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What is the Role of Respiratory Viruses in Community-Acquired Pneumonia?

What is the Best Therapy for Influenza and Other Viral Causes of Community-Acquired Pneumonia?

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KEYWORDS

- Respiratory viruses • Respiratory viral infections • Influenza • Antiviral agents
- Viral pneumonia

KEY POINTS

- Respiratory viruses, particularly influenza and RSV, are a common cause of CAP.
- Respiratory viruses are detected in 45% to 75% of children and 15% to 54% of adults hospitalized with CAP.
- Coinfection with viruses and bacteria is common: 22% to 33% of children and 4% to 30% of adults hospitalized with CAP.
- The role of *Streptococcus pneumoniae* relative to viral causes of CAP may have decreased because of widespread use of pneumococcal conjugate vaccines in children.
- Neuraminidase inhibitors reduce ICU admission and mortality among patients hospitalized with influenza, including those with pneumonia, and should be started when influenza is suspected.
- Differentiating viral CAP from mixed infection and bacterial CAP remains challenging, but better approaches could reduce antibiotic overuse.

Respiratory viruses including influenza have long been appreciated as a cause of community-acquired pneumonia (CAP), particularly among children, people with serious medical comorbidities, and military recruits. Recent advances in molecular virology have led to the discovery of previously unrecognized respiratory viruses, including human metapneumovirus (hMPV), parainfluenza virus (PIV) 4, human coronaviruses (HCoV) HKU1 and NL-63, and human bocavirus. Polymerase chain reaction (PCR)-based testing has allowed detection of newer agents and improved the ability to detect old viral infections, such as influenza virus and rhinovirus (**Table 1**).

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Common	Less Common or Predominantly in Specific Hosts or Settings
Respiratory syncytial virus	Measles
Influenza virus A and B	Cytomegalovirus
Human metapneumovirus ^a	Varicella zoster virus
Adenovirus	Herpes simplex virus
Parainfluenza virus 1, 2, 3, and 4 ^a	Epstein-Barr virus
Human coronavirus types 229e, OC43, HKU1, ^a and NL-63 ^a	Hantavirus
Rhinovirus ^a	Enterovirus
Bocavirus ^a	Parechovirus ^a
	Severe acute respiratory syndrome coronavirus

^a Those recently discovered or recently appreciated as associated with pneumonia. The role of all bocavirus and parechovirus has not been clearly established.

Widespread use of newer vaccines against *Streptococcus pneumoniae* and *Haemophilus influenzae* has changed the epidemiology of childhood and adult pneumonia. These changes have led to recognition of the greater and more widespread role of respiratory viruses in CAP in all age groups. Although not addressed in this article, respiratory viruses are a very important cause of severe pneumonia and respiratory failure in patients who are immunocompromised, particularly recipients of hematopoietic stem cell transplant.^{1,2}

One challenge is that respiratory viruses in patients with CAP can be the sole cause of a viral pneumonia (often referred to as primary viral pneumonia); can be present as a coinfection (virus- bacteria or virus-virus); and can act as a predisposing factor to facilitate or worsen bacterial pneumonia. Moreover, detection of some viruses in the upper respiratory tract of asymptomatic patients is relatively common and therefore may indicate convalescent shedding or asymptomatic infection.³

There are several critical questions that are not fully answered. What is the role of individual viruses in pneumonia? What is the prevalence of specific viruses among patients of CAP? Which patients are most likely to have viral pneumonia? What does the detection of a respiratory virus from a patient with CAP tell about the cause? How should viral detection effect clinical management and when can antibiotics be avoided or stopped?

SPECIFIC VIRUSES

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is a paramyxovirus that causes upper respiratory tract infection (URI) and bronchiolitis in children but is also associated with a substantial proportion of CAP among children. RSV has been detected in 3% to 31% of children hospitalized with CAP. The incidence and severity varies with age; younger children are generally more likely to have RSV-associated pneumonia and are the most severely affected. Important studies in the mid-1990s demonstrated that RSV was an important cause of CAP in adults.^{4,5} Dowell and coworkers⁵ studied noninstitutionalized adults admitted to two Ohio hospitals and found that 53 (4.4%) of 1195 adults admitted during the RSV seasons and 4 (1%) of 390 in the off-season had serologic evidence of RSV infection. RSV has been identified in 4% to 7% of adults with CAP.⁶⁻⁹

RSV-associated CAP seems to be more common and severe among older adults.¹⁰ Using viral surveillance, hospitalization, and mortality data, Zhou and colleagues¹¹ from the Centers for Disease Control and Prevention (CDC) estimated that the rate of hospitalization for RSV for persons older than 65 was 86 per 100,000 persons per year, compared with a hospitalization rate for influenza of 309 per 100,000 in that age group. RSV was listed in the discharge codes in fewer than 2% of the hospitalizations for RSV among older persons, suggesting marked underrecognition. RSV causes substantial mortality. Thompson and colleagues¹² estimated that during the 1990s, RSV was associated with an average of more than 11,000 deaths each year in the United States. Most of these deaths were in persons older than 65.

In studies comparing adults with RSV and pneumonia with those with influenza or other causes, wheezing is more common,⁵ but clinical characteristics cannot reliably differentiate those with RSV.¹³

Influenza Virus

Pneumonia was recognized as a complication of influenza during the pandemic of 1918 to 1919, long before the virus was identified. During the “Asian influenza” pandemic of 1957 to 1958, Louria and coworkers¹⁴ and others codified the concept that influenza could cause a primary viral pneumonia or lead to bacterial pneumonia with each having distinct pathologic appearance. Animal studies are beginning to yield insights into the nature of the complex and synergistic interaction in the lung between influenza and *S pneumoniae* and *Staphylococcus aureus*,^{15,16} which is thought to be responsible for much of the mortality during pandemics.¹⁷

Among patients hospitalized with influenza, radiographic pneumonia has been reported in 16% to 55%, with lower rates in studies among children.^{18–21} Patients admitted with influenza who have pneumonia are more likely to be admitted to the intensive care unit or die.^{19,22} Differentiating viral pneumonia caused by influenza from bacterial coinfection or superinfection is not always clear. The classical presentation of superinfection is biphasic, with typical influenza-like illness that begins to resolve over several days followed by acute deterioration with the development of chest pain and new infiltrates, and bacteriologic evidence of infection, but this represents a minority.

Human Metapneumovirus

Dutch researchers first described hMPV in 2001 in children with bronchiolitis.²³ Subsequent studies identified it as an important cause of acute respiratory infections in children and adults, with a worldwide distribution.^{24,25} hMPV is a paramyxovirus in the subfamily pneumovirinae that includes RSV, but hMPV is most closely related to avian pneumovirus. In temperate climates, infection occurs predominantly in the winter months, and there is significant year-to-year variation. Clinical manifestations of hMPV infection include asymptomatic infections, colds, febrile seizures, bronchiolitis, asthma exacerbations, chronic obstructive pulmonary disease (COPD) exacerbations, pneumonia, and respiratory failure. Symptomatic infection occurs in all age groups,^{24–30} but pneumonia is most commonly seen among younger children, older adults, and those with underlying medical conditions.^{23,31} In prospective studies of adults hospitalized in Rochester, New York, and Nashville, Tennessee, with acute respiratory illness, the prevalence of hMPV infection and clinical characteristics of patients were similar to patients with influenza and RSV.^{29,30} Using prospective surveillance in central Tennessee, Widmer and coworkers³⁰ estimated the incidence of hospitalization for hMPV among persons older than 65 years was 220 per 100,000 compared with 254 per 100,000 and 123 per 100,000 for RSV and influenza virus, respectively.

Adenovirus

Shortly after the discovery of adenovirus in 1953, it was recovered from military personnel with acute respiratory disease, thus making it one of the first viruses clearly linked with pneumonia.³² Adenoviruses are lytic nonenveloped DNA viruses, which contrasts with most respiratory viruses that are RNA viruses. More than 50 serotypes have been described. Adenoviruses cause a wide variety of infections, including conjunctivitis, epidemic keratoconjunctivitis, pharyngitis, URI, pneumonia, meningitis, hepatitis, and gastroenteritis. Conjunctivitis, pharyngitis, or rash may be present with pneumonia and provide a clue to the cause, but this is uncommon. Serotypes differ in tissue tropism and their tendency to cause severe respiratory disease, although the mechanisms for this are poorly understood. Severe respiratory disease is associated with adenovirus serotypes 5, 7, 14, and 21. Historically, adenovirus pneumonia has been primarily documented among children; immunocompromised adults³³; and outbreaks in hospitalized patients^{34,35} and healthy adults in closed settings, such as military recruits.^{36–38} However, severe disease can occur in immunocompetent adults.³⁹ The genetic diversity of adenoviruses has limited the sensitivity of culture and PCR-based diagnostics, so the true rate of adenoviral pneumonia may be underestimated.

Adenovirus vaccine was used in the US military for more than two decades, resulting in a marked decrease in adenoviral pneumonia among recruits. When the sole manufacturer ceased production there was a marked resurgence in adenoviral disease.^{36,40} Beginning in 2005, a new variant of serotype 14 emerged as a cause of severe lower respiratory tract disease in immunocompetent adults in the community⁴¹ and in the military.⁴²

Parainfluenza Virus

PIVs are paramyxovirus that are antigenically divided in to four serotypes (PIV1–4).⁴³ They are common causes of acute respiratory infections including URI, croup, bronchiolitis, and pneumonia.^{44,45} Seasonal outbreaks occur in the fall and spring. Most infections are mild, but in a prospective surveillance study of children in three regions, Weinberg and coworkers⁴⁵ found that PIVs were associated with an average annual rate of 100 hospitalizations per 100,000 persons younger than 5 years or roughly 23,000 hospitalizations per year. Similar population-based estimates for adults are not available. In one study, Marx and coworkers⁴⁶ used serology to detect PIV1 from 2.5% of 721 and PIV3 from 3.1% of 705 adults hospitalized with lower respiratory tract infection. However, they predominantly tested patients hospitalized during “the parainfluenza season.”

Most pneumonia associated with PIVs occurs in infants, young children, and immunocompromised hosts. However, PIV has been detected in 0% to 8% of adults with CAP.^{6–9,47,48} PIV3 is more commonly associated with pneumonia than other types, although fewer studies have systematically sought PIV4.

Non-Severe Acute Respiratory Syndrome Coronaviruses

HCoV 229E and OC43 have been long recognized as causes of viral URI and were linked to pneumonia in children and immunocompromised adults.⁴⁹ Two novel HCoV, NL63⁵⁰ and HKU1,⁵¹ were identified in the past decade. All four HCoV show distinct winter seasonality. They are associated with upper and lower respiratory tract infections in all age groups.^{52–54} In a prospective study from Scotland that included a control group of patients with no respiratory symptoms, HCoV HKU1, HCoV NL63, and HCoV OC43 were isolated significantly more often from patients with lower

respiratory tract infections than from control subjects, supporting the etiologic role of these viruses.⁵² In a prospective study of hospitalized patients with pneumonia in Thailand, coronaviruses were detected by PCR in 5.9% of 734 patients in the first year of the study. However, in the second year when a control group was included, coronaviruses were detected in only 1.8% of 1156 patients and were detected in 2.1% of control subjects.⁵⁵ Thus, this study did not demonstrate an epidemiologic association of coronaviruses with pneumonia, but it is unclear if this was caused by variation in intensity of the season. In a prospective study of patients with severe pneumonia undergoing bronchoalveolar lavage about half of whom were transplant recipients, coronaviruses were detected in 5.8%, mostly as the sole pathogen.⁵⁶ Thus, the role of coronaviruses in pneumonia has not been completely clarified but it seems clear that they cause some cases of CAP in normal hosts and cause severe pneumonia in transplant patients.

Rhinovirus

Rhinoviruses are among the most common cause of respiratory infections in people of all ages. However, elucidating their role in pneumonia has proved complex.⁵⁷ The use of PCR and sequencing has greatly enhanced detection of rhinoviruses in severely ill patients and led to the recognition of a third rhinovirus species, genogroup C.⁵⁸ Many rhinovirus PCR assays also detect other picornaviruses, particularly enterovirus, which complicates the literature. Rhinoviruses were long known to cause common colds, otitis media, asthma exacerbations, and exacerbations of COPD, but lower respiratory tract infections were thought to be rare, perhaps because of the belief that rhinoviruses grow poorly at 37°C. Recent data clearly demonstrate that rhinoviruses can replicate at body temperature⁵⁹ and infect cells of the lower respiratory tract.⁶⁰ Rhinovirus infection of respiratory endothelium induces potent inflammatory responses, but in contrast in several other respiratory viruses does not induce cell lysis.⁶¹

Studies using PCR consistently identify rhinoviruses in nasopharyngeal or pharyngeal specimens from children and adults with lower respiratory tract infections.^{62–65} Rhinovirus has also been detected in 4% to 45% of children^{66–70} and 2% to 17% of adults with CAP (**Tables 2 and 3**).^{6–9,47,48} Determining whether rhinovirus has a causal role in any single case of CAP is particularly problematic because of the high rate of codetection of rhinovirus with other viruses and bacteria, and because of the detection of rhinovirus in asymptomatic patients, representing convalescent shedding or asymptomatic infection. Shedding generally does not persist beyond 2 to 3 weeks, but few studies have done careful molecular subtyping, making it difficult to separate shedding from reinfection. The rates of rhinovirus detection in asymptomatic patients are generally substantially lower than among patients with lower respiratory tract infection or pneumonia. In a review of published studies of viral detection in asymptomatic subjects, Jartti and coworkers³ found a mean rate of rhinovirus/enterovirus detection by PCR of 15%, with higher rates among children and very low rates (2%) among the elderly. In preliminary results from the CDC Etiology of Pneumonia in the Community (EPIC) Study, rhinovirus was detected in 31% of 1320 children hospitalized with CAP and 22% of 442 control children who were undergoing elective surgery.

It seems likely that rhinovirus is a cause of CAP, but questions remain. Are some rhinovirus strains more likely to cause CAP? Are higher viral loads in the nasopharynx better predictors of lower respiratory tract infection and rhinovirus pneumonia? Does coinfection with rhinovirus facilitate infection with a second viral or bacterial pathogen and does rhinovirus coinfection increase the severity?

Table 2
Cause of community-acquired pneumonia in hospitalized children and role of viruses in six recent studies

	Juven et al, ⁶⁸ 2000 (N = 254)	Michelow et al, ⁶⁹ 2004 (N = 154)	Cevey-Macherel et al, ⁶⁶ 2009 (N = 99)	Tsolia et al, ⁷⁰ 2004 (N = 75)	Garcia-Garcia ⁷⁸ (N = 884)	Jain et al, ⁶⁷ 2011 (N = 1320 ^a)
Age	1 mo–17 y	2 mo–17 y	2 mo–5 y	5–14 y	<14 y	1 mo–17 y
Any pathogen	85%	79%	86%	77%	Not stated	82%
Any bacteria	53%	60%	52%	40%	2.2%	10%
Any virus	62%	45%	66%	65%	73% ^b	77%
Coinfection	30%	23%	33%	28%	22%	23%
RSV	29%	13%	13%	3%	31%	25%
Influenza virus	4%	22%	14%	7%	5%	4%
hMPV	NS	NS	13%	1%	5%	1%
Adenovirus	7%	7%	7%	12%	13%	1%
Parainfluenza virus	10%	13%	13%	8%	5%	1%
Rhinovirus/enterovirus ^c	24%	4%	33%	45%	19%	31%
Coronavirus	3%	NS	7%	NS	1%	<1%

Abbreviation: NS, not sought.

^a Preliminary results from an ongoing study.

^b Includes detection of bocavirus in 13%.

^c Most assays identify both rhinovirus and enterovirus.

Table 3
Cause of community-acquired pneumonia in hospitalized adults and role of viruses in six recent studies

	Charles et al, ⁴⁷ 2008 (N = 885)	Johansson et al, ⁷ 2010 (N = 184)	Johnstone et al, ⁸ 2008 (N = 193)	Lieberman et al, ⁹ 2010 (N = 183)	Jennings et al, ⁶ 2008 (N = 225) ^a	Templeton et al, ⁴⁸ 2005 (N = 105)
Age	Not stated	Mean 63	Median 71	Mean 60	Median 70	Median 60
Any pathogen	46%	67%	39%	Not stated	58%	76%
Any bacteria	38%	58% ^b	20%	Not stated	48%	46%
Any virus	15%	29%	15%	32%	34%	54%
Coinfection	9%	23%	4%	Not stated	30%	27%
RSV	2%	4%	3%	7%	4%	3%
Influenza virus	8%	8%	4%	4%	12%	10%
hMPV	NS	2%	4%	1%	0%	0%
Adenovirus	<1%	2%	1%	2%	4%	4%
Parainfluenza virus	<1%	4%	2%	0%	1%	8%
Rhinovirus/enterovirus ^c	5%	7%	2%	5%	13%	17%
Coronavirus	NS	2%	2%	13%	2%	13%

Abbreviation: NS, not sought.

^a Includes those with complete viral testing.

^b PCR assays were used for bacterial pathogens including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella*, *Legionella* sp, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.

^c Most assays identify both rhinovirus and enterovirus.

Other Viruses

Table 1 shows the range of viruses associated with CAP. Human bocavirus is a recently described parvovirus that has been frequently detected in respiratory secretions of children with respiratory tract infection.^{71,72} The role of bocavirus in CAP remains unclear. Interpretation of human bocavirus detection has been complicated by relatively common detection in asymptomatic children and prolonged detection after infection. However, in a study of Thai patients hospitalized with pneumonia, Fry and colleagues⁷³ found that compared with control patients, detection of human bocavirus was associated with hospitalization for pneumonia. Four patients with human bocavirus and pneumonia were older than 65. However, 83% of pneumonia patients with human bocavirus had coinfection with another pathogen. Brieu and coworkers⁷² detected human bocavirus in 10.8% of 508 children hospitalized with respiratory illness and none of 68 control subjects. Pneumonia was diagnosed in four of the children with human bocavirus. Most bocavirus-infected children had a coinfection, but viral loads were higher in the mono-infected children. Christensen and coworkers⁷⁴ detected bocavirus in 10% of 1154 children with respiratory tract infection and a similar proportion of control subjects. Of those with bocavirus, a second virus was detected in 75%. Bocavirus viral load greater than 10⁶ copies/mL was not associated with respiratory infection; higher viral load was however associated with LRTI. Thus, the exact role of bocavirus in pneumonia remains unclear.

Varicella zoster virus, herpes simplex virus, cytomegalovirus, and measles virus can cause severe pneumonia in immunocompromised hosts, but can cause pneumonia in otherwise normal hosts. Parechoviruses are rapidly emerging as important causes of

sepsis and meningitis in infants. Parechoviruses have been occasionally isolated from children with pneumonia.^{75,76} The systematic investigation of parechovirus infections is just beginning and their true role in CAP is unknown.

RESPIRATORY VIRUSES IN CAP IN CHILDREN

Viral infections are the most common cause of CAP in children in recent studies where sensitive molecular methods were used.^{66–70,77,78} It is challenging to compare individual studies because of differences in populations studied (age, severity of illness); seasons; samples obtained; agents sought; and the technologies used (eg, viral culture, viral or bacterial PCR, viral or bacterial serology). Moreover, the introduction of conjugate vaccines for *H influenzae* and *S pneumoniae* has decreased the incidence of these important pathogens compared with older studies.^{79,80} Several recent studies of hospitalized children with CAP that use PCR to enhance viral detection are summarized in **Table 2**. A virus was detected in 45% to 77% of children and a potential bacterial cause in 2% to 60%. The frequency of coinfection ranged from 22% to 33%. Mixed bacterial viral infections were found in 28% to 33% and viral-viral infections in 8% to 14%.^{66,69,70} In general, viral infections are more predominant among infants and children younger than 5 years old compared with older children.

RSV (3%–30%), influenza virus (4%–22%), and rhinovirus (4%–45%) were the viruses most commonly detected. The highly variable rates of detection of hMPV (1%–13%) and PIV (1%–13%) may reflect differences in the populations studied or year-to-year variation in the epidemiology of these infections. The ongoing CDC EPIC study⁶⁷ when finished will encompass approximately 2400 children over 2.5 years and include population-based data from three cities. This will provide more detailed and stable estimates of the role of viruses in CAP among children.

It is remarkable that no pathogen can be identified in 14% to 23% of pediatric CAP in recent studies, suggesting the need for improved diagnostics and the possibility of unrecognized pathogens.

RESPIRATORY VIRUSES IN CAP IN ADULTS

It is likely that the epidemiology of CAP in adults has also changed in recent years because of the indirect impact of pneumococcal conjugate vaccine in children and the increasing age of the population. In four recent studies of adult patients hospitalized with CAP that used at a minimum blood and sputum culture plus urinary antigen detection, *S pneumoniae* was detected in 7% to 38%.^{6–8,47} The highest proportion of *S pneumoniae* (38%) was in the study of Johansson and coworkers,⁷ which included the use of PCR to detect *S pneumoniae* in sputum. The apparently lower proportion of *S pneumoniae* has led to speculation that viruses now cause an increasing proportion of CAP in adults. It is hard to determine if this is true or reflects recent advances in viral diagnosis, the difficulty of establishing the cause of pneumonia, and the prevalence of dual infections.

Table 3 summarizes six prospective studies that included viral PCR to determine the cause of CAP in 1762 hospitalized adults (a small number of outpatients are included in the study by Templeton and coworkers⁴⁸). At least one virus was detected in 15% to 54%. In the five studies that reported bacterial causes, bacterial pathogens were detected in 20% to 58% and coinfection was detected in 4% to 30%. Viral infections are generally a more prominent cause of CAP among older adults.⁸¹ Johnstone and coworkers⁸ reported that patients with viral infections were significantly older than those without viral infections (median age, 76 vs 64 years), and were more likely to have underlying cardiac disease (66% vs 32%) and to be frail. Influenza virus was

among the most commonly detected viruses in adults hospitalized with CAP, detected in 4% to 12%. RSV was detected in 2% to 7% of adults. Influenza and RSV detection were highly seasonal. Detection of rhinovirus/enterovirus varied from 2% to 17%, but these viruses were often detected as a coinfection. Parainfluenza and coronaviruses were detected at variable rates (0%–8% and 2%–13%, respectively). HMPV and adenovirus were somewhat less commonly detected (0%–4% and <1%–4%, respectively). A putative pathogen could not be detected in 24% to 61% of patients in these studies despite the use of multiple methods including PCR for detection of viruses. This proportion is considerably higher than in studies of CAP in children, but the reasons are unclear. Possible explanations include a greater role of bacterial infection for which current diagnostics remain inadequate, the greater role of viral infection and coinfection in children, greater incidental detection of viral shedding in children, or lower viral copy number in the nasopharynx of adults with viral infections of the lower respiratory tract, making detection more difficult.

QUESTIONS

What is the Role of Mixed Infections in CAP?

When sophisticated diagnostic tests are applied, more than one pathogen can be identified in 23% to 33% of children and 4% to 30% of adults in prospective studies of CAP (see **Tables 2** and **3**). This raises several important questions. What proportion of patients in whom a virus is detected by PCR truly has a bacterial coinfection? Does viral-bacterial coinfection influence the course of illness?

The clinical interaction between influenza and *S pneumoniae* and *S aureus* has long been appreciated, and is a major contributor to influenza mortality.^{16,17,82} Several pathologic mechanisms have been proposed including epithelial damage, changes in airway function, upregulation of receptors, and changes in the innate immune response.¹⁶ It is becoming clear that similar interactions may occur with other respiratory viruses, including RSV, hMPV, and possibly rhinovirus and PIV.^{83,84}

Clinical evidence from prospective studies on the role of coinfection on severity is somewhat conflicting. There is a suggestion that viral-bacterial coinfection is associated with more severe disease among adults. Johansson and coworkers^{7,85} found that compared with those with only bacterial infections, adults with coinfection were much more likely to have pneumonia severity index (PSI) scores of IV or V (62% vs 26%; odds ratio, 4.6; $P < .001$) and had longer length of stay (7 vs 4 days; $P = .002$). Templeton and coworkers⁴⁸ reported that age older than 60, rhinovirus in mixed infection, and mixed infection were all associated with PSI score classes IV and V. Similarly, Jennings and coworkers⁶ reported that rhinovirus infection with pneumococcal infection was independently associated with more severe disease by either PSI or CURB-Age criteria. In contrast, Charles and coworkers⁴⁷ reported similar 30-day mortality among those with coinfection and single infection (8% vs 5.4%).

What Findings Differentiate Viral Pneumonia from Mixed or Bacterial Pneumonia?

Differentiating viral pneumonia from infection with bacteria alone or mixed viral-bacterial infection could significantly decrease antibiotic use with the associated risk of adverse reactions and the selective pressure for the development of resistance. However, developing clinical and laboratory tools to differentiate has been challenging.

Viral pneumonia is more likely during fall, winter, and early spring when outbreaks of respiratory viruses are occurring.^{6,8,86} Age less than 2 years⁸⁷ or older age among adults⁸ is associated with an increased likelihood of viral pneumonia. Wheezing in

children⁷⁸ and adults⁵ has been significantly associated in some studies with viral pneumonia compared with mixed or bacterial infection. High temperature,⁶⁹ rigors,⁶ and chest pain⁸ are significantly more common on presentation in patients with bacterial or mixed infection. Significant overlap limits the use of these findings.

There has been significant interest in the ability of inflammatory markers to discriminate between viral and bacterial cause in CAP.⁸⁸ In children, procalcitonin and C-reactive protein are consistently higher among children with bacterial infection,^{69,89,90} but it is unclear if specific cutoffs can be identified. Toikka and coworkers⁹⁰ found that procalcitonin (median, 2.09 vs 0.56 ng/mL; $P = .019$) and C-reactive protein concentrations (96 vs 54 mg/L; $P = .008$) were significantly higher in children with bacterial CAP than those with sole viral cause, but there was substantial overlap. Nascimento-Carvalho and coworkers,⁸⁹ however, reported that a cutoff of procalcitonin less than 2 ng/mL had a negative predictive value of 95% for excluding bacterial infection. In adults, procalcitonin levels are also higher in bacterial pneumonia.⁹¹ However, procalcitonin values are not static; they increase rapidly during bacterial infection and fall during appropriate therapy. To get around the limitations of a single cutoff value, treatment algorithms using sequential procalcitonin levels have been studied in several randomized trials as a way to guide therapy.^{88,92,93} For a complete discussion see the article by Niederman elsewhere in this issue.

Chest radiographs are only moderately useful in discriminating viral from bacterial CAP.^{86,87,94,95} Interstitial infiltrates with a patchy distribution are typical of viral pneumonia, whereas alveolar infiltrates, particularly with a lobar pattern, are suggestive of bacterial infection. However, there is marked overlap. In one study, 72% of 134 children with bacterial infection had alveolar infiltrates, as did 49% of 81 children with only viral infection ($P = .001$). Exclusively interstitial infiltrates were present in 28% of children with bacterial infection and 49% of those with viral infection.⁸⁷ The presence of pleural effusions was predictive of bacterial infection in several studies.^{69,78}

It is tempting to hypothesize that the use of sensitive PCR assays in conjunction with biomarkers, such as procalcitonin, could lead to diagnostic algorithms with adequate predictive value to improve the use antibiotics in CAP, but this has not been adequately studied.

What is the Best Treatment of Influenza Virus in CAP?

Effective antiviral therapy may prevent the development of CAP, and treatment of patients with influenza-associated pneumonia may improve outcomes. However, the evidence base is not optimal. Two classes of drugs are available for the treatment of influenza virus infection: the adamantanes (amantadine and rimantidine) and neuraminidase inhibitors (oseltamivir [Tamiflu] and zanamivir [Relenza]). Widespread and stable resistance to the adamantanes has rendered this class of limited use.⁹⁶ Oseltamivir and zanamivir were initially studied in randomized controlled trials among adults and children with uncomplicated influenza.⁹⁷ These studies demonstrated reductions in the time to the primary endpoint of resolution of all symptoms of approximately 1.25 days when neuraminidase inhibitors were begun within 48 hours of symptom onset; larger benefits were seen for return to functional status. Few patients with risk factors for complications were enrolled in these studies and with low rate of events the individual studies did not demonstrate reductions in hospitalizations or pneumonia. Kaiser and coworkers⁹⁸ performed a pooled analysis of oseltamivir clinical trials including 1340 patients, and reported statistically significant reductions in the development of lower respiratory tract infections resulting in antibiotic use and in hospitalizations and a nonsignificant reduction in pneumonia. Although statistically significant, the absolute risk reductions in generally healthy patients were relatively modest.

A critical question is whether treatment is beneficial among patients at high risk of complications, those with more severe disease requiring hospitalization, or with lower respiratory tract infections caused by influenza (with or without bacterial coinfection). A large body of carefully conducted but observational studies in seasonal^{99–101} and pandemic 2009 H1N1 influenza^{19,22,102–109} demonstrated improved outcomes among hospitalized patients treated with neuraminidase inhibitors including decreased intensive care unit admission and mortality. Benefits were independently demonstrated among children,¹⁰⁸ pregnant women,¹⁰⁴ and critically ill patients.¹⁰⁹ A formal meta-analysis by Hsu and colleagues¹¹⁰ concluded that among high-risk patients, oral oseltamivir may reduce mortality, hospitalization, and duration of symptoms, but the quality of the evidence was deemed low. Earlier initiation of therapy is associated with the greatest benefit, but among hospitalized patients, benefits were observed when oseltamivir was started as late as 5 days after symptom onset compared with no therapy.

Bacterial coinfection is an important cause of severe pneumonia and mortality in patients with influenza and pneumonia. In studies among critically ill children¹¹¹ and adults⁸² with pandemic 2009 H1N1 influenza, bacterial infection, particularly with methicillin-resistant *S aureus*, was associated with mortality. It is not possible from existing data to conclusively demonstrate that oseltamivir in addition to appropriate antibiotic therapy improves outcomes in patients with documented bacterial coinfection, but animal data^{15,16} and limited observational data suggest an independent benefit of antiviral therapy.

Thus, antiviral therapy with neuraminidase inhibitors should be started empirically in all hospitalized patients in whom influenza is suspected without waiting for laboratory confirmation, including those with CAP.^{96,112} Influenza testing and empiric antiviral therapy in addition to antibiotic therapy is appropriate for patients at increased risk of influenza complications who present with signs of CAP during outbreaks of seasonal influenza. It is important to remember that current rapid antigen-based influenza tests have relatively low sensitivity and a negative test does not rule out influenza.^{113,114}

Resistance to oseltamivir became widespread among seasonal strains of H1N1 influenza in 2008 in the H275Y mutation in the neuraminidase gene,^{115,116} and sporadic resistance to oseltamivir has emerged on therapy and been transmitted in other strains, including pandemic 2009 H1N1 influenza.^{117–119} These strains remain sensitive to zanamivir, but it is only available as a dry powder for inhalation, which is not appropriate for treatment of children younger than 5 years old and is not recommended for those with asthma or COPD because of the risk of bronchospasm. Continued spread of oseltamivir resistance would greatly reduce the ability to treat influenza-associated CAP.

What is the Best Treatment for Other Respiratory Viruses in CAP

Although effective therapy exists for influenza-related CAP in children and adults, options for the treatment of other viruses are extremely limited. Ribavirin has broad antiviral activity in vitro that includes RSV, hMPV, PIV, and influenza, but there are scarce data to demonstrate clinical use. Observational studies of inhaled ribavirin for RSV demonstrated limited benefits among severely immunocompromised patients¹²⁰ but the single randomized trial was underpowered.¹²¹ Among other populations, the benefits are questionable and the costs and risks limit the use of inhaled ribavirin.¹²² Palivizumab, a monoclonal antibody directed against the fusion glycoprotein of RSV, is recommended for the prevention of RSV hospitalization in specific subgroups of premature infants and infants with some types of congenital heart

disease or chronic lung disease. Unfortunately, it has not demonstrated any value in the treatment of RSV disease.

Based on anecdotal experience, intravenous ribavirin may have a potential role for overwhelming viral pneumonia in severely immunocompromised patients caused by RSV, hMPV, or PIV.¹²³ Cidofovir has potent activity against adenovirus and case reports suggest clinical benefit in immunocompromised patients with adenovirus infection.^{124,125} Cidofovir should be considered for patients with overwhelming adenovirus pneumonia including adenovirus type 14.¹²⁶ Because of the toxicity and difficulty with administration, cidofovir is not appropriate for CAP in immunocompetent hosts. An orally available prodrug of cidofovir, CMX001, is in advanced development and may prove useful for a wider array of patients with adenovirus pneumonia.¹²⁷ Pleconaril, a drug with activity against picornaviruses including rhinovirus, inhibits viral uncoating. A clinical trial showed reduction in the duration of symptoms for naturally occurring colds.¹²⁸ Pleconaril is no longer in development but this class of agents could be useful in lower respiratory tract disease caused by picornaviruses.

Because of the ubiquity of respiratory viruses, most pools of intravenous immunoglobulin have significant titers of antibody, including neutralizing antibody against common respiratory viruses. Intravenous immunoglobulin should be considered for hypogammaglobulinemic and severely immunocompromised patients with viral pneumonia.

UNANSWERED QUESTIONS AND FUTURE DIRECTIONS

Much remains to be learned about viral infections in CAP and how to translate the knowledge into improved patient care. How can it be determined if the detection of a virus in the upper airway in a patient with CAP indicates a causal role? This problem is common to interpreting prospective studies and tests in individual patients. The problem is more difficult for rhinovirus and coronaviruses that have been detected in 2% to 45% and 0% to 6% of asymptomatic subjects, respectively, by PCR than for influenza and hMPV, which are rarely detected in the absence of symptoms.³ Some studies have shown higher viral loads in patients with pneumonia, suggesting that quantitative assays might increase the specificity.^{74,129–132}

Which patients with CAP should be tested for viral infections and how should it alter clinical care? Detection of influenza infection can clearly lead to use of antivirals and in most cases limit the use of antibiotics. The use of sensitive and specific influenza tests is appropriate for children and adults with CAP during influenza season, and is recommended in recent guidelines.^{133,134} In younger children with moderate to severe CAP and immunocompromised patients viral pneumonia is common and testing for an array of viral causes of pneumonia can direct therapy and improve infection control. However, additional studies are needed to determine the impact of viral testing in other groups. The combined use of biologic markers and viral testing holds the promise of correctly identifying patients for whom antibiotic exposure can be safely limited. This would be facilitated by tests that can accurately detect multiple viruses with rapid turnaround time and that can be deployed in a variety of settings.

There is a critical need for influenza antivirals that are effective for viruses resistant to oseltamivir. Moreover, effective treatments, including antiviral agents, immunomodulatory agents, or siRNA, are needed for respiratory viruses other than influenza. RSV and hMPV are particularly attractive targets, because an effective drug could decrease morbidity, hospitalization, and mortality in many young children, older adults, and immunocompromised patients. Targets have been identified, but clinical development has been slow.^{135,136} Effective vaccines against respiratory viruses

could have a substantial impact on CAP by preventing primary viral pneumonia and preventing secondary bacterial infections.

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