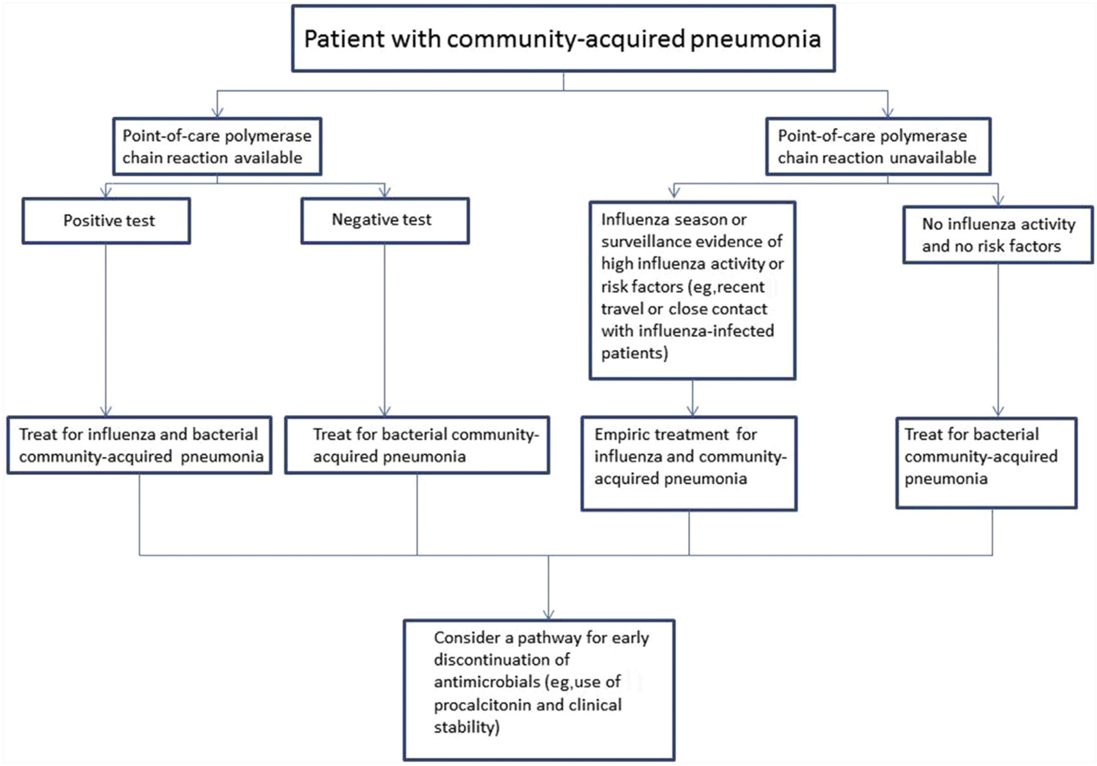

Fig. 6. Treatment approach in patients presenting with community-acquired pneumonia.

immunosuppressed is important. In immunocompetent patients, current antiviral treatment options are limited, generally reserved for severely ill patients, and based on anecdotal data. For instance, case reports and series have reported the use of cidofovir for the treatment of severe pneumonia caused by adenovirus in non-immunocompromised patients.[96,97] Even though patients had clinical improvement in these series, those studies were uncontrolled and thus do not allow a firm conclusion as to the efficacy of cidofovir. Antiviral treatment for pneumonia caused by viruses of the Herpesviridae family in immunocompetent hosts has been reported in severe cases.[98,99] In pregnant women with varicella zoster virus pneumonia, the mortality is high, and treatment with intravenous acyclovir is indicated.[100]

In immunosuppressed patients, aerosolized ribavirin, oral ribavirin, intravenous immunoglobulin, hyperimmunoglobulin, and palivizumab are treatment options that have been used in respiratory syncytial virus infection, particularly in patients with hematological malignancy or transplant recipients.[101] For cytomegalovirus pneumonia, treatment includes intravenous ganciclovir.[102] The addition of cytomegalovirus immunoglobulin to ganciclovir appears to lead to improved survival according to a case series.[103] An alternative treatment for cytomegalovirus pneumonia is intravenous foscarnet.[104] For the treatment of varicella pneumonia, the indicated treatment is intravenous acyclovir.[105] Similarly, herpes simplex virus pneumonia is treated with intravenous acyclovir.[106] The evidence for the use of these therapies is weak and comes in the form of observational studies (Fig. 7).

DISCONTINUATION OF ANTIBIOTIC THERAPY

The identification of a viral pathogen in pneumonia should not in itself prompt a clinician to discontinue the initial empirical antibiotics because dual bacterial-viral infection is common. In fact, the recognition that dual bacterial-viral is common seems to be reflected in clinical practice. In an observational study, most patients with respiratory tract infection admitted to the hospital who turned out to have an identified viral pathogen did not have their antibiotics discontinued.[107] On the other hand, the use of a clinical pathway integrating the results of viral microbiology testing with clinical findings and procalcitonin testing could have a role in the safe discontinuation of antibiotics. It is now well established that use of procalcitonin to guide initiation and discontinuation of antibiotic in

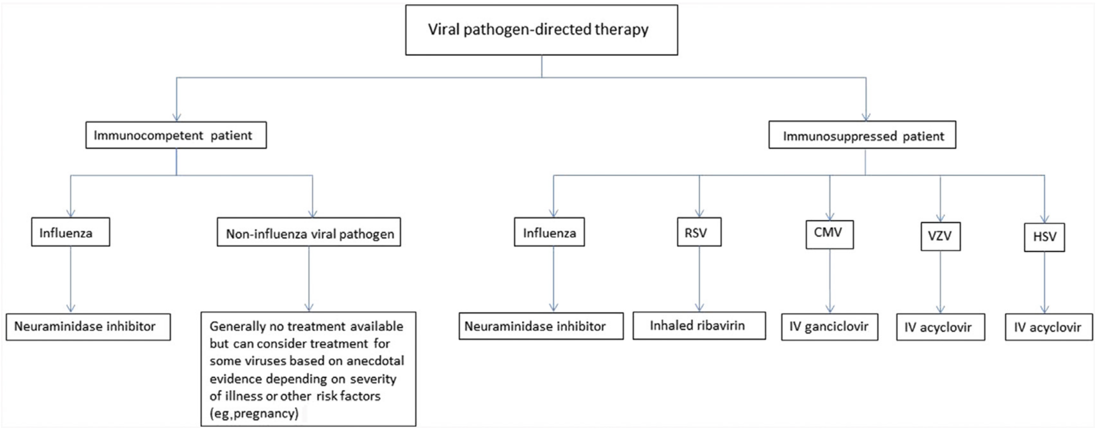

Fig. 7. Viral pathogen-directed therapy. CMV, cytomegalovirus; HSV, herpes simplex virus; IV, intravenous; RSV, respiratory syncytial virus; VZV, varicella zoster virus.

patients with acute respiratory tract infection leads to less use of antibiotics without worsening the outcomes.[108]

In a randomized clinical trial of 300 hospitalized patients with lower respiratory tract infection, the use of combined procalcitonin and viral polymerase chain reaction tests was compared with standard care. Both groups had similar antibiotic exposure. However, a lower proportion of patients with a positive viral polymerase chain reaction test and low procalcitonin received antibiotic on discharge as compared with standard care.[109] This study suggests that the result of a viral polymerase chain reaction test has the impact to further influence decision making even after procalcitonin and clinical evolution are factored in. It should be noted, however, that this was a feasibility study and patients with pneumonia were excluded. Additionally, viral polymerase chain reaction test result may not influence antibiotic decision in the absence of a protocol. This was shown in an observational, retrospective study in which only 10.5% of patients had antibiotic discontinued within 48 hours of a positive viral respiratory panel and a low procalcitonin result.[110]

Another randomized clinical trial assessed the effect of point-of-care respiratory viral panel in patients with acute respiratory illness or fever. The study enrolled 720 patients. There was no difference in the primary endpoint, which was the proportion of patients treated with antibiotics. However, the relevance of the primary outcome was impaired because many patients received antibiotics before the results of the point-of-care test. A significantly greater proportion of patients in the point-of-care group received only a single dose of antibiotics (10% vs 3%) or antibiotics for less than 48 hours (17% vs 9%).[111]

In summary, there is weak but mounting evidence that the use of nucleic acid amplification tests have the potential to aid in the decision to discontinue antibiotics in patients with respiratory infection (including pneumonia) but it is more likely to do so if integrated with clinical findings and procalcitonin. Additionally, continuing clinician education will be important to ensure implementation of strategies to minimize antibiotic exposure.

CORTICOSTEROID THERAPY

An exuberant inflammatory response can play a major role in the morbidity and mortality of patients with pneumonia. Corticosteroid has been used as a way of mitigating the exacerbated inflammatory response in these patients. A systematic review has synthesized the results of clinical trials assessing systemic corticosteroids. The clinical trials are mostly small with sample sizes ranging from 30 to 784 patients. Although no statistically significant improvement in mortality was observed in general, corticosteroids led to a reduction in mortality in patients with severe community-acquired pneumonia (risk ratio 0.39; CI 0.20–0.77).[112] Corticosteroids may be particularly beneficial in patients with community-acquired pneumonia and heightened inflammatory state, as demonstrated in a trial that enrolled patients with severe community-acquired pneumonia and a C-reactive protein greater than 150 mg/L.[113] In summary, despite the small sample size of most trials, the weight of evidence currently favors the use of systemic corticosteroids in patients with community-acquired pneumonia admitted to the hospital, particularly in patients with a high inflammatory state and severe pneumonia. Our approach currently is to reserve the use of corticosteroids for patients with community-acquired pneumonia with C-reactive protein greater than 150 mg/L and a lactic acid greater than 4 nmol/L or acidosis with pH <7.30.[114]

The 2009 H1N1 pandemic brought to light the use of systemic corticosteroid in influenza pneumonia. Some studies revealed that 40% to 50% of patients with severe influenza pneumonia received corticosteroid during the pandemic.[115,116] Unfortunately, although corticosteroid appears to be beneficial in patients with severe community-acquired pneumonia, the same does not hold true for patients with influenza pneumonia, a condition in which corticosteroids may actually be detrimental, as demonstrated in the systematic review. In this study, the investigators pooled 10 observational studies (total of 1497 patients) and found that corticosteroid therapy was associated with higher odds of death (OR 2.12; 95% CI 1.36–3.29). Of note, the studies included in the meta-analysis were predominantly conducted during the 2009 H1N1 influenza pandemic and in the ICU setting.[117]

A clinical trial designed to evaluate the effect of systemic corticosteroid in ICU patients with the 2009 H1N1 influenza pneumonia was unable to enroll the planned number of patients, highlighting the difficulties in conducting a clinical trial during a pandemic.[116] A limitation of the observational studies assessing corticosteroid therapy in influenza pneumonia is the possibility of confounding by indication; that is, the possibility that sicker patients are more often prescribed systemic corticosteroid. This has the potential to cause the false impression that corticosteroid therapy leads to worse outcomes in influenza pneumonia. Some studies adjusted for confounding factors, but residual confounding can still occur. In the absence of randomized clinical trials, and in view of the results of observational studies, it is our opinion that currently corticosteroid therapy should not be administered in influenza pneumonia. The effect of corticosteroid in patients with noninfluenza viral pneumonia is unclear.

FUTURE RESEARCH

The advent of nucleic acid amplification tests improved our understanding of the epidemiology of viral infections in pneumonia, and enables an etiologic diagnosis of viral infection in a large proportion of patients with pneumonia. However, one of the downsides of nucleic acid amplifications tests was a relatively long turnaround, limiting its clinical utility. This has been overcome by the development of "point-of-care" polymerase chain reaction tests that have a turnaround time of approximately 1 hour.[118] The assessment of these point-of-care tests in clinical pathways is a promising venue for clinical investigation. As these tests are being rapidly integrated into clinical practice, it is important to study their cost-effectiveness and whether they influence outcomes or decision making.

Ongoing research on antiviral treatment is promising. Just as for bacterial infection, combination therapy has been studied in influenza infection with different goals, such as preventing pathogen resistance,[119,120] mitigating the inflammatory response,[121] or achieving synergy.[122,123] There has been development of new compounds for the treatment of respiratory syncytial virus. These include a fusion inhibitor, which prevents the fusion of respiratory syncytial virus viral envelope with the host cell membrane, and a nucleoside analog, which prevents respiratory syncytial virus replication.[124,125]

SUMMARY

Viral respiratory infection is common in pneumonia and is present in approximately 25% of patients with community-acquired pneumonia. It is also common in immunosuppressed patients, but the latter are susceptible not only to the usual community-acquired respiratory viruses but also to viruses of the Herpesviridae family. Recent data show that respiratory viruses are also identified in hospital-acquired infections. The clinical diagnosis of viral infection is challenging. Clinical prediction rules have been developed for the diagnosis of influenza infection but they showed only modest accuracy. Similarly, radiological studies are nonspecific. In the end, the diagnosis of viral infection relies on the recognition that respiratory viruses are commonly present in pneumonia, and on the systematic performance of viral microbiology studies, particularly nucleic acid amplifications tests. The treatment of influenza pneumonia is currently with a neuraminidase inhibitor. The treatment options for pneumonia caused by other viruses in immunocompetent patients with pneumonia are limited, and the data are largely anecdotal. In immunosuppressed patients with infection by respiratory syncytial virus or a virus of the Herpesviridae family, there are antiviral treatments available. There is ongoing research involved with the development and testing of new treatment strategies both for influenza and noninfluenza viruses.

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