Viral pneumonia

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Purpose of review

Community-acquired pneumonia (CAP) has traditionally focused little on viral causes, and few studies have done an extensive and appropriate evaluation for viral cause. The purpose of the present article is to review several issues of viral infection in CAP in light of recent studies that included exhaustive evaluation of viruses.

Recent findings

The introduction of better quality diagnostic tests, such as nucleic acid amplification techniques, have markedly improved our ability to detect multiple viral pathogens. With these diagnostic tools, a viral cause can be established in more than half of patients with CAP. Influenza A and respiratory syncytial virus are the most frequent causes of viral pneumonia followed by adenovirus, parainfluenza virus types 1, 2, and 3, and influenza. Although some clinical findings have been more frequent with viral infection, no clear-cut clinical signs have been shown to be predictive of specific cause. Of more interest is the association of mixed virus–bacteria infection with poorer severity scores found in some studies. The diagnostic approach with new techniques should be taken for a true estimation of viral infection in epidemiologic studies.

Unfortunately, there are no other licensed antivirals or vaccines against the large variety of clinically important respiratory viruses with the notable exception of influenza.

Summary

Given the high rate of viral infection in CAP and its probable association with poorer prognosis in mixed virus–bacteria infection, an extensive evaluation for virus in some populations seems appropriate. These findings can be useful for a more appropriate management of these patients.

Keywords

antiviral drugs, infection, pneumonia, virus

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Introduction

More than 55 million people die each year worldwide, and pneumonia is among the leading causes. Specifically, lower respiratory tract infections (primarily pneumonia) are the third largest cause of death after ischemic heart disease and cerebrovascular disease and account for 6.6% of deaths [1]. Community-acquired pneumonia (CAP) has traditionally focused little on potential viral causes, largely because of the lack of specific antiviral agents and the impression that viral pathogens play a relatively minor role in adult pneumonia. In recent years, the introduction of better quality diagnostic tests has markedly improved our ability to detect multiple viral pathogens, shifting attention to the potential importance of viruses as a cause of CAP. This review focuses on different issues in light of these findings.

Epidemiology and cause

It is well known that the principal etiologic agents of CAP in adults are bacteria, with *Streptococcus pneumoniae* being the most frequently occurring pathogen. In recent years, however, the respiratory viruses have been recognized as a potential common cause of pneumonia in adults, ranging from 2 to 35%, because of inclusion of nucleic acid amplification tests in the diagnostic testing repertoire [2–4].

Influenza A and respiratory syncytial virus (RSV) are the most common causes of viral pneumonia, followed by adenovirus, parainfluenza virus types 1, 2, and 3, and influenza B. In these studies, seasonality of all viruses does not appear to be different from influenza, with the exception of rhinovirus, parainfluenza, and adenovirus, which may be present throughout the year.

Influenza virus causes outbreaks every winter. These outbreaks are of variable intensity but usually affect between 5 and 30% of the population, resulting in a highly variable degree of morbidity and some mortality, virtually confined to elderly individuals, especially those with underlying medical conditions [5]. In highly vaccinated populations, only 30% of hospitalized patients with influenza have pulmonary infiltrates [6].

In one population-based study with nucleic acid amplification tests for influenza and RSV [7], the latter infection occurred in 3–7% of prospectively monitored healthy elderly persons and in 4–10% of high-risk adults (those with chronic heart or lung diseases); pneumonia occurred in 2–7% of infected persons. In addition, RSV infection accounted for 11% of winter discharge diagnoses for pneumonia. Importantly, the RSV infection rate was twice that of patients with influenza.

Rhinovirus and coronavirus 229 E and OC43 have been largely ignored by the medical community because their clinical impact was considered to be minor. It is now clear that these viruses, once thought to cause only a common cold, can also cause pneumonia in adults [8]. All these viruses are common causes of sporadic cases or outbreaks of community-acquired infections and can be fatal in immunosuppressed patients and the elderly.

Several viruses not previously described have been identified since 2001. These are human metapneumovirus (HMPV), H5N1 strain of influenza virus, three new human coronaviruses – the severe acute respiratory syndrome (SARS)-associated coronavirus, coronavirus HKU1, and coronavirus NL63 – and the recently described human bocavirus. Zoonotic infections caused by SARS-associated coronavirus and avian influenza A/H5N1 are examples of acute atypical pneumonia with epidemic and pandemic potential; however, they have, to date, been restricted geographically and have only been associated with limited, sporadic outbreaks of human disease. The other emerging viruses are considered causative agents of CAP in adults and appear more frequently in patients with other illnesses or immunosuppression [4,9–11]. Polymicrobial infections involving bacterial and viral pathogens or two viruses are common in adults and could enhance the severity of pneumonia, although further research needs to be carried out [3,10,12].

Clinical findings

Patients with pneumonia usually present a constellation of symptoms and signs that include cough, dyspnea, sputum production, and pleuritic chest pain, although nonrespiratory symptoms (mainly in elderly patients who may report fewer symptoms) such as changes in level of consciousness or falls may also predominate. Classically, it has been considered that these signs and symptoms cannot predict the etiologic agent [13]. Although this statement is probably correct, its main limitation is the fact that the cause is unknown in more than 40% of patients in most studies. Very few of the more comprehensive evaluations of the cause in CAP have used PCR tests for virus and atypical bacteria [14]. In one study [12], it was possible to determine the cause using these tools in almost 80% of patients.

Compared with bacterial pneumonia, data from recent studies with exhaustive virus evaluation have shown viral pneumonia in an older and frail population with more cardiac disease [4], lower probability of chest pain and rigors [3,4] and lower white blood cell and neutrophil counts (an exception to this is rhinovirus infection, in which a higher number of neutrophils can be present) [3]. Levels of C-reactive protein may be lower in viral infection [2].

In the only report to evaluate clinical findings because of the recently described HMPV [15], all patients had cough, dyspnea, and fatigue; fever was infrequent, and the leucocyte count was normal. Although the above studies did not find a correlation between cause and mortality rate, an important finding is the association between the mixed viral–bacterial cause (especially for rhinovirus) and severity of disease measured by the pneumonia severity index and CURB score [3,12]. Table 1 shows a summary of causes, clinical findings, and outcomes of studies evaluating CAP with an exhaustive investigation for viral cause.

Diagnosis

There is still a considerable deficit in the etiologic diagnosis of CAP. More than 50% of cases in studies remain without an etiologic diagnosis, resulting in the unnecessary or inappropriate prescription of antibiotics. It is clear now that the involvement of viruses in CAP may have been underestimated; this underestimation has been attributed to a lack of appropriate diagnostic methods. The benefit of a more accurate diagnosis of viral infection is four-fold; first, it benefits the patient in terms of receiving the appropriate antiviral drugs such as oseltamivir in the case of influenza virus; second, it assists infection control practitioners in providing appropriate infection control measures such as droplet containment when necessary to minimize the risk of nosocomial spread; third, it can stop the search for a diagnosis even if there is no beneficial antiviral agent for the respiratory virus that was found; and fourth, it provides more accurate information to public health authorities regarding what viruses are circulating in the community so that they can adjust public health policy accordingly.

A variety of specimens can be tested for respiratory viruses in CAP. Nasal washes are the preferred specimen in children but are difficult to obtain in the acutely ill or uncooperative older patients. Adequately collected nasopharyngeal swab specimens remain an acceptable method of specimen collection [7]. Although bronchoalveolar lavage specimens provide the best samples from the lower respiratory tract, they are generally not

Table 1 Results of studies evaluating community-acquired pneumonia in adults with extensive diagnostic tests for virus (conventional tests and nucleic acid amplification) and reporting of clinical data

Reference	Population	Cause	Clinical findings comparing viral and bacterial pneumonia[a]	Relevant outcomes
Johnstone *et al.* [4]	Consecutive immunocompetent patients admitted to hospital with CAP; overall cohort, 300; patients with comprehensive viral tests, 193	Overall microbiologic diagnosis, 39%; bacteria, 20%; virus, 15%; mixed (bacterial–virus), 8%; influenza A and B, 4%; metapneumovirus, 4%; respiratory syncytial virus, 3%; rhinovirus, 2%; coronavirus, 2%; adenovirus, 1%	Patients older and more frail; more heart disease; less chest pain; fewer leucocytes	Mortality, 3%; no difference in outcomes according to pathogens identified (mortality, ICU admission, length of stay)
Jennings *et al.* [3]	Consecutive patients admitted to hospital with CAP; overall cohort, 304; patients with comprehensive viral tests, 225	Overall microbiologic diagnosis, 58%; bacteria, 48%; virus, 30%; mixed (bacterial–virus), 15%; influenza A and B, 12%; metapneumovirus, 0%; respiratory syncytial virus, 4%; rhinovirus, 13%; coronavirus, 1%; adenovirus, 4%	More myalgia; fewer neutrophils in nonrhinovirus infection; more neutrophils in rhinovirus infection; fewer rigors; fewer smokers	Mortality, 7% for viral cause[b]; rhinovirus–pneumococcal coinfection has independent association with severe pneumonia[c]
Marcos *et al.* [2]	Consecutive immunocompetent and immunosuppressed patients admitted to hospital with CAP; overall cohort, 340; patients with comprehensive viral tests, 198	Overall microbiologic diagnosis, 57%; bacteria, 33%; virus, 13%; mixed (bacterial–virus), 10%; influenza A and B, 8%; metapneumovirus, NA; respiratory syncytial virus, 3%; rhinovirus, 4%; coronavirus, 2%; adenovirus, 4%; parainfluenza 1–4, 3%	Fewer leucocytes; less C-reactive protein; no differences in monthly distribution	Overall mortality, 2.5%; no difference in outcomes according to pathogens identified (mortality, ICU admission and severity according to PSI)
Templeton *et al.* [12]	Consecutive patients admitted to hospital with CAP ($n = 92$) and patients with CAP not hospitalized ($n = 13$); patients with comprehensive viral tests, 105 (overall cohort)	Overall microbiologic diagnosis, 76%; bacteria, 44%; virus, 50%; mixed, 27%; influenza A and B, 10%; metapneumovirus, 0%; respiratory syncytial virus, 1%; rhinovirus, 17%; coronavirus, 14%; adenovirus, 4%; parainfluenza 1–4, 2%	No data of signs/symptoms or laboratory reported; 87% of patients more than 60 years of age and all patients admitted to ICU have microbiologic diagnosis using conventional and PCR tests	Overall mortality, 3%; coinfection rhinovirus or coronavirus–bacterial infection has independent association with severe pneumonia according to PSI

CAP, community-acquired pneumonia; NA, not available; PSI, pneumonia severity index.
[a] Difference with statistical significance when comparing viral with bacterial causes.
[b] Not reported for overall cohort.
[c] Pneumonia severity index IV–V and CURB score more than 2 (odds ratio, 9.95).

available in immunocompetent adults with CAP. Four methods for detection of respiratory viruses are available and include viral culture, rapid antigen detection, serology, and nucleic acid amplification methods.

Although viral culture has been the gold standard, it has considerable limitations. Adults with CAP generally shed lower titers of viruses and for a shorter period of time than adults with upper respiratory tract illnesses. In addition, the virus is thermolabile and may not survive transport from the patient's bedside to the laboratory. Both these facts are responsible for the lower sensitivity of viral culture relative to serology or PCR [2,7]. Furthermore, cultures take between 3 and 14 days to yield results, depending on the virus; they require specific technical expertise and are labor-intensive and expensive. Also, a considerable number of respiratory viruses, including rhinovirus, HMPVs, the novel coronaviruses NL63 and HKU1, and human bocavirus, grow poorly or not at all in viral culture.

Viral antigens can also be detected in respiratory secretions by immunofluorescence or enzyme immunoassay. Unfortunately, a relatively high viral load is required to generate a positive result, and therefore, as with viral culture, these tests are less sensitive in adults with CAP. Additional limitations of these tests are the lack of reagents for some of the viruses (bocavirus, rhinovirus, and coronavirus) and, as with viral culture, lower sensitivity in detecting dual infections compared with nucleic acid amplification methods [16]. In recent years, immunochromatographic methods have been developed for detecting RSV, adenovirus, and influenza virus. These are rapid and simple assays, but their low sensitivity restricts their use in adults to screening tests. Thus, a negative test cannot rule out the involvement of a respiratory virus [17,18,19•].

All adults have measurable baseline antibody titers, and for this reason, a single serum IgG antibody titer is not useful as a diagnostic test. Although detection of IgM in

acute-phase sera has also been used with variable success [20], the most reliable method for serological diagnosis is the demonstration of a more than four-fold increase in virus-specific IgG. Although useful in epidemiological studies and outbreak investigations, serology is of limited value to a clinician given its retrospective nature [21].

Developments in nucleic acid amplification tests have improved the ability to detect viruses in clinical samples and characterize the epidemiology of respiratory virus infections. Nucleic acid amplification tests, particularly PCR, combine improved sensitivity and specificity with very rapid results compared with conventional methods.

Diagnosis of respiratory infections is further complicated by the wide range of potential pathogens that can present with the same clinical symptoms. Multiplex PCR assays that simultaneously detect a large number of viral agents using a single test can be very useful. Some of these assays are based on traditional PCR [2,22••] and some others on real-time PCR [12,23,24]. Real-time amplification has two major advantages; the results can be obtained on the same day and viral load can be quantified. The implementation of quantitative tests can shed further light on the relation between virus load and severity of disease and help to differentiate between colonization and infection [25]. Multiplex PCR coupled with fluidic microarrays using microbeads or DNA chips (oligonucleotides spotted onto a slide or chips) represents the latest diagnostic approach to detect multiple bacterial and viral pathogens in a single PCR [26–28].

Prevention and treatment

The three steps for control of viral respiratory infections are prevention of exposure, provision of immunity, and administration of antiviral drugs. Transmission of influenza may occur via small-particle aerosols; thus, respiratory isolation of patients with documented or suspected infection during periods of high influenza activity is appropriate. Hand washing is also very important. Other major respiratory viruses are spread via fomites and large-particle droplets, making respiratory isolation unnecessary.

Annual immunization programs using the inactivated trivalent vaccine remain the most important means of reducing influenza-related morbidity and mortality. With the notable exception of influenza, there are, as yet, no approved vaccines for the prevention of most respiratory viral infections. Immunotherapy and immunoprophylaxis appear to be promising directions for future research [29•].

Similarly, with the exception of antiinfluenza agents, including adamantanes (amantadine and rimantadine) and neuraminidase inhibitors (zanamivir and oseltamivir), there are no other licensed antivirals against the large variety of clinically important respiratory viruses. Although ribavirin has been approved for the treatment of RSV, its clinical use is limited by its side effects and its low clinical efficacy [7].

Amantadine and its analogue, rimantadine, are effective for the prevention of influenza A [30]. However, they cannot prevent complications associated with influenza A [31], they have no activity against influenza B virus, and rates of resistance of between 30 and 80% have been reported after only a few days of therapy [32]. Adamantanes are therefore no longer recommended as first-line antiviral therapy.

Several clinical studies and systematic reviews of randomized clinical trials have shown therapeutic and prophylactic efficacy of zanamivir and oseltamivir against influenza A and influenza B infections [32]. Neuraminidase inhibitors have been shown to be 70–93% effective in preventing influenza in immunocompetent adults and children [33]. Antiviral treatment is usually only recommended for at-risk patients and those who develop severe disease and complications [34]. Both zanamivir and oseltamivir reduce the duration of symptoms, the risk of lower respiratory tract complications, and the need of hospitalization or antibiotic therapy [35]. For maximum benefit, antiviral treatment must start as early as possible and no later than 48 h after onset of symptoms. Early institution of antivirals is essential to limit virus multiplication and the concomitant tissue damage and activation of the proinflammatory response. Rapid diagnosis of influenza is therefore essential for antiviral therapy to be effective. However, the impact of such treatments on patients who are hospitalized with influenza pneumonia or a bacterial pneumonia complicating influenza is unclear. Influenza viruses resistant to neuraminidase inhibitors are infrequent in clinical trials, with estimated rates of resistance varying from 0.4 to 1% in the adult population [36].

Bacterial superinfections, particularly pneumonia, are important complications of influenza pneumonia. The bacterial causes of CAP after influenza infection have included *S. pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae*. Appropriate agents would therefore include cefotaxime, ceftriaxone, and respiratory fluoroquinolones. Thus, the appropriate use of diagnostic tests will be even more important in targeting antibacterial therapy whenever possible, especially in patients admitted to hospital [37].

Conclusion

With the introduction of new diagnostic tests, it has become apparent that infections with respiratory viruses are more frequent than originally thought. In patients presenting with pneumonia, it remains difficult

to differentiate patients with viral infections from those with bacterial infections, on the basis of clinical findings. Routine testing for respiratory viruses with nucleic amplification tests enables timely results with important implications for drug therapy and infection control. For these reasons, extensive viral tests may be warranted for all adults hospitalized with CAP. Polymicrobial infections involving bacterial and viral infections are also frequent and appear to be associated with severe pneumonia.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 207–208).

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