The evolving burden of viruses in pneumonia

Nicole R. Brenner and Andrew F. Shorr

Purpose of review
To describe the evolving microbiology of various forms of pneumonia and the importance of viruses as etiologic causes of pneumonia.

Recent findings
Multiple studies utilizing novel diagnostic modalities demonstrate that the prevalence of viruses as causes for pneumonia varies from approximately 10–30% depending on the specific pneumonia type evaluated. Viral pneumonias appear similar in presentation and severity of illness to bacterial causes of pulmonary infection. Clinical criteria do not reliably allow the differentiation of viral from bacterial causes in pneumonia.

Summary
Viruses represent a pool of important culprit organisms in pneumonia and identification of a viral pathogen may facilitate attempts at antibiotic stewardship.

Keywords
bacteria, cause, outcomes, pneumonia, virus

INTRODUCTION

Pneumonia has historically been considered an infection caused predominantly by bacterial pathogens. This notion has resulted in the uniform use of empiric antibiotics in all forms of pneumonia: community-acquired pneumonia (CAP), healthcare-associated pneumonia (HCAP), and ventilator-associated pneumonia (VAP). Overuse of antibiotics, however, is not benign and creates selection pressure, which results in the emergence of antibacterial resistance and other negative consequences – such as *Clostridium difficile*-associated diarrhea (CDAD). The concept that bacterial pathogens predominate in pneumonia, though, has recently been questioned. Multiple epidemiologic studies, employing new diagnostic technologies, in various types of pneumonia have recently demonstrated the importance of viral pathogens in this syndrome. As such, appreciating the burden of viruses in pneumonia presents an opportunity to target therapies more appropriately and to enhance efforts at antimicrobial stewardship.

REVIEW

Prior to reviewing studies documenting the prevalence of viruses in pneumonia, one requires an appreciation of the novel diagnostic tests used to identify these organisms. Historically, direct immunofluorescence, serology, and viral cultures were the diagnostic tests of choice for viral pneumonias, with none ever considered the clinical gold standard. Direct immunofluorescence, with low sensitivity in adults, has limited utility, given its inapplicability to multiple important viruses, especially human rhinovirus, which has been shown to be the most prevalent viral etiologic agent [1] Serology, although beneficial in its ability to identify viral infection and distinguish between colonization and infection via paired antibody testing (acute and convalescent phase seroconversion), also has limited applicability at the bedside.

The emergence of PCR-based testing for viral pathogens, though, has resulted in a dramatic shift in how we think about pathogenic cause of pneumonia. PCR provides the benefit of higher sensitivity when compared with viral cultures [2] Combination assays (i.e. multiplex PCR) further increase one's ability to detect viruses [and bacteria]). Readers should note that prompt collection of

Pulmonary and Critical Care Medicine Service, Medstar Washington Hospital Center, Washington, DC, USA

Correspondence to Andrew F. Shorr, MD, MPH, Room 2-A68d, Medstar Washington Hospital Center, 110 Irving Street, NW, Washington 20010, DC, USA. Tel: +1 202 877 7856; fax: +1 202 291 0386; e-mail: Andrew.shorr@gmail.com

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KEY POINTS

- Viruses are common causes of pneumonia not only in community-onset infections but also in hospital-acquired processes.
- Viral pneumonia is clinically indistinguishable from bacterial pneumonia.
- Viral pathogens can cause severe pneumonia that results in significant mortality, even in immunocompetent patients.

samples is important, as shown by Sawatwong *et al.* [3]. In a single-center prospective study in rural Thailand, these authors documented that a significantly longer time to sample collection results in more negative PCR tests compared with those with a positive diagnostic yield (1.77 and 1.28 days, respectively; $P = 0.03$).

Multiplex PCR technologies hold promise for rapid bedside diagnostic utility in pneumonia, but many of these technologies have limited direct clinical applicability because of turn-around times and cost. Benefits of some of the innovative lab-based technologies include identification of unexpected or evolving pathogens (i.e. PLEX-ID Technology, Abbot Molecular; Chicago, IL, USA) and quantification of the viral load, which may aid in distinguishing colonization from infection [i.e. Scalable Target Analysis Routine (STAR) Technology, Primer aDx; Salt Lake City, UT, USA] [4,5]. FilmArray and the Jaguar system (D Diagnostics-GeneOhm; Franklin Lakes, NJ, USA) are near-patient facility multiplex PCR technologies with rapid turnover times, closed systems with lower carryover contamination risk, and simple utilization at the expense of lower throughput with fewer targets that can be identified than in lab-based technologies [5].

With respect to analyses employing several of these multiplex testing modalities, many demonstrate the burden of viruses in pneumonia. Templeton *et al.* [6], for example, found an increase in diagnostic yield among patients with CAP with real-time PCR (RT-PCR) compared with traditional viral cultures and serology (56.2 and 14%, respectively). The observed increase in yield was predominantly because of higher rates of respiratory virus detection. Subgroup analysis showed a nonstatistically significant trend towards increased diagnostic yield in patients with severe pneumonia. More importantly, the only cases in which RT-PCR failed to detect a viral pathogen that was otherwise identified by conventional methods occurred with influenza A infection. Significantly, this was one of the first CAP studies to reveal the importance of rhinovirus in CAP in nonimmunosupressed patients [6]. Additionally, these investigators showed that RT-PCR enhanced the ability to identify when CAP arose because of multiple causative agents (35 vs. 10.2% by conventional methods) [6]. In a similar analysis, which confirmed the observations by Templeton *et al.,* Swedish researchers examining consecutive patients admitted for CAP showed that RT-PCR increased the rate of pathogen identification by more than 50%, mainly because of the recognition of previously undiagnosed viral organisms [7].

Expanding on these earlier projects in CAP, a recent Centers for Disease Control and Prevention project clearly confirmed that viruses are prevalent in CAP [8]. Among 2259 patients with CAP requiring hospitalization (without severe immunosuppression) in Chicago and Nashville, an extensive diagnostic testing approach relying on traditional cultures and PCR [from blood, nasopharyngeal, oropharyngeal, endotracheal aspirates, and/or bronchoalveolar-lavage (BAL) samples] along with serologies and urinary antigen testing resulted in an overall diagnostic yield of 38%. More importantly, among cases with identified pathogens, viral-only infections were more common than bacterial-only infections (23 vs. 11%) with bacterial–viral co-infections occurring in 3% of cases [8]. Strengths of this study, which underscore its importance, include its prospective and multicenter design. Readers should note, though, that several of the diagnostic techniques employed are investigational. Nonetheless, this report highlights in a broad population of CAP patients that viruses are prevalent and important pathogens that can cause infections indistinguishable from traditional bacterial pathogens.

Focusing on just ventilated, severe CAP – in contrast to the patients studied by Jain *et al.* – Finnish authors reported the identification of a viral cause in a majority of patients [9]. In this small case series, only 10% of patients had a pure viral infection whereas 39% suffered from co-infection with both virus and bacterial pathogens. Notably in this study, bronchial specimens more often than nasopharyngeal swabs resulted in the identification of viral pathogens (81 and 19%, respectively). Comparison of diagnostic yield between lab-based and near-bedside in-house PCR studies was also performed, and 53.3% of cases with rhinovirus identified by in-house PCR were not detected by commercial PCR testing [9].

In both studies noted above, human rhinovirus was the most common viral agent identified. In the analysis by Jain *et al.*, 9% of cases (yielding an incidence of two cases per 10 000 adults per year)

were caused by rhinovirus whereas for Karhu and coworkers, rhinovirus accounted for 58% of viral pathogens [7–9]. Following human rhinovirus, the most common viruses identified included influenza and adenovirus. Strikingly, Jain *et al*. found *Streptococcus pneumoniae*, historically considered as the most common cause of pneumonia, to have an annual incidence lower than that of either human rhinovirus or influenza (1.2 cases/10 000 adults) [8]. Other viruses that have now clearly been implicated as causative in CAP include human metapneumovirus (HMPV), respiratory syncytial virus (RSV), parainfluenza viruses (PIVs), coronaviruses, and human bocavirus. Recent evidence also reflects an increase in the incidence of RSV, PIV, and coronavirus identification among patients over 80 years of age with CAP requiring hospitalization, each with an incidence similar to that of *S. pneumoniae* [8].

The difference in relative frequencies of viral vs. bacterial causes identified between these studies is multifactorial. In addition to geographic variation, the relative frequency of different viruses likely differs between the United States and Finland. The populations studied also differ, with the first including all cases, including those in the ICU whereas the study in Finland only included those patients with the need for mechanical ventilation. The inclusion of only patients with mechanical ventilation also afforded the opportunity to obtain lower airway cultures in all cases for Karhu *et al*. [8,9].

Beyond CAP, viruses have further been shown to cause infection in the setting of other types of pneumonia that often require initiation of broad-spectrum antimicrobials. As such, these instances represent a key opportunity for antibiotic stewardship. Confirming that viruses also are important in HCAP, researches from Korea, in a single-center prospective cohort study of patients with severe CAP ($n = 64$) and HAP ($n = 134$) determined that viral and bacterial pathogens occurred with nearly equally frequency (36.4 and 35.9%, respectively) [10]. In fact, irrespective of pneumonia type, 9.1% of cases had a bacterial and viral co-infection. With respect to the proportions of bacterial, viral, and mixed infections, there was no difference in CAP compared with HAP groups. Bronchoscopic BAL was performed in 57.0% of these cases, with other samples including blood culture, sputum or endotracheal aspirate, and nasopharyngeal aspirate for viral multiplex RT-PCR analysis (Seeplex RV15 ACE Detection) and shell viral culture (for influenza virus, RSV, PIV, adenovirus, and CMV). BAL samples had viral detection that was not present from an NP aspirate in 5 of the 23 cases that had simultaneous BAL and NP sample testing, with 3 cases of the opposite occurrence [10]. Among cases of any positive virus identification, a single virus was identified in 59.7% of cases, with human rhinovirus again as the most common (23.6%), followed by PIV (20.8%), HMPV (18.1%), and influenza virus (16.7%). Of the identified viral pathogens, only RSV was more common in cases of CAP than HAP (10.9 and 2.2%, respectively, $P = 0.01$). Two or more viruses were found in 12.5% of cases, and co-infection with bacteria in 25.0% with the most common co-infections with PIV, influenza, rhinovirus, and HMPV, in order of highest to lowest frequency. Notably, these investigators found that rhinovirus was associated with the highest mortality (52.9%) followed by influenza virus (33.3%) [10].

Further exploring more severe cases of pneumonia and extending the search for viral causes beyond purely CAP syndromes, a retrospective single-center 1-year study of 174 cases of nonventilated HAP (NVHAP) was conducted with a focus on organism identification [11▪]. The overall diagnostic yield was 46% and specimens were collected so as to apply qualitative PCR testing for respiratory viruses (FilmArray Respiratory Panel, BioFire Diagnostics, Inc; Salt Lake City, UT, USA). These investigators identified a viral cause in 22.4%, whereas in 23.6%, bacterium was the culprit organism. As with other analyses, human rhinovirus represented the most common virus ($n = 19$) followed by influenza ($n = 7$) [11▪]. Patients with positive virus identification were observed to be significantly less likely to have comorbid coronary artery disease [adjusted odds ratio (AOR) 5.16, $P = 0.003$] and were twice as likely to have a prolonged hospitalization (more than 10 days) prior to onset of NVHAP (41.0 compared with 20.7%, $P = 0.020$). Comparing cases of NVHAP because of viruses with bacteria, there were no observed statistically significant differences in hospital mortality, readmission at 30 days, or length of stay after onset of NVAP [11▪]. In other words, viruses are clearly capable of causing severe disease in previously hospitalized patients. Moreover, clinical characteristics do not allow the clinician to readily differentiate a viral cause from bacterial cause.

Hong *et al*. [12] recently reported similar findings in addressing the cause of HAP. These authors examined 262 patients with severe HAP (e.g. required intensive care admission for septic shock or mechanical ventilation) in a single tertiary care center. In contrast to earlier studies, patients with hematologic malignancy, diabetes mellitus, structural lung disease, and solid cancers were included with nearly half the cohort classified as immunocompromised. Multiplex RT-PCR (Seeplex 15RV ACE Detection kit) and shell viral cultures resulted

in a diagnostic yield of 76.7% [12]. Bacterial infections were the predominant cause (59.5%) with viral infections identified in only 22.5% of cases and viral-only infections in 11.8% of the cohort. Viral–fungal co-infections accounted for 2.7% of the cases with multiple viruses simultaneously detected in 17% of the cases with any positive virus identification. Unique from other epidemiologic studies, RSV and PIV were the most commonly identified viruses (each in 16/59 cases) followed by rhinovirus. There was a statistically significant increase in frequency of viral infections diagnosed in immunocompromised compared with nonimmunocompromised patients (36.1 and 11.2%, respectively, $P < 0.001$) with no difference with respect to individual viruses [12]. In concordance with findings from Choi *et al.* viruses were detected from lower respiratory tract specimens (BAL or endotracheal aspirates; 62.7%) more often than from nasopharyngeal specimens (37.3%) and mortality rates at 28 days did not significantly differ between bacterial, viral, and bacterial–viral co-infections [10,12].

Shifting the perspective from type of pneumonia (e.g. CAP vs. HAP) to addressing the burden of viruses in pneumonia encountered in the ICU, Shorr *et al.* [13▪▪] evaluated 364 patients undergoing mechanical ventilation, irrespective of pneumonia type. The cohort only included subjects with a high severity of illness (mean Acute Physiology and Chronic Health Evaluation II score 24.4 ± 7.3) and subjects underwent testing by qualitative nucleic acid tests (FilmArray Respiratory Panel, BioFire Diagnostics) of sputum, tracheal aspirate, BAL, and cultures from blood and pleural fluid). The overall diagnostic yield was 67.6% [13▪▪]. Similar to prior studies in mechanically ventilated patients, the predominant pathogens were bacteria (45.9%), with viruses identified as the sole isolates in 21.7% of cases. Rhinovirus predominated ($n = 20$), followed by influenza A ($n = 12$), and RSV ($n = 11$). Consistent with the observations of Choi *et al.*, these researchers reported no difference in the cause of pneumonia (i.e. virus or bacteria) as a function of pneumonia type. In an attempt to identify at-risk populations for viral causes compared with bacterial causes, most subgroup analyses failed to reveal any factors associated with viruses. However, stratification of patients by APACHE II score linked a higher score (>26) to a lower risk (AOR 0.51, 95% confidence interval (CI) 0.28–0.93) for viral identification [13▪▪]. Conversely, stem cell transplantation (SCT) was associated with a higher risk (2.5 times more likely; OR 2.51, 95% CI 1.20–5.27) of a viral cause. After exclusion of patients with ongoing SCT, two factors remained independently associated with recovery of a virus alone: APACAHE II score greater than 26 (AOR 0.41, 95% CI 0.20–0.81) and treatment with noncorticosteroid immunosuppressive drugs (AOR 2.36, 95% CI 1.09–5.08) [13▪▪].

The important potential for viruses to lead to pneumonia in severely immunosuppressed subjects has been known for some time. The findings by Shorr *et al.* [13▪▪] document, however, that immunosuppression is neither a necessary nor sufficient precondition for a viral pneumonia. On the other hand, the role of viruses as a cause of pneumonia in the immunosuppressed should not be underemphasized. Underscoring this point, an analysis of lung transplant patients undergoing BAL for suspected pneumonia demonstrated that 17.4% suffered from a viral pneumonia [14]. Unlike other recent studies, coronarvirus (32.3%) was the most common viral pathogen followed by rhinovirus (22.6%). Importantly, these infections were associated with a lack of antibiotic treatment response (OR 2.2; 95% CI 1.2–4.1) and an absence of radiologic infiltrate (OR 0.3, 0.2–0.8) [14].

CONCLUSION

In conclusion, several important recent reports clearly demonstrate that viral pathogens are important causes of pneumonia in patients with various types of infection (e.g. community vs. hospital onset) and varying degrees of severity of illness. Furthermore, the viruses recovered are heterogeneous in type, although rhinovirus appears to predominate. Additionally, there is a degree of diversity in the range of viruses encountered that is similar to that seen with bacterial organisms. Outcomes for patients with a viral pneumonia are akin to those with bacterial infections and, unfortunately, clinical variables do not allow the clinician to reliably differentiate patients with distinct microbial causes. More aggressive efforts to search for viral pathogens, though, represent a potential means for enhancing antibiotic stewardship as early identification of a viral cause can reassure the clinician that antibiotics can be safely discontinued. Clearly, further work is needed in this area to help us better understand the burden of viruses in pneumonia.

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- ■ of special interest
- ■■ of outstanding interest

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