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CHEST Commentary

Rapid Diagnostic Testing for Community-Acquired Pneumonia

Can Innovative Technology for Clinical Microbiology Be Exploited?

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Two nonsynchronous events have affected the management of community-acquired pneumonia (CAP): spiraling empiricism for CAP and the "golden era" of clinical microbiology. The development of broad-spectrum antibiotics has led to widespread empiric use without ascertaining the etiology of the infecting microbe. Unfortunately, this approach clashes with the second event, which is the advent of molecular-based microbiology that can identify the causative pathogen rapidly at the point of care. The urinary antigen is a most effective rapid test that has allowed targeted therapy for Legionnaire disease at the point of care. The high specificity (> 90%) allows the clinician to administer appropriate anti-Legionella therapy based on a single rapid test; however, its low sensitivity (76%) means that a notable number of cases of Legionnaire disease will go undiagnosed if other tests, especially culture, are not performed. Further, culture for Legionella is not readily available. If a culture is not performed, epidemiologic identification of the source of the bacterium cannot be ascertained by molecular fingerprinting of the patient and the putative source strain. We recommend resurrection of the basic principles of infectious disease, which are to identify the microbial etiology of the infection and to use narrow, targeted antimicrobial therapy. To reduce antimicrobial overuse with subsequent antimicrobial resistance, these basic principles must be applied in concert with traditional and newer tests in the clinical microbiology laboratory. ***(CHEST 2009; 136:1618–1621)***

Abbreviation: CAP = community-acquired pneumonia

In this issue of *CHEST* (see page 1576), Shimada et al[1] have presented a systematic review and metaanalysis of the urinary antigen test for Legionella, which is one of the most successful diagnostic aids for infectious diseases today. It is a rapid test (results can be seen within 15 min of testing) that can have an impact on the point of care of one of the most common and lethal infectious diseases facing mankind, community-acquired pneumonia (CAP).

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CAP remains a hot clinical topic. Emerging pathogens, such as the severe acute respiratory syndrome (or SARS) coronavirus and avian influenza A (H5N1 virus) coupled with the emerging resistance of microbes to both antibacterial and antiviral agents have made this infection a constant challenge. However, the following two important events have transpired and come to a climax in the past few years: (1) the development of antimicrobial agents directed against the most common and most feared pathogens of CAP; and (2) the advent of innovative technology for the rapid identification of microbial pathogens for CAP, one of which is the urinary antigen test for Legionella. Both events are favorable to patient care, but, paradoxically, they are nonsynchronous.

The First Event: Spiraling Empiricism for CAP

Broad-spectrum antibiotic agents that are safe and effective have been formulated by the much-maligned

pharmaceutical industry. The advent of the quinolones and respiratory tract macrolides has led to a tremendous reduction in the morbidity and mortality from the once-feared Legionnaire disease because of the high mortality seen in the original American Legion outbreak. As a result, the physician-clinician has the capability to initiate empiric therapy that covers the most likely pathogens of CAP with only one or two broad-spectrum antibiotics. The empiric broad-spectrum therapy eradicates the offending pathogen and assures a favorable outcome.

The Second Event: The Golden Era of Clinical Microbiology

Pneumonia is the most common infectious cause for hospital admission, with notable morbidity, and the prescription of active antibiotic therapy has a salutary impact on outcome. The situation often is sufficiently urgent that antibiotic therapy only should be administered based on suspicion of diagnosis. So, the results of laboratory tests, if they are to have clinical relevance, must be rapidly available at the point of care.

The polymerase chain reaction methodology was developed successfully in the 1980s, and automated instrumentation that harnessed the power of molecular biology has been applied successfully to laboratory testing. Molecular-based tests finally have moved from the research bench to the clinical diagnostic laboratory and now are becoming commercially available. Complex instruments can survey an entire pantheon of pathogens, including viral pathogens and the classic bacterial pathogens of CAP. Moreover, the results are available within a few hours of obtaining a patient specimen. This technical advance should allow targeted antimicrobial therapy because numerous pathogens of CAP now can be identified at the point of care. It appears that the long-anticipated "golden era" for clinical microbiology finally can have an impact on medical practice for CAP.

Deemphasis of Clinical Microbiology

Disappointingly, a few studies have shown that knowledge of the identity of the offending pathogen has less of an impact on outcome than anticipated. Targeting the pathogen with a narrow-spectrum antibiotic after laboratory results have become available often is not exploited; rather, therapy with the broad-spectrum agent (or agents) merely is continued by the physician.[2,3]

As a result, an unanticipated and insidious deemphasis of the use of clinical microbiology has occurred, and therein lies the asynchronicity. For example, the Infectious Diseases Society of America and American Thoracic Society guidelines[4,5] no longer recommend sputum culture, Gram stain, blood culture, and Legionella testing as a routine necessity. Disappointingly, these microbiology tests instead are listed as an option in these guidelines. So, the most important functions of a clinical microbiology laboratory have been usurped in the stampede for empiric antibiotics.

Quality assurance guidelines[6] now require that therapy be initiated within 6 h of the diagnosis of CAP, placing pressure on physicians to provide immediate antimicrobial therapy at the point of care. This has also led to the unanticipated practice of administering empiric, broad-spectrum antibiotics to patients who do not have pneumonia.[7,8] Antimicrobial resistance is the expected consequence. A requisite waiting period required for specimen collection, delivery to the laboratory, and microbiology processing has become a major impediment to targeted antimicrobial therapy. This deemphasis of clinical microbiology has led to budgetary cuts for the laboratories and the loss of trained personnel. Moreover, many laboratories now are being moved from the proximity of the patient to a location outside of the hospital. The physical separation produces a disconnect in the collaborative nature of infectious disease management and clinical microbiology.

Legionella Urinary Antigen

The urinary antigen for Legionella was developed in the late 1970s[9,10] and is one of the most successful of the rapid diagnostic microbiology tests. Unfortunately, the test only can reliably detect one species, *Legionella pneumophila*, and only one serogroup. Nevertheless, it has significant advantages over direct fluorescent antibody testing for Legionella, antibody serology, and culture, including its relatively low cost and rapid performance. Most importantly, the results affect management at the point of care. As a result, the urinary antigen test now is the most common method used to make the diagnosis of Legionnaire disease. A dramatic increase in the proportion of cases of Legionnaire disease diagnosed as a result of the urine antigen test has occurred worldwide. In Europe, only 15% of cases were diagnosed with use of the urine antigen test in 1995 compared with $>$ 90% in 2006.[11] Among the 10,753 cases of Legionnaire disease reported to the Centers for Disease Control and Prevention between 1980 and 1998, a significant increase was seen in the proportion of patients with a positive urine test; diagnosis as a result of urine antigen testing in-

creased from 0% to 69% over this period, and the proportion likely is higher today.

Simultaneously, the use of Legionella culture and direct fluorescent antibody testing has notably declined.[12] For example, only 5% of travel-associated cases of Legionnaire disease were diagnosed by use of culture compared with 89% diagnosed by the use of urine antigen testing.[13] Among health-care–associated cases of Legionnaire disease reported in the United States, 76% were diagnosed through the use of the urine antigen test, and only 3% through culture.[14]

The test has evolved from a radioimmunoassay to an enzyme immunoassay to an immunochromatographic test (Binax NOW urinary antigen test; Binax; Portland, ME). As the metaanalysis by Shimada et al[1] has shown, among the three immunochromatographic assays, the immunochromatographic test (Binax NOW urinary antigen test; Binax) had a sensitivity and specificity of 91.8% and 100%, respectively, compared with 71.2% and 96.6%, respectively, and 31.5% and 98.9%, respectively, for the other two tests. It is important to note that with these different formats, substantial differences in sensitivity and specificity would be expected.

The metaanalysis by Shimada et al[1] gives a good overview of the advantages and weaknesses of the Legionella urinary antigen, and a number of points are worth reemphasizing. An advantage of the urinary antigen test is its simplicity of collection and the rapidity of the test results. These tests are much less influenced by prior antibiotic therapy than sputum culture. Because the specificity is high (99.1%, as shown in the metaanalysis), the message of relevance to the clinician is that when a test result is positive, initiating anti-Legionella antibiotic therapy is imperative. However, as the metaanalysis[1] also has shown, the sensitivity is not as high (74%), even with the more sensitive commercially available tests. At least one-quarter of patients with confirmed legionellosis can have a negative test result. The sensitivity also is affected by the course of the infection. In milder cases, the disease may not be sufficiently advanced such that the amount of antigen in the urine is not detectable. Although the Centers for Disease Control and Prevention reported[12] that the urine antigen test is more sensitive than a culture, we found[15] that when performed properly with selective and dye-containing media, culture is useful as a "gold standard."

More than 90% of cases of Legionnaire disease in patients with CAP are caused by *L pneumophila*, and 50% to 90% of these are caused by *L pneumophila* serogroup 1.[12,16] The next most common species obtained from patients with CAP are *Legionella micdadei* and *Legionella longbeachae*. Surprisingly, *L longbeachae* is common in Australia and New Zealand for reasons that are uncertain. Consequently, the urinary antigen is less valuable in these countries. Other serogroups, especially in hospital-acquired infections, also can cause disease, particularly *L pneumophila* serogroup 6. The urinary antigen is insensitive for these other species and serogroups, so the diagnosis of legionellosis due to other serogroups of *L pneumophila* or other species depends on the recovery of the organism from the culture or from serologic antibody tests.

Another consequence of the deemphasis of clinical microbiology is the decreased use of Legionella culture. Too many hospitals outsource these tests to reference laboratories, which causes an unacceptable delay in reporting results. All too often, clinicians order a urine antigen test without submitting or requesting a sputum culture. Both the urine antigen test and the Legionella culture should be performed on site for maximal effectiveness. Urine antigen test results should be available in 3 h instead of 3 days to allow for the opportunity to initiate targeted anti-Legionella therapy quickly. The ease of performing the ICT card-type urine test makes it ideal for use in EDs, long-term care facilities, and physician offices.

We believe that culture also should be readily available within the hospital if the hospital water supply is colonized with Legionella, and 70% of hospitals in the United States may well be colonized.[17] Culture allows the isolation of the organism so that molecular fingerprinting can be performed. Microbiology laboratories should freeze these isolates or forward them to a public health laboratory in anticipation of epidemiologic investigation. The simple practice of holding respiratory specimens in the refrigerator for 7 days allows the microbiology laboratory to retrieve the respiratory specimen if or when the urine antigen test result is positive. One reason that so many cases of Legionnaire disease (including the Pittsburgh pneumonia agent or *L micdadei*) were seen in Pittsburgh, PA, was because of the widespread availability of culture capability in Pittsburgh community hospitals as well as in academic tertiary care centers. Thus, more cases of Legionnaire disease were diagnosed annually in the Pittsburgh area than in most states.[18]

Given the recent increase in the incidence of Legionnaire disease in the United States and Europe,[19–21] there is motivation to reverse this trend and provide public health officials with the opportunity to determine the source of exposure. The isolate cultured from the patient is useful for diagnosis, case finding, and identification of the source.

The article by Shimada et al[1] concluded with a plea for more high-quality studies. However, in our opinion, more studies of statistical rigor are not the key. The key is to resurrect the use of culture (or to develop rapid diagnostic tests that can identify all the

Legionella species and serogroups) and to strengthen the role of the clinical microbiology laboratory. Although dramatic progress has been made in molecular biology, with increasing roles for nucleic acid amplification, sequencing, and typing methods, there remains a need for validation of these newer tests. The results of molecular diagnostic assays must be correlated with clinical findings and culture results.

Physicians must resurrect the application of the basic principles of infectious diseases, which are to identify the etiology of CAP and then use narrow, targeted therapy. To do so, the full clinical microbiology armamentarium with the newer molecular tests must be exploited. The return of the sputum Gram stain, sputum culture, and blood cultures also would provide information that allows the use of penicillin for pneumococcal pneumonia.[22] With the advent of sensitive rapid tests for viral pathogens (especially influenza), empiric antibacterial agent therapy, which is ineffective while promoting drug resistance, can be replaced by effective antiviral therapy. If there truly is to be a golden era of clinical microbiology and a reduction in antibiotic misuse and overuse, we will need to be smarter in the use of all of the weapons at our disposal, including traditional tests and the newer molecular-based tests.

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