Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

for staging of lung cancer: a systematic review and meta-analysis. *Eur J Cancer*. 2009;45(8):1389-1396.

3. De Leyn P, Lardinois D, Van Schil PE, et al. ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer. *Eur J Cardiothorac Surg*. 2007;32(1):1-8.
4. Detterbeck FC, Jantz MA, Wallace M, Vansteenkiste J, Silvestri GA; American College of Chest Physicians. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132 (3 Suppl): 202S-220S.
5. Annema JT, Versteegh MI, Veselić M, et al. Endoscopic ultrasound added to mediastinoscopy for preoperative staging of patients with lung cancer. *JAMA*. 2005;294(8):931-936.
6. Vilmann P, Krasnik M, Larsen SS, Jacobsen GK, Clementsen P. Transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsy: a combined approach in the evaluation of mediastinal lesions. *Endoscopy*. 2005;37(9):833-839.
7. Wallace MB, Pascual JM, Raimondo M, et al. Minimally invasive endoscopic staging of suspected lung cancer. *JAMA*. 2008;299(5):540-546.
8. Hwangbo B, Lee G-K, Lee HS, et al. Transbronchial and transesophageal fine-needle aspiration using an ultrasound bronchoscope in mediastinal staging of potentially operable lung cancer. *Chest*. 2010;138(4):795-802.
9. Herth FJF, Krasnik M, Kahn N, Eberhardt R, Ernst A. Combined endoscopic-endobronchial ultrasound-guided, fine-needle aspiration of mediastinal lymph nodes through a single bronchoscope in 150 patients with suspected lung cancer. *Chest*. 2010;138(4):790-794.
10. Rintoul RC, Skwarski KM, Murchison JT, Hill A, Walker WS, Penman ID. Endoscopic and endobronchial ultrasound real-time fine-needle aspiration for staging of the mediastinum in lung cancer. *Chest*. 2004;126(6):2020-2022.
11. Tournoy KG, Annema JT, Krasnik M, Herth FJ, van Meerbeeck JP. Endoscopic and endobronchial ultrasonography according to the proposed lymph node map definition in the seventh edition of the tumor, node, metastasis classification for lung cancer. *J Thorac Oncol*. 2009;4(12): 1576-1584.
12. Annema JT, Bohoslavsky R, Burgers S, et al. Implementation of endoscopic ultrasound for lung cancer staging. *Gastrointest Endosc*. 2010;71(1):64-70.

Viral Community-Acquired Pneumonia

If We Do Not Diagnose It and Do Not Treat It, Can It Still Hurt Us?

Viruses are a generally neglected cause of community-acquired pneumonia (CAP) for a number of understandable reasons. They are included in investigational and epidemiologic studies, but are not routinely sought in clinical practice because they are difficult to diagnose, primarily because the methods used for this purpose (culture, immunofluorescence for viral antigens, and serology) are expensive and often unavailable, and the results do not become known in a timely manner. In addition, there are few

available antiviral agents, and when these are used therapeutically, they are not as rapidly and clinically effective as we have come to expect from antibacterial therapies.

However, viral epidemics do attract our attention, as became clear with Hantavirus in New Mexico in 1993, Severe Acute Respiratory Syndrome (SARS)-associated coronavirus in Asia in 2003, and novel 2009 influenza A(H1N1) [A(H1N1)] worldwide in 2009. In the latter instance, we appreciated the important clinical role of this pathogen, which could lead to nonpneumonic lower respiratory tract infection (tracheobronchitis), viral pneumonia (often with acute lung injury), secondary bacterial pneumonia, and probably asymptomatic colonization and carriage.¹ The severity of the infection with the novel A(H1N1) in patients of all ages, and not just the elderly as in seasonal influenza, made us pay attention, and we all became familiar with nucleic acid amplification testing (NAAT) methods for definitive diagnosis as we sought new strategies for therapy. Compelling reasons for establishing a definitive diagnosis of epidemic viral infection, even in the absence of optimal therapy, were to identify infected patients so that they could be effectively isolated and also to identify noninfected patients so that they could be removed from isolation when they had a clinical presentation of a lower respiratory tract infection.

Viruses are recognized as a common cause of CAP, yet little attention is paid to these organisms in clinical practice because of the diagnostic and therapeutic limitations discussed above. Although influenza remains the predominant viral cause of CAP in adults, the American Thoracic Society/Infectious Diseases Society of America guidelines for CAP includes other commonly recognized viruses such as respiratory syncytial virus (RSV), adenovirus, and parainfluenza virus, as well as less common viruses, including human metapneumovirus, herpes simplex virus, varicella-zoster virus, SARS-associated coronavirus, and measles virus.² In studies of CAP from Spain and Chile, using immunofluorescent antigen detection methods, the incidence of CAP caused by viral infection in immune-competent individuals has varied from 18% to 32%, and in the Chilean study, viral pneumonia was particularly common in elderly patients.^{3,4} Interestingly, in the Chilean study, pure viral infection was present in 23% of patients with CAP, and was more commonly found in patients receiving outpatient antimicrobials, implying that many of these patients may have had bacterial coinfection, but that the bacterial component was eliminated by the use of antibiotics before hospitalization.³ The incidence of viral CAP can be as high as 56% when outpatients are included and when NAAT testing is used.⁵

Viruses also probably play a pathogenic role in ventilator-associated pneumonia and in those with severe illness in the ICU, serving both as a primary etiologic pathogen, and probably as a copathogen with bacterial organisms, potentiating their role when the virus is reactivated in the setting of acute illness, as can occur with cytomegalovirus.^{6,7} Herpes simplex virus bronchopneumonitis was diagnosed in 21% of immunocompetent mechanically ventilated patients who showed a clinical deterioration.⁸ Cytomegalovirus (CMV) has been reported in 16% of mechanically ventilated immunocompetent patients, but in up to 32% of ICU patients with severe illness.^{6,7} It seems likely that patients with critical illness acquire disease-related immune suppression, which predisposes to CMV reactivation, which can in turn potentiate other inflammatory and infectious processes, although it remains uncertain if antiviral therapy will provide clinical benefit to these patients.

The exact incidence of viruses in CAP is still uncertain because of the methodologic limitations of prior studies. As mentioned, only recently have NAAT techniques become widely used, and the findings with this methodology may differ from the findings obtained with older and potentially less sensitive and specific methods. NAAT is able to diagnose infection with viruses not detectable by conventional methods, such as metapneumovirus, rhinovirus, and coronavirus, and in one study using this technique, viruses were detected in 56% of 105 patients with CAP, compared with only 14% with conventional methods.⁵ NAAT techniques are currently available that can simultaneously detect multiple viruses from a respiratory tract sample in a rapid fashion, giving results in hours. These methods are based on reverse transcriptase polymerase chain reactions (PCRs), aimed to detect viral RNA, using amplification of the viral target combined with viral-specific probes labeled with fluorescent beacons to detect and quantify the amount of viral material present in real time.⁹ When multiple viruses can be detected simultaneously, these are referred to as multiplex real-time PCR assays.

Most previous studies of viral CAP have only examined patients with pneumonia and have not compared the findings in this population to the frequency of viruses in patients with other lower respiratory infections or to the frequency in healthy adults (carriers, who do not have acute infection). In addition, it is uncertain which respiratory sample can provide the highest sensitivity for detecting viral pathogens. In this issue of *CHEST* (see page 811), Lieberman and colleagues¹⁰ used NAAT methodology to provide data on the frequency and identity of viral causes in hospitalized patients with lower respiratory tract infections. They compared the findings in those with radiographically confirmed CAP to the findings

of those in an ambulatory control population without respiratory tract infections and to a hospitalized population with nonpneumonic lower respiratory tract infections (NPLRTI). In the study, all patients had samples collected by three methods and evaluated by multiplex real-time PCR. The samples came from nasopharyngeal swabs, oropharyngeal swabs, and nasopharyngeal washes. In a separate study, the authors demonstrated that nasopharyngeal washes were the most sensitive method for detecting the presence of viral infection.¹¹ The frequency of viral CAP was 31.7% of 183 patients, compared with 7.1% of 450 controls and 51.7% of 201 with NPLRTI. The most common viral cause of CAP was coronavirus, an agent that is not usually recovered unless NAAT testing is done. Coronavirus occurred significantly more commonly in patients with CAP than in controls, but the recovery rate in patients with NPLRTI was similar to patients with CAP. Rhinovirus, RSV, and influenza virus were the next most common causes of viral CAP, in that order, but interestingly, influenza virus was much more common in NPLRTI than in CAP. In the study, the presence of viral infection was not correlated with any clinical findings other than the radiographic presence of pneumonia, patient age, and smoking history. Patients with viral CAP were less likely to be smokers than those without.

The findings in this study are unique in several ways. The population was not only studied with NAATs that are not usually clinically available, but the yield was likely increased by the inclusion of samples collected by three different methods. In addition, the frequency of viral CAP was put into context by demonstrating that viruses were even more common in patients with NPLRTIs and that the frequency of a positive test was not zero in controls, implying that some patients are carriers of viral infection or are colonized without becoming ill. The major limitations of the study are that it was performed over two winter seasons and not over a continuous 1-year period and also that the presence of viral infection was not correlated with the severity of illness or the presence of bacterial copathogens. Thus, we do not know how many patients with CAP and positive viral NAAT results could have been managed without receiving antibiotic therapy. In addition, it is possible that NAAT testing was too sensitive, and that a positive result does not always mean that the virus was the cause of CAP; the virus could simply have been colonizing the patient or serving as a predisposing factor to a secondary bacterial pneumonia. Thus many questions remain, including the role that viruses play in CAP pathogenesis and the potential benefit that antiviral therapy would have, if available in the future. If viruses are common as primary pathogens, then antiviral therapy might be valuable for CAP management, and in some

instances, antibiotics could be avoided. Similarly, if viruses are copathogens, then therapy could potentially mitigate the severity of illness or even prevent the development of a bacterial superinfection. However, if the viruses are simply colonizers, as suggested by the 7.1% recovery in the control population when NAAT methods were used, then it is unclear if antiviral therapy would have a benefit when these colonized patients develop CAP.

The data from the study by Lieberman and colleagues¹⁰ are provocative because they have demonstrated that when NAAT methods are used, there is a high frequency of viral detection in patients with lower respiratory tract infection. With the availability of new diagnostic tools, such as NAAT, we will now be able to ask questions about the clinical relevance and impact of respiratory viruses. We might be able to combine a positive test for a respiratory virus with the measurement of a serum biomarker, such as procalcitonin, in patients with radiographic CAP to define individuals who can be managed without antibiotics. New diagnostic tools for viral respiratory tract infections might also encourage the development of new antiviral therapies that could be effective in improving patient outcome. Thus, the currently available data have shown that viruses are commonly present in patients with CAP and that they can cause harm, yet in clinical practice we rarely try to diagnose their presence. This may change once these new diagnostic tools become more widely available, especially if they help us define an etiologic role of these pathogens and if they encourage the development of new and effective antiviral therapies.

Michael S. Niederman, MD, FCCP
Mineola, NY

Affiliations: From the Department of Medicine, Winthrop-University Hospital; and the Department of Medicine, SUNY at Stony Brook.

Financial/nonfinancial disclosures: Dr Niederman has served as a consultant to Aerogen, Bayer, Ceragenix, Merck, Johnson and Johnson, and Pfizer. He has received grant support from Aerogen and Biomerieux, and lecture fees from Pfizer, Bayer, Johnson and Johnson, and Merck. These activities are not relevant to the content of this editorial.

Correspondence to: Michael S. Niederman, MD, FCCP, 222 Station Plaza N, Ste 509, Mineola, NY 11501; e-mail: mniederman@winthrop.org

© 2010 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (<http://www.chestpubs.org/site/misc/reprints.xhtml>).

DOI: 10.1378/chest.10-0820

REFERENCES

1. Dawood FS, Jain S, Finelli L, et al; Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med*. 2009;360(25):2605-2615.
2. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society

- consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27-S72.
3. Díaz A, Barria P, Niederman M, et al. Etiology of community-acquired pneumonia in hospitalized patients in Chile: the increasing prevalence of respiratory viruses among classic pathogens. *Chest*. 2007;131(3):779-787.
4. de Roux A, Marcos MA, Garcia E, et al. Viral community-acquired pneumonia in nonimmunocompromised adults. *Chest*. 2004;125(4):1343-1351.
5. Templeton KE, Scheltinga SA, van den Eeden WC, Graffelman AW, van den Broek PJ, Claas EC. Improved diagnosis of the etiology of community-acquired pneumonia with real-time polymerase chain reaction. *Clin Infect Dis*. 2005;41(3):345-351.
6. Chiche L, Forel JM, Roch A, et al. Active cytomegalovirus infection is common in mechanically ventilated medical intensive care unit patients. *Crit Care Med*. 2009;37(6):1850-1857.
7. Kalil AC, Florescu DF. Prevalence and mortality associated with cytomegalovirus infection in nonimmunosuppressed patients in the intensive care unit. *Crit Care Med*. 2009;37(8):2350-2358.
8. Luyt CE, Combes A, Deback C, et al. Herpes simplex virus lung infection in patients undergoing prolonged mechanical ventilation. *Am J Respir Crit Care Med*. 2007;175(9):935-942.
9. Templeton KE, Scheltinga SA, Beersma MF, Kroes ACM, Claas ECJ. Rapid and sensitive method using multiplex real-time PCR for diagnosis of infections by influenza A and influenza B viruses, respiratory syncytial virus, and parainfluenza viruses 1, 2, 3, and 4. *J Clin Microbiol*. 2004;42(4):1564-1569.
10. Lieberman D, Shimoni A, Shemer-Avni Y, Keren-Naos A, Shtainberg R, Lieberman D. Respiratory viruses in adults with community-acquired pneumonia. *Chest*. 2010;138(4):811-816.
11. Lieberman D, Lieberman D, Shimoni A, Keren-Naos A, Steinberg R, Shemer-Avni Y. Identification of respiratory viruses in adults: nasopharyngeal versus oropharyngeal sampling. *J Clin Microbiol*. 2009;47(11):3439-3443.

Role of Contrast Echocardiography in Screening for Pulmonary Arteriovenous Malformation in Patients With Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT) is a hereditary disease characterized by the widespread development of telangiectasias and arteriovenous malformations (AVMs). The most frequent genotypes are due to mutations in ENG (HHT1) or ACVRL1 (HHT2). AVMs are most commonly seen in the liver, lung, and brain. The incidence of pulmonary AVM (PAVM) varies widely depending on the screening technique and the underlying genotype. Because PAVMs are associated with significant morbidity if untreated and embolization therapy is highly effective, accurate diagnosis is important.^{1,2}

During the past decade, transthoracic contrast echocardiography (TTCE) with agitated saline contrast