Influenza and Viral Pneumonia

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KEYWORDS

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

KEY POINTS

- 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.
- 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 infections on clinical grounds.
- Patients with influenza pneumonia should be treated with a neuraminidase inhibitor.

INTRODUCTION

Respiratory viral infections cause a 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 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, several devastating pandemics and outbreaks related

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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 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.[3] Influenza A virus is subcategorized into subtypes such as H1N1, H1N2, and H3N2 based on hemagglutinin (H) and neuraminidase (N) composition. 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] Small genetic mutations that influenza undergoes every year are called antigenic drift and are 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, human parainfluenza virus, 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 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) which 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] The coronaviruses contain 2 important structural proteins: membrane protein M, which is expressed in large amounts, and the spike protein S.[13] The latter is a class I viral fusion protein and mediates the entry of the virus into the cell.[19] See **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% CI 21.5%–27.5%; I2 = 92.9%).[20] 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%; I2 = 0.0%).[21] The pooled proportion of viral infection was 44.2% (95% CI 35.1%–53.3%; I2 = 0%) from 2 studies of patients with community-acquired pneumonia admitted to the intensive care unit (ICU) and in which a lower respiratory sample was obtained in more than half of the patients.[22,23] The proportion of dual bacterial and viral infection was 10% (95% CI 8%–11%; I2 = 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.[20] A population-based study from Louisville estimated that 1,591,825 patients are admitted for community-acquired pneumonia each year in the United States.[24] Assuming a prevalence of viral infection of 24.5% among patients hospitalized for community-acquired pneumonia, it is estimated that around 390,000 patients each

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 polypeptides[11]
Human parainfluenza virus	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]

year are admitted to hospitals in the United States for viral community-acquired pneumonia. 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 the majority of immunosuppressed patients infected with a respiratory viral pathogen.[25] 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 allogenic bone marrow transplantation, cytomegalovirus was the most common viral pathogen.[26] Varicella zoster virus reactivation can occur in patients after hematopoietic stem cell transplantation with early series reporting incidences ranging from 22% to 41%[27,28] It is not unusual for the infection to present in a disseminated form in these patients, and pneumonia is one of the complications.[27–29]

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 hospital-acquired pneumonia was established when patients developed clinical findings of pneumonia 48 hours or more after hospital admission. The median time from hospital admission to development of hospital-acquired pneumonia was 20 days. The proportion of viral infection was 36.1% in immunocompromised patients and 11.2% in nonimmunocompromised 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

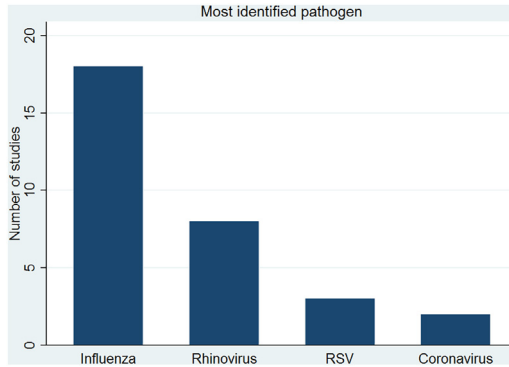

Fig. 1. Number of studies according to most commonly identified viral pathogen. Studies were conducted before the COVID-19 pandemic. (*Data from* Burk M, El-Kersh K, Saad M, Wiemken T, Ramirez J, Cavallazzi R. Viral infection in community-acquired pneumonia: A systematic review and meta-analysis. *Eur Respir Rev.* 2016;25(140):178-188.)

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[155]
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[156]
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[20]
Virus caused a recent infection that prompted a secondary bacterial infection	This occurs particularly with *S pneumoniae* or *Staphylococcus aureus* infection following influenza infection[157] Lag time of 2–4 wk between the viral and bacterial infection[158] Polymerase chain reaction test may remain positive for up to 5 wk after a viral infection[159]

(0.8%), and adenovirus (0.4%).[30] These findings, which could be due to exposure visitors and health-care workers, underscore the importance of infection control measures in hospitalized patients. Conceivably, these findings could also be due exposure before hospital admission.

Pandemics and Outbreaks Before Coronavirus Disease 2019

Since the last century, there have been 5 influenza pandemics: 1918 to 1919 Spanish influenza, 1957 H2N2 Asian influenza, 1968 H3N2 Hong Kong 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 aged younger than 65 years.[31] 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.[32] Subsequently, the etiologic agent of this disease was identified as a novel coronavirus,[33,34] which was named the Urbani strain of severe acute respiratory syndrome-associated coronavirus.[33] In 2012, another novel coronavirus was isolated from a patient with pneumonia in Saudi Arabia.[35] The virus was subsequently named Middle East respiratory syndrome coronavirus.[36] 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.[37] 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 Arabian Peninsula.[38–40] Middle East respiratory syndrome coronavirus can be acquired by exposure to dromedary camels, products from animals, and humans. Cases continue to be identified particularly in Saudi Arabia but also in other countries in the Middle East. However, person-to-person transmission has been limited mostly to health-care facilities. As of November of 2022, there had been 2600 reported cases of Middle East respiratory syndrome coronavirus.[41]

Influenza

The incidence of influenza can vary substantially in different seasons. For example, the influenza activity was lower in the 2021 to 2022 compared with other seasons before

the coronavirus disease 2019 (COVID-19) pandemic. In the 2021 to 2022 season, it is estimated there were 101,262 (95% CI: 82,653–185,191) admissions and 4601 (95% CI: 3769–20,814) deaths associated with influenza in the United States. Adults aged 65 years or older accounted for 51% of the hospitalizations and 83% of the deaths associated with influenza.[42]

Different studies showed that approximately one-third of hospitalized patients with laboratory-confirmed influenza have pneumonia.[43–45] In a study that included 4765 patients hospitalized with influenza, those with pneumonia were older 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 (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]).[44] 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, milligram per deciliter (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]).[45]

During an influenza season, the attributed mortality to pneumonia and influenza in the United States ranges from 5.6% to 11.1%.[46] 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 ICU admission (27% vs 10%), mechanical ventilation (18% vs 5%) and to die (9% vs 2%).[44] See **Fig. 2**.

Severe Acute Respiratory Syndrome Coronavirus 2

COVID-19, the disease caused by the coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first recognized in a cluster of patients in December of 2019. It then spread throughout the world and caused a devastating pandemic. As

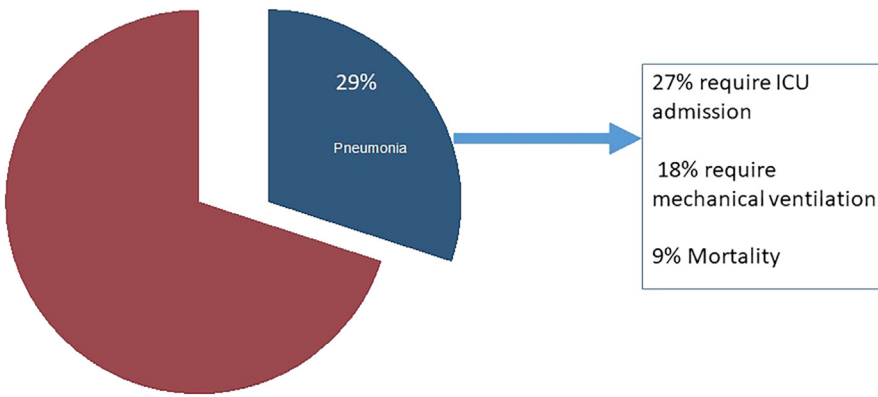

Fig. 2. Proportion of pneumonia and associated outcomes in patients admitted to the hospital with influenza infection. (*Data from* Garg S, Jain S, Dawood FS, et al. Pneumonia among adults hospitalized with laboratory-confirmed seasonal influenza virus infection-united states, 2005-2008. *BMC Infect Dis*. 2015;15:369-015-1004-y.)

of September of 2023, there have been close to 7 million deaths worldwide caused by COVID-19.[47] SARS-CoV-2 undergoes periodic mutations, which lead to different variants over time: Alpha, Delta, and Omicron. Currently, the variant predominantly circulating is the Omicron.[48] Clinical manifestations and severity of COVID-19 differ with each variant predominance, which may reflect not only the changing variant virulence but also the effects of increasing immunity in the population and restructuring of health care.[49] The risk of hospitalization during the Omicron period has been 1.9%.[50] For patients hospitalized primarily for COVID-19, the mortality risk was 13.1% in the early Omicron period (January–March 2022) and 4.9% in the later Omicron period (April–June 2022).[51] Risk factors for higher mortality include increasing age, presence of underlying medical conditions, and disability.[52] Racial and ethnic minorities have been disproportionally affected by COVID-19, likely a reflection of worse living conditions, less access of health care, and jobs that are often frontline or essential.[53] Unvaccinated status is also a major risk factor for mortality. During the late Omicron BA.4/BA.5 variant period (September 18–December 3, 2022) in the United States, unvaccinated persons had a mortality rate ratio that was 5 times higher compared with those who received monovalent vaccines only and 14 times higher compared with those who received bivalent booster.[54]

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 infection per 100 person-months in high-risk adults and 0.9 in healthy elderly subjects.[55] 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 aged 50 to 64 years and 86.1 (95% CI: 37.3–326.2) for patients aged 65 years or older. In contrast to influenza-associated hospitalizations, the rates of respiratory syncytial virus-associated hospitalizations were relatively similar across the years.[56] In a cohort of 1388 hospitalized adults aged 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.[55]

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.[57]
- Rhinovirus tends to occur more often in the early fall or spring.[58]
- 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 CAP conducted in the United States.[2]

Common human coronavirus

- Occurs more commonly in the winter and follows a seasonal pattern that resembles that of influenza.[59]
- Coronaviruses HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 have ubiquitous circulation and are a usual etiology of common cold.[37]
- Coronaviruses have also been commonly associated with lower respiratory tract symptoms.[59]
- Adult hospitalized patients with coronavirus infection are often immunocompromised, and pneumonia is a common occurrence.[60]
- 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.[37]

Adenovirus

- Adenovirus is a common cause of upper respiratory tract symptoms and conjunctivitis.[61]
- 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.[62,63]
- 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.[64]
- No clear seasonality although cases may spike in some months.[65]
- Several outbreaks caused by adenovirus have been reported. Some examples include reports of outbreaks in military personnel,[66] psychiatric care facility,[67] and ICU.[68]

Parainfluenza

- Most infections are caused by parainfluenza 1 and 3.[69] Parainfluenza 2 is less commonly identified, and parainfluenza 4 is a rare cause of respiratory infection.
- In adults, influenza-like symptoms are a common manifestation of parainfluenza infection.[70] In children, common presentations are croup and bronchiolitis.[69]
- In a population-based study of adults hospitalized for lower respiratory tract infection in 2 counties in Ohio, parainfluenza-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.[71]

Metapneumovirus

- It has been identified in 4.5% of acute respiratory illnesses of adults prospectively followed as outpatient.[72]
- It has been identified in 4% of patients with community-acquired pneumonia.[73]
- 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.[72]

- Mean age in a series of community-acquired pneumonia and metapneumovirus infection: 62 years.[73]
- In the outpatient setting, cough and nasal congestion are the most common symptoms.[72]
- In patients with metapneumovirus infection and pneumonia, common symptoms are cough with sputum production, dyspnea, and fatigue.[73]

Human bocavirus

- Commonly identified in symptomatic and asymptomatic children but it seems to be a less common cause of respiratory symptoms in adults.[74]
- Human bocavirus infection is more common in the winter.[75]
- Common clinical presentations include upper respiratory tract symptoms, bronchiolitis, and pneumonia.[76] Cases of encephalitis have been reported.[77,78]
- It has been detected in acute respiratory illness of adults with immunosuppression and chronic lung disease.[79,80]
- A study showed that it can be often identified in the sinus tissue specimens of adult patients with chronic sinusitis.[81]

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.[82] 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.[83] 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 greater than 37.8°C make influenza very unlikely in patients presenting with influenza-like illness outside an influenza epidemic but has a lesser impact on the likelihood of influenza if the same patient presented during an epidemic. However, the presence of these symptoms during an epidemic substantially increases the probability of influenza but has a lesser impact outside of an epidemic.[84]

Several 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.[85] More recent studies used a prospective design and viral polymerase chain reaction test as the reference standard. A prospective study enrolled 100 patients with influenza-like illness who presented to 3 different clinics. Viral polymerase chain reaction test was used for the diagnosis of influenza. The accuracy of several symptoms was tested. On multivariate analysis, only cough and temperature remained significant predictors of influenza.[86] 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.[82] 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 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.[87] 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 considering the pretest probability.[88] See **Fig. 3**. See **Table 3** for a summary of these studies.

Overall, the above 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 is 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.[87] 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 because a high possibility in the differential diagnosis. This is line with recent guidelines that recommend different testing strategies according to whether there is circulation of seasonal influenza A and B.[89] 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.[90]

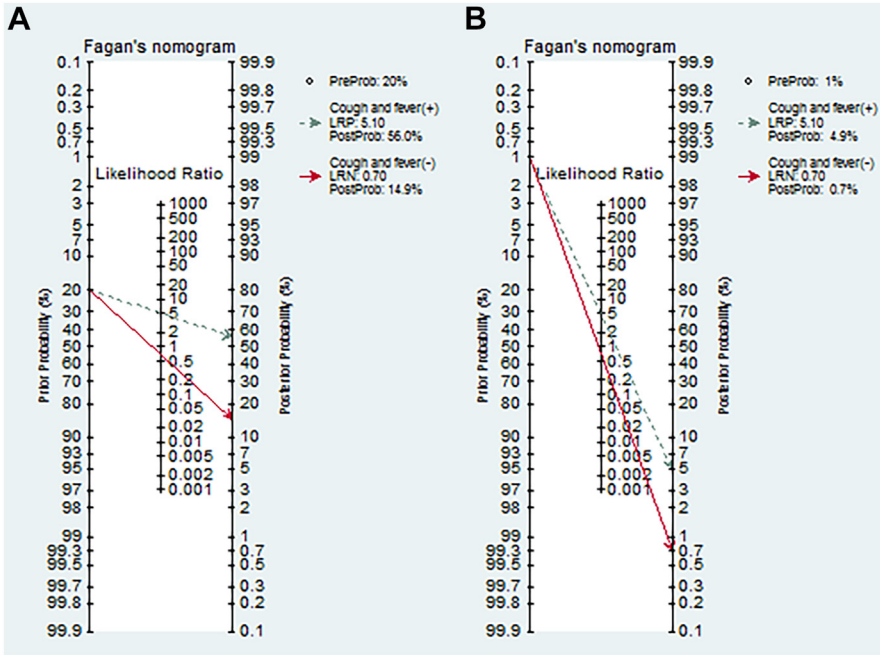

Fig. 3. Probability of influenza according to presence of combined cough and fever in patients presenting during influenza season (*A*) and outside the influenza season (*B*). (Data for likelihood ratios from Stein J, Louie J, Flanders S, et al. Performance characteristics of clinical diagnosis, a clinical 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):412-419.)

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,[86] 2000	Prospective cohort	Patients presenting to 3 outpatient clinics	100	Flu-like illness of <72h 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,[82] 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% to 43%) Spec of 92% (95% CI 87% to 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% to 54%) Spec of 92% (95% CI 87% to 95%) PLR of 5.1 (95% CI 2.7–9.6) NLR of 0.7 (95% CI 0.5–0.8)

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Table 3
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Author, Year	Design	Setting	Sample	Inclusion Criteria	Reference	Results
Dugas et al,[87] 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) *Influenza-like illness (fever $\geq$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: NLR, negative likelihood ratio; NPV, negative predictive value; PCR, polymerase chain reaction; PLR, positive likelihood ratio; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

The clinical manifestations and prognosis of COVID-19 vary according to the host immune status, the SARS-CoV-2 variant and subvariant, and age. In a community study, representative symptoms of COVID-19 in vaccinated persons during the Omicron variant period included runny nose (76.5%), headache (74.7%), sore throat (70.5%), sneezing (63%), persistent cough (49.8%), hoarse voice (42.6%), joint pain (41.2%), fever (29.3%), brain fog (24.9%), diarrhea (16.7%), loss of smell (16.6%), and dyspnea (4.9%). Symptoms such as loss of smell, fever, and brain fog were less common when compared with prior Delta variant period. Both the median duration of acute symptoms (6.87 days vs 8.89 days, $P<.01$) and the risk of hospitalization (1.9% vs 2.6%, $P = .03$) were lower in the Omicron period compared with the Delta period.[50]

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 seem 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 greater than 39°C was only present in 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.[91] 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%), fever (61%), and runny nose (58%). On physical examination, the most common findings were wheezing (53%), rhonchi (46%), and crackles (40%).[92]

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.[93] The usual clinical manifestations of pneumonia, including fever greater than 37.8°C, heart rate greater than 100 beats per minute, crackles, and decreased breath sounds,[94] 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 cause 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.[91,95–98] Bilateral involvement is fairly common, and some series in influenza pneumonia show that bilateral involvement is slightly more common than unilateral involvement.[95] However, other series in respiratory syncytial virus or coronavirus pneumonia show that unilateral involvement is more common.[91,96] Pleural effusions are not usual but have been reported.[98] 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, can also be present.[97] See **Figs. 4** and **5**.

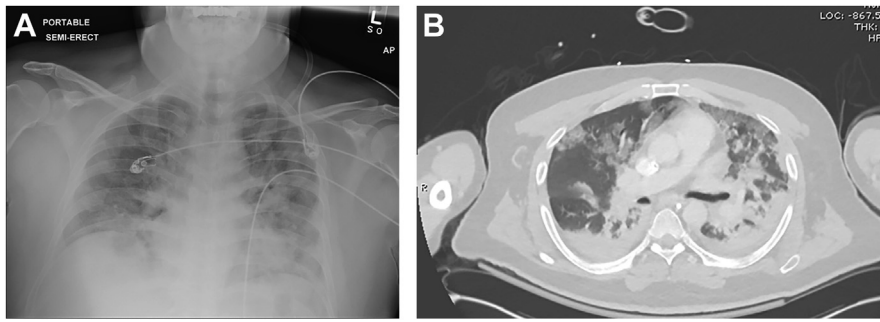

Fig. 4. Chest radiograph and computed tomography of the chest of a 42-year-old male patient admitted with pneumonia and 2009 H1N1 influenza infection leading to acute respiratory failure. Chest radiograph (*A*) reveals diffuse consolidation, and the computed tomography of the chest (*B*) reveals bilateral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

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 which a viral pathogen has been identified by oropharyngeal swab, the demonstration of patchy ground-glass opacities in the lung is suggestive of a viral pneumonic infiltrate. Additionally, the radiological findings on chest CT have had a prominent role both in corroborating the diagnosis and the prognostication of patients with COVID-19. The typical radiological manifestations of COVID-19 include ground-glass opacities that are peripheral and predominate in the lower lobes.[99]

PATHOGEN-DIRECTED THERAPY

Influenza

The 3 main classes of antiviral drugs for the treatment of influenza include neuraminidase inhibitors, cap-dependent endonuclease inhibitors, and adamantanes.[7,100,101] Influenza viruses infect cells through the binding of its surface glycoprotein hemagglutinin to the

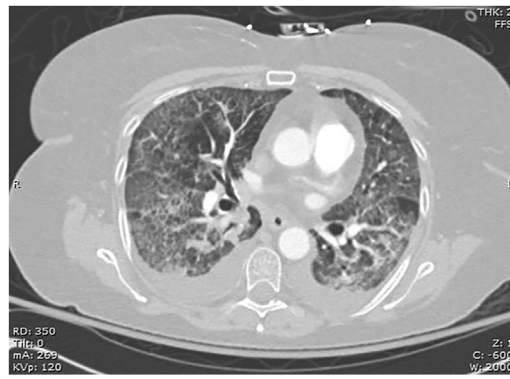

Fig. 5. Computed tomography of the chest revealing diffuse ground-glass opacities and small bilateral pleural effusion in a 62-year-old female patient with respiratory syncytial virus infection who developed pneumonia and acute respiratory distress syndrome.

sialic acid receptor. The attached virus is then released into the cells by another surface glycoprotein, neuraminidase, which is the target of neuraminidase inhibitors.[102] The cap-dependent endonuclease inhibitor baloxavir marboxil is hydrolyzed into an active form, baloxavir acid. The latter inhibits the endonuclease responsible for cleaving the mRNA bound to a cap-binding domain.[103] The cleavage of the bound mRNA is an important step in influenza virus transcription. The adamantanes, which include amantadine and rimantadine, block the M2 protein, a membrane protein with ion channel activity.[104] 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, and the cap-dependent endonuclease inhibitor baloxavir marboxil. The adamantanes are not recommended for the treatment of influenza because of high resistance of influenza A against these drugs.[105]

Several clinical trials 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% to 1.49%]). For the assessment of hospitalization prevention in adults with influenza, 7 studies were pooled, which 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]; $P<.001$]).[106] 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 seem ill. For instance, studies that enrolled patients with immunosuppressive conditions such as HIV infection or malignancy were not included in the meta-analyses. The inclusion criterion for the pooled studies was the presence of influenza-like-illness rather than pneumonia. Additionally, only one 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 authors 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 (odds ratio: 0.23 [CI: 0.13–0.43]).[107] 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, which were not and likely will not be addressed by clinical trials.

The efficacy of intravenous peramivir was evaluated in a trial that included 300 previously healthy adults aged 20 to 64 years with the onset of symptoms within the

48 hours before enrollment and a confirmed diagnosis of influenza. Patients were randomized to 300 mg of peramivir, 600 mg of peramivir, or placebo. The primary endpoint was time to alleviation of symptoms. The time to alleviation of symptoms was significantly lower on the groups that received peramivir compared with placebo: 59.1 hours (95% CI 0.9–72.4) in the group that received 300 mg of peramivir, 59.9 hours (95% CI 54.4–68.1) in the group that received 600 mg of peramivir, and 81.8 hours (95% CI 68.0–101.5) in the group that received placebo.[108]

The efficacy of inhaled zanamivir was evaluated in a trial that included 262 previously healthy patients with confirmed influenza. The primary endpoint was time to alleviation of major symptoms of influenza. The mean time to alleviation of symptoms was shorter in the inhaled zamamivir group compared with the placebo group (5.5 vs 6.3 days; $P = .05$).[109]

The efficacy of baloxavir was demonstrated in a phase 3 clinical trial that enrolled 1064 patients with acute uncomplicated influenza. The comparison was to placebo and oseltamivir. The primary endpoint was alleviation of symptoms. The median time to alleviation of symptoms with baloxavir was shorter when compared with placebo (65.4 hours vs 88.6 hours, $P < .001$) and similar when compared with oseltamivir (53.5 hours vs 53.8 hours).[101]

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. For these patients, the first choice antiviral agent is oseltamivir given the relative paucity of data for inhaled zanamivir and intravenous peramivir.[105] 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. In the absence of a sensitive point-of-care polymerase chain reaction, clinicians have to decide whether to initiate empiric treatment of 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.[110,111] 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.[112] See **Fig. 6**.

Coronavirus Disease 2019

The treatment can be divided into outpatient and inpatient. In the outpatient setting, treatment should be selected for those at high risk of disease progression.[113] Factors and conditions leading to high risk of disease progression include older age (especially >50 years old), racial and ethnic minorities, residence in long-term care facility, underlying medical problems (eg, chronic lung and heart diseases), and immunocompromised status.[52] In the outpatient setting, the preferred treatment is ritonavir-boosted nirmatrelvir, which is an oral antiviral agent that inhibits the SARS-CoV-2-3CL protease. The inhibition of the cytochrome P450 3A4 by the ritonavir component leads to several interactions between ritonavir-boosted nirmatrelvir and other medications. Clinicians should review the patient's medication list, including prescribed and nonprescribed medications, before initiating treatment with ritonavir-boosted nirmatrelvir. If potential interactions are identified, strategies such as dose reduction or temporary discontinuation of a chronic medication while patient takes ritonavir-boosted nirmatrelvir, can be implemented. Second choice is remdesivir,[113,114] which is an intravenous antiviral drug that inhibits the RNA-dependent RNA polymerase of coronaviruses, thereby stopping the replication and transcription of the coronavirus genome.[115] The intravenous route

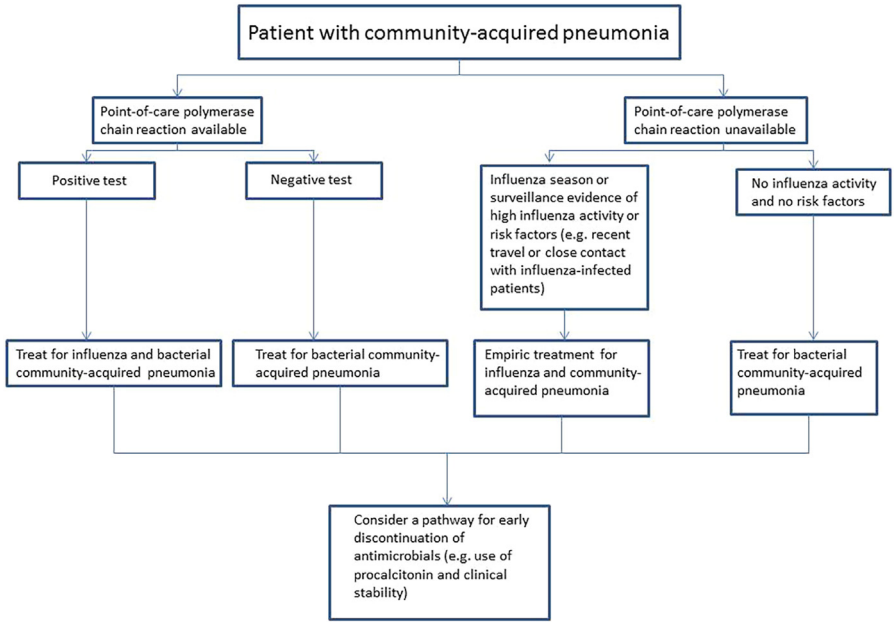

Fig. 6. Treatment approach in patients presenting with community-acquired pneumonia.

of administration can pose logistic barriers to the widespread use of this medication in the outpatient setting, particularly in times of surge of COVID-19 transmission. An alternative medication is molnupiravir, an oral antiviral agent that is converted from a ribonucleoside into N-hydroxycytidine. The latter form inhibits SARS-CoV-2 replication by biding to its genome. The modest efficacy of molnupiravir has led the National Institutes of Health to recommend molnupiravir only when the other options are not available or feasible to use.[113,114] Data from studies in animals show molnupiravir has the potential to cause fetal harm. The use of molnupiravir in pregnancy is not recommended. Concern for fetal harm with molnupiravir mandates pregnancy test in women of childbearing potential and contraception during treatment and for 4 days after treatment completion. Men should use contraception during treatment and for 3 months after treatment completion if they are sexually active and have a female partner of childbearing potential.[114,116]

In hospitalized patients, the treatment options of COVID-19 depend on the severity of the disease. In patients hospitalized for COVID-19 who have infiltrate on chest imaging or tachypnea or oxygen saturation less than 94%, the use of remdesivir led to a faster recovery. Remdesivir seems mainly beneficial early in the disease process and did not lead to better outcomes in patients on mechanical ventilation or extracorporeal membrane oxygenation.[117] The use of systemic corticosteroid leads to better outcomes in patients hospitalized for COVID-19. The largest trial assessing systemic corticosteroid in patients with COVID-19 enrolled 6425 patients. Dexamethasone led to a reduction in mortality in those requiring oxygen therapy or mechanical ventilation. The mortality benefit was more pronounced in those requiring mechanical ventilation.[118] Other immunosuppressive medications such as the interleukin-6 inhibitor tocilizumab and Janus kinase inhibitors (eg, Baricitinib) have improved outcomes in hospitalized patients with COVID-19[119,120] and are currently recommended for patients who deteriorate despite therapy with dexamethasone.[113]

Other Respiratory Viruses

For the treatment of pneumonia caused by respiratory viruses other than influenza and SARS-CoV-2, defining whether the patient is immunocompetent or 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 nonimmunocompromised patients.[121,122] 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 of pneumonia caused by viruses of the Herpesviridae family in immunocompetent hosts has been reported in severe cases.[123,124] In pregnant women with varicella-zoster-virus pneumonia, the mortality is high, and treatment with intravenous acyclovir is indicated.[125]

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.[126] For cytomegalovirus pneumonia, treatment includes intravenous ganciclovir.[127] The addition of cytomegalovirus immunoglobulin to ganciclovir seems to lead to improved survival according to a case series.[128] An alternative treatment of cytomegalovirus pneumonia is intravenous foscarnet.[129] For the treatment of varicella pneumonia, the indicated treatment is intravenous acyclovir.[130] Similarly, herpes simplex virus pneumonia is treated with intravenous acyclovir.[131] The evidence for the use of these therapies is weak and comes in the form of observational studies. See **Fig. 7**.

DISCONTINUATION OF ANTIBIOTIC THERAPY

The identification of a viral pathogen in pneumonia does not always warrant deescalation or discontinuation of empirical antibiotics because dual bacterial-viral infection can occur. The clinical context and the identified viral pathogen should be factored in the decision to initiate and deescalate or discontinue empirical antibiotic. The prevalence of dual bacterial-viral infection varies according to the virus. For example, coinfection and superimposed infections are common with influenza. In a study that included 645 critically ill patients with 2009 influenza A (H1N1) virus infection, coinfection occurred in 17.5% of the patients. Of these, more than half were due to *Streptococcus pneumoniae*.[132] However, coinfection on presentation is not as common with SARS-CoV-2. A pooled analysis found that 7% of patients hospitalized with COVID-19 have bacterial coinfection.[133] Another pooled analysis found that on presentation bacterial coinfection was present in 5.9% (95%CI 3.8%–8.0%) in all hospitalized patients and 8.1% in critically ill patients (95%CI 2.3–13.8).[134] Bacterial coinfection is thus infrequent in SARS-CoV-2 infection, and for most patients diagnosed with COVID-19 pneumonia, empirical antibiotic therapy is not warranted on presentation.

The recognition that dual bacterial-viral may occur seems to be reflected in clinical practice. In an observational study before the COVID-19 pandemic, 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.[135] However, 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 the use of procalcitonin to guide initiation and discontinuation of antibiotic in patients with acute respiratory tract infection leads to less use of antibiotics without worsening the outcomes.[136]

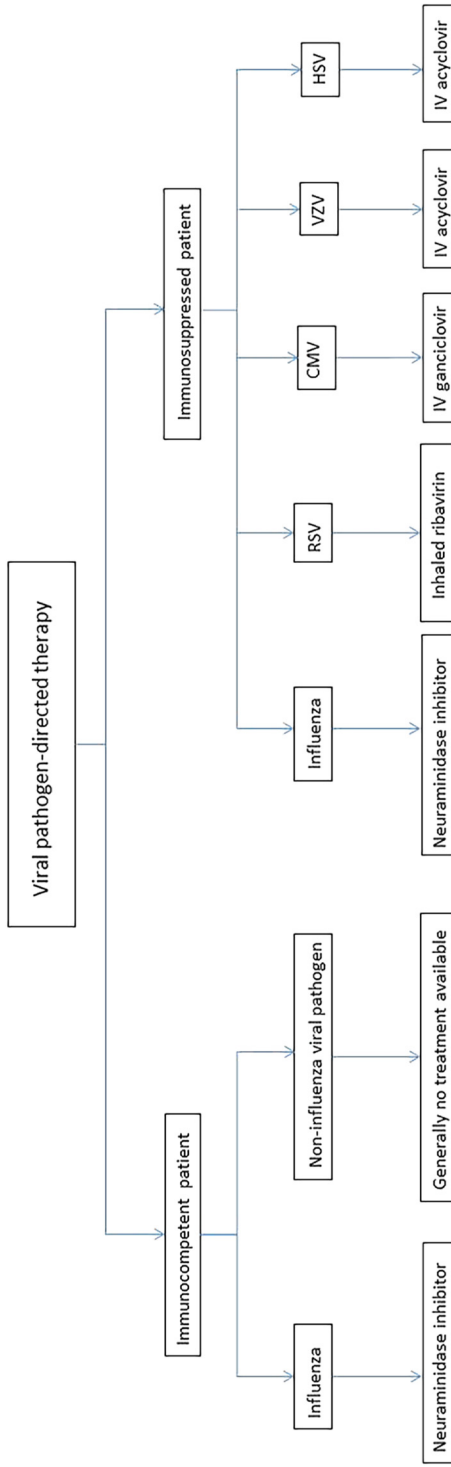

Fig. 7. Viral pathogen-directed therapy. CMV, cytomegalovirus; HSV, herpes simplex virus; RSV, respiratory syncytial virus; VZV, varicella-zoster virus.

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.[137] 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.[138]

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%).[139]

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. Antibiotic stewardship programs can play an important role in minimizing inadequate antibiotic prescriptions for hospitalized patients through monitoring of emerging information and update of guidelines, revision of the relevant literature, and education of treating clinicians.[140]

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. Recently, 2 large clinical trials that addressed systemic corticosteroid in severe CAP have been published. In one trial that included 795 patients, the use of dexamethasone for patients with CAP admitted to the ICU lead to a 28-day mortality benefit compared with placebo (6.2%; 95% CI, 3.9–8.6 in the vs 11.9%; 95% CI, 8.7–15.1; $P = .006$). This study excluded patients with influenza.[141] In another trial that included 584 patients with severe CAP, the use of methylprednisolone, as compared with placebo, did not lead to a significant improvement in 60-day mortality (16% in the methylprednisolone group vs 18% in the placebo group; $P = .61$) but the systemic corticosteroid was initiated later in this trial. This study did not exclude patients with influenza but only 4% of the patients tested positive for influenza.[142]

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.[143,144] Unfortunately, although corticosteroid seems to be beneficial in patients with severe CAP, the same may not hold true for patients with influenza pneumonia, a condition in which

corticosteroids might be detrimental as demonstrated in the systematic review. In this study, the authors 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.[145]

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.[144] 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.

As previously discussed, systemic corticosteroid leads to better outcomes in patients hospitalized for COVID-19.[118] The effect of corticosteroid in patients with non-influenza and non-SARS-CoV-2 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 enabled 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 turn around, 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.[146] 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. A potential downside of polymerase chain reaction test is that persistent viral shedding leading to positive result occurs in some patients despite symptom resolution and no evidence of contagiousness.[147]

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,[148,149] mitigating the inflammatory response,[150] or achieving synergy.[151,152] 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.[153,154]

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. Treatment of COVID-19 is also available and differs according to the setting (inpatient vs outpatient). 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 non-influenza viruses.

DISCLOSURE

R.Cavallazzi: Site investigator for a study that aims to assess the safety of a monoclonal antibody for community-acquired bacterial pneumonia.

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