Quantitative Molecular Approach to Diagnosing Pneumonia

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(See the Major Article by Gadsby et al on pages 817–23, and the Editorial Commentary by Jain and Pavia on pages 826–8.)

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In the preantibiotic era, 95% of community-acquired pneumonia (CAP) was shown to be caused by Streptococcus pneumoniae [1]; another bacterial pathogen was isolated in the remaining 5%. Viruses, mycoplasma, and chlamydia had not been discovered, yet there were no cases for which the cause of pneumonia was listed as unknown. Since the 1950s, pneumococcus has been detected less frequently, and many other potential pathogens have been implicated [2]. Two recent prospective studies of US adults with CAP [3,4] used conventional microbiology and urine antigen detection to identify bacteria and commercially available polymerase chain reaction technology to identify viruses. Both obtained similar results, identifying pneumococci in <10% of cases and a respiratory virus in 20%–27%. Most importantly, each failed to identify a known respiratory pathogen in about 55%–62% of cases. One study [4] implicated “atypical” organisms, in total, in about 5% of cases, far below the numbers detected using a variety of serologic techniques in earlier studies. Using enhanced technology, some recent European investigations have found pneumococcus in 37%–64% of cases [5–7].

In this context, Gadsby et al used newly described technology [8] to determine the cause of pneumonia in patients hospitalized for CAP and from whom lower respiratory secretions could be obtained within 48 hours of admission. They detected a likely bacterial etiology in 72%–82% of cases, which is 3 to 4 times the yield by conventional microbiology. A virus was detected in 30% of cases, and mycoplasma, Legionella, and Chlamydia pneumoniae were detected in 2%, 1%, and 0%–1% of samples, respectively. In total, the authors identified an etiologic agent in 87% of CAP cases. Mean bacterial counts in respiratory secretions of CAP patients were between $10^7$ and $10^8$ colony-forming units (CFU)/mL, which is consistent with an earlier study from my laboratory [9]. At a cutoff of $10^5$ CFU/mL, which is not unreasonable, a likely bacterial pathogen was detected by molecular testing in specimens from 81% of patients. The similarity of Gadsby et al’s findings of viral and so-called atypical pathogens to those from recent US studies appears to validate their results, as does the ratio of detection of pneumococci to that of Haemophilus.

The importance of this work is that it provides potential insight into the most vexing problem in all recent studies, namely, the failure to find a causative organism in one half to two thirds of cases. In the United States, however, I do not believe that this gap will be filled by the finding of Streptococcus pneumoniae. The incidence of pneumococcal pneumonia in US adults has declined steadily with the use of 23-valent pneumococcal vaccine and then precipitously with the widespread vaccination of children with protein-conjugate polysaccharide vaccine. Using a molecular probe that detects 16S rRNA of S. pneumoniae (AccuProbe Streptococcus pneumoniae Culture Identification Test, Hologic, Inc., Bedford, Massachusetts), Charles Stager and I (unpublished) tested sputum obtained from patients with CAP within 48 hours of admission. This technique identified pneumococcal 16S rRNA in nearly all samples that were culture positive for S. pneumoniae and in 20% of those that were culture negative. In other words, this technique might have lowered the number of cases of undetermined etiology but would still leave a large proportion of cases unknown.

Microscopic examination of gram-stained sputum often reveals a large number of gram-positive cocci that do not resemble pneumococci, and cultures yield so-called normal respiratory flora. Thorn-er and I [10] recently suggested that other nasopharyngeal streptococci or mixed flora might be responsible. Gadsby et al would greatly enhance our understanding of the etiology of CAP if they were to expand their quantitative techniques to detect streptococci that comprise usual oral flora. The significantly greater sensitivity in pathogen detection could make this technology the standard approach for microbiological diagnosis in hospitalized CAP patients. It might render unnecessary the use of tests such as serum procalcitonin that have low sensitivity and specificity in diagnosing bacterial pneumonia [3,11].
Regarding utility and cost analysis, my basic philosophical conviction is that, in general, patients respond better to treatment if physicians know what they are treating than if they do not. I would prefer leaving a patient’s bedside having told him or her that we found the cause of the pneumonia and are treating it with an appropriate antibiotic rather than resorting to the clichés about “strong antibiotics that should work very well for you.” The costs for hospitalization in the United States are so high that the addition of a laboratory test to identify a causative organism of pneumonia would add minimally to the cost of a hospital stay; some of that additional cost would be recouped through appropriate antibiotic stewardship.

In summary, diagnostic techniques that can identify causative organisms at the time a patient is hospitalized for CAP are an important tool for the medical profession. Gadsby et al add substantially to the literature on this subject.

**Note**

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**References**