

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

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(See the Major Article by Karhu et al on pages 62–70.)

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The impact of respiratory virus infections (RVIs) on community-acquired pneumonia (CAP) in adults is increasingly recognized. The role of influenza A virus in causing pneumonia has been well known since its discovery in 1933 and was reinforced by the 2009 influenza A (H1N1) pandemic. However, the role of other RVIs in adults with CAP was long underestimated simply because available technologies such as virus culture or virus antigen detection lacked sensitivity in detecting the full range of respiratory viruses. The availability of nucleic acid amplification tests (NAATs) has greatly increased our ability to detect RVIs and characterize viral pneumonia. Recent studies employing a full set of tests suggest that a third of adult cases of CAP are associated with RVIs. In addition to influenza, rhinoviruses, respiratory syncytial virus (RSV), coronaviruses, and human metapneumovirus are most often detected among 30 viruses known as putative causative agents of CAP [1].

Viral–bacterial coinfections occur in 10%–15% of patients [1–3]. Although RVIs are often associated with CAP, the pathogenesis and clinical impact of viral lung infection is not well understood. In the most recent clinical practice article on adult CAP, only influenza viruses are recommended to be searched for during influenza season, and other RVIs viruses are not even mentioned [4].

In this issue of *Clinical Infectious Diseases*, Karhu and colleagues [5] from Oulu, Finland, report their observations on the role of viruses in severe community-acquired pneumonia (SCAP) in adults. Their article contains 3 interesting messages.

First, half of 49 patients with SCAP had evidence of RVI when both upper and lower respiratory sampling was used. Importantly, viruses were found most often in bronchial samples (bronchoalveolar lavage [BAL] or bronchial suction aspirate). Only half of the cases would have been detected from nasopharyngeal aspirates, which found only 4 cases that were not detected in bronchial samples. These observations are in agreement with the recent study of Choi et al [6], who demonstrated RVI in 41% of 64 patients with SCAP. In their patients, shell vial cultures were positive only in 11% of 101 BAL samples, once again demonstrating the superiority of NAATs. However, it must be remembered that a

positive NAAT does not necessarily reflect active virus replication, in contrast to virus culture, or prove direct causation in the pneumonia. In both studies, virus serology would have confirmed some infections and probably found some unrecognized ones.

Second, rhinoviruses and adenovirus were the most common viruses among 7 different viruses detected. Influenza A was found only in 1 patient. Viruses were searched for by a commercial multiplex reverse transcription polymerase chain reaction (RT-PCR) test kit capable of detecting 16 different respiratory viruses. Multiplex RT-PCR tests are now in fashion, and at least 6 commercialized kits have been on the market in Europe. However, many experts think that their sensitivity cannot reach that of a multiplex PCR test. This is difficult to prove because a gold standard is missing. Karhu et al [5] were careful and used also an in-house duplex RT-PCR test of an established virus laboratory to detect rhinoviruses and enteroviruses. Only 7 of 15 cases positive for rhinovirus by their assays would have been detected by the multiplex PCR test. Choi et al [6] found 12 different viruses by their multiplex PCR test made by the same manufacturer as that used by Karhu et al [5]. The most common viruses were rhinoviruses, human metapneumovirus (detected mostly in nasopharyngeal specimen),

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influenza viruses, and RSV. Obviously, with a multiplex PCR test the yield of rhinoviruses would have increased. In a third study on viral etiology of SCAP, rhinoviruses were detected in nasopharyngeal swabs in 33 of 393 (8%) patients [7]. The role of rhinoviruses in lower respiratory tract infections has been long questioned. Already 15 years ago, Kaiser and Hayden [8] in this journal asked whether rhinovirus pneumonia is a clinical entity. We think it is becoming well established that the answer is “yes.” The role of rhinoviruses in pneumonia has been often questioned because of the frequent detection of rhinoviruses in asymptomatic persons, particularly children. Detection of rhinovirus RNA in asymptomatic subjects most probably reflects subclinical infection or residual viral RNA from a mild preceding illness. In otherwise healthy subjects, rhinoviruses are not known to induce chronic infection, and virus shedding lasts 2–4 weeks after acute infection [9]. In the study of Karhu et al [5] the duration of symptoms before diagnosis of pneumonia was 1–5 days, showing the acute nature of infection. A difficulty with rhinoviruses is the lack of available serologic tests, except for serotype-specific ones, to verify acute infection. The observations of Karhu et al [5] strongly support the important role of rhinoviruses in the pathogenesis of SCAP. Karhu et al [5] did not study rhinovirus load, possibly because its clinical significance is not well understood. On the other hand, quantitative detection of adenovirus may have been helpful to distinguish acute infection from latent infection. High adenovirus DNA load in blood is often associated with more severe disease in immunocompromised hosts [10]. Studies are needed to assess the possible value of testing for viral RNA in blood in nonimmunocompromised hosts with CAP.

Third, Karhu et al [5] found evidence of viral–bacterial coinfection in 39% of their patients with SCAP, which is much higher than in earlier studies on CAP [1].

This figure might have been even higher if comprehensive bacterial diagnostics had been used, that is, PCR for *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Streptococcus pyogenes*. These tests were used in a study of Honkinen and coworkers [11] who found viral–bacterial coinfections in 66% of 76 children with CAP. In that study, PCR broadened the detection rate of bacteria substantially. In a study on elderly adults with serious respiratory illness, Falsey et al [12] used comprehensive bacterial testing plus serum procalcitonin to define bacterial infections and found that nearly 40% of RVIs were viral–bacterial coinfections. Bacterial coinfection in influenza is the prototype of viral–bacterial infection, and it leads to increased morbidity and mortality. During the 2009 influenza A(H1N1) pandemic, up to 55% of the fatal cases were complicated by bacterial coinfection. How influenza paves the way to secondary bacterial pneumonia is not yet well defined [13, 14]. Karhu et al [5] extend the clinical significance of viral–bacterial coinfections to other viruses than influenza. Not surprisingly, the most common combination in their study was rhinovirus plus *S. pneumoniae*, as in many other studies [1]. Several mechanisms through which rhinoviruses increase susceptibility to bacterial coinfection have been presented [15]. In the study of Karhu et al [5], clinical characteristics and outcome were similar between patients with sole bacterial and bacterial–viral infections. This observation is in agreement with those of Choi and coworkers [6]. This certainly raises the question of the real role of viruses in SCAP. Could they be innocent bystanders at the time of diagnosis, or, perhaps more likely, pathogens that both increase the risk of secondary bacterial invasion and contribute to its severity? Of note, mortality during treatment in the intensive care unit was observed only in patients with viral–bacterial coinfection [5]. Furthermore, highest

serum C-reactive protein (CRP) levels and plasma procalcitonin levels were recorded in viral–bacterial coinfections, which is in agreement with previous studies [1]. The question whether there were any cases with sole viral pneumonia remains open because all 5 possible cases had markedly increased CRP and procalcitonin levels and high white blood cell counts, suggesting undetected bacterial coinfection.

Unfortunately, opportunities for use of antivirals in the treatment of pneumonia in clinical practice are limited [16]. The use of neuraminidase inhibitors for influenza pneumonia is well established, and empiric use in addition to antibiotics for treating CAP during influenza outbreaks may make sense. In the Karhu et al study [5], no patient was treated with antivirals. It is of note that in the study of Choi et al [6], oral ribavirin was used for treatment of SCAP associated with human metapneumovirus, parainfluenza virus, and RSV infections. Ribavirin has a broad antiviral range, but its efficacy in the treatment of CAP has not been carefully studied. No antiviral drug for rhinoviruses is available in clinical practice, but the efficacy of oral vapendavir and inhaled interferon- β are being studied [16]. We found that subcutaneous interferon α -2a and oral ribavirin treatment was associated with rapid decrease and clearance of rhinovirus RNA in 4 patients with hypogammaglobulinemia and persistent rhinovirus infection [17]. Whether inhibition of rhinovirus replication is associated with clinical benefits remains to be seen. Severe adenovirus infections have been treated with intravenous cidofovir, and an orally administered derivative of cidofovir, CMX001, is a promising new product in clinical studies [16].

What are we to conclude from these observations for clinical practice? We think that the observations support the use of multiplex NAATs for respiratory virus detection in patients with SCAP. Sampling from both the nasopharyngeal and lower respiratory tract (bronchoalveolar lavage, tracheal aspirates) should be

performed. Although possibilities for antiviral treatment remain limited, several investigational agents are worthy of clinical study. Better understanding of the complex pathogenesis of SCAP is a prerequisite for improved therapy.

Note

Potential conflicts of interest. Both authors: No reported conflicts.

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