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Current and Potential Usefulness of Pneumococcal Urinary Antigen Detection in Hospitalized Patients With Community-Acquired Pneumonia to Guide Antimicrobial Therapy

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Background: The role of pneumococcal urinary antigen detection in the treatment of adults with community-acquired pneumonia (CAP) is not well defined. We assessed the usefulness of pneumococcal urinary antigen detection in the diagnosis and antimicrobial guidance in patients hospitalized with CAP.

Methods: A prospective study of all adults hospitalized with CAP was performed from February 2007 through January 2008. To evaluate the accuracy of the test, we calculated its sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios. The gold standard used for diagnosis of pneumococcal pneumonia was isolation in blood or pleural fluid (definite diagnosis) and isolation in sputum (probable diagnosis). Antibiotic modifications, complications, and mortality were analyzed.

Results: A total of 474 episodes of CAP were included. *Streptococcus pneumoniae* was the causative pathogen in 171 cases (36.1%). It was detected exclusively by urinary antigen test in 75 cases (43.8%). Sixty-nine patients had CAP caused by a pathogen other than *S pneumoniae*. Specificity was 96%, positive predictive value ranged from 88.8% to 96.5%, and the positive likelihood ratio ranged from 14.6 to 19.9. The results of the test led the clinicians to reduce the spectrum of antibiotics in 41 patients. Pneumonia was cured in all of them. Potentially, this optimization would be possible in the 75 patients diagnosed exclusively by the test.

Conclusion: When its findings are positive, the pneumococcal urinary antigen test is a useful tool in the treatment of hospitalized adult patients with CAP because it may allow the clinician to optimize antimicrobial therapy with good clinical outcomes.

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ACCORDING TO CURRENT Infectious Diseases Society of America guidelines,[1] hospitalized patients with community-acquired pneumonia (CAP) should receive an empirical broad spectrum antibiotic therapy to cover the most frequent etiologies. The same guidelines[1] encourage investigation for specific pathogens that would significantly alter standard treatment. Rational use of antibiotics, using an appropriate pathogen-focused agent or narrowing empirical therapy, may decrease cost, drug adverse events, and the threat of antibiotic resistance.[1-4]

The yield of traditional microbiological investigations is limited for several reasons: routine difficulties in obtaining good-quality sputum and the uncertainty of the value of its culture results, low sensitivity of blood cultures, and administration of antibiotics before samples collection.[5,6]

Tests based on urinary detection of bacterial antigens and nucleic acid amplification techniques try to solve these difficulties and, because of their rapidity, to minimize time in receiving microbiological results and provide an early and appropriate treatment.[7]

See Invited Commentary at end of article

A quick and simple urinary antigen test, based on an immunochromatographic membrane technique, is widely available to detect the C-polysaccharide antigen of *Streptococcus pneumoniae*, the leading cause of CAP. This test has demonstrated reasonable sensitivity and good specificity in different studies.[8-13] Nevertheless, the clinical usefulness of this pneumococcal urinary antigen test is not well defined, and, consequently, current guidelines do not clearly recommend the situations in which testing should be performed. A prospective controlled study concluded that the pneumococcal urine test allows the tar-

geted antibiotic therapy in young immunocompetent outpatients with nonsevere CAP.[14] In hospitalized patients, a recently published randomized study[15] found no benefit of targeted therapy based on urine antigen detection tests; however, its results were affected by design problems and the low number of patients included in the study.[16]

The aims of our study were to assess (1) the current use of pneumococcal urinary antigen detection in our setting, (2) its reliability for the etiologic diagnosis of pneumococcal pneumonia and its contribution to increase the etiologic diagnosis of CAP, and (3) the current and potential optimization of antimicrobial therapy according to pneumococcal urinary antigen detection results analyzing the outcomes of patients in whom treatment was modified according to the test result.

METHODS

SETTING AND STUDY POPULATION

We performed a prospective study of all consecutive adult patients (≥16 years old) hospitalized with CAP from February 2007 through January 2008. The study was performed in the Hospital Universitari Vall d'Hebron (Barcelona, Spain), a 1200-bed teaching hospital that serves a population of about 500 000 people. The study was approved by the commission of medical ethics of our hospital.

DEFINITIONS

Community-acquired pneumonia was defined as the presence of a new infiltrate on a chest radiograph with at least 1 of the following symptoms of acute respiratory illness: fever, new onset of cough, sputum production, dyspnea and/or tachypnea, pleuritic chest pain, and auscultatory findings consistent with pulmonary consolidation. Patients who were diagnosed as having diseases other than CAP during the follow-up (pulmonary tuberculosis, pneumonia caused by *Pneumocystis jiroveci*, lung cancer, or criptogenetic organizing pneumonia) were excluded.

The following criteria were used to classify a case of pneumonia as being of known etiology: (1) definite diagnosis proved by recovery of a pathogen from a normally sterile sample (blood or pleural fluid), positive result of a urinary antigen test for detection of *Legionella pneumophila*, 4-fold increase in the antibody titer for *Mycoplasma pneumoniae, Chlamydophila pneumoniae*, *Coxiella burnetii,* and *L pneumophila* between acute and convalescent serum samples and positive result in the polymerase chain reaction (PCR) for *S pneumoniae* in pleural fluid; (2) probable diagnosis shown by isolation of 1 predominant microorganism in a culture of a good-quality sputum sample with a concordant morphotype on Gram stain; (3) aspiration pneumonia, diagnosed on a clinical and radiological basis for patients who had a predisposing cause of aspiration (compromised consciousness, altered gag reflex, or dysphagia); and (4) mixed infections, diagnosed on the basis of the isolation of 2 or more microorganisms in a good-quality sputum sample with concordant morphotypes on Gram stain or more than 1 microorganism isolated in blood cultures.

Antimicrobial therapy was prescribed by the attending physician according to hospital protocol. In brief, empirical treatment for CAP consists in amoxicillin plus clavulanic acid or a third-generation cephalosporin. In those patients with severity criteria (based on clinical findings and current prediction rules) or with clinical suspicion of an atypical microorganism, azithromycin is added. Levofloxacin is the alternative agent in case of β-lactams allergy. If the patient has risk factors for *Pseudomonas aeruginosa,* piperacillin-tazobactam or cefepime is used.

STUDY PROCEDURES

The following baseline data were recorded from each patient: age, sex, smoking (≥5 cigarettes/d at CAP presentation or ≥1 month before), harmful alcohol consumption (≥60 g/d in men or ≥40 g/d in women), underlying diseases (chronic obstructive pulmonary disease [COPD], diabetes mellitus, chronic liver disease or cirrhosis, chronic heart disease, chronic renal failure, cerebrovascular disease, and cancer), immunosuppressive condition (long-term corticosteroid use defined as consumption of ≥10 mg/d of prednisone or equivalent during ≥130 days, chemotherapy for solid tumor, hematological malignant disease, human immunodeficiency virus [HIV] infection, and solid organ or bone-marrow transplantation), severity-of-illness scores (Pneumonia Severity Index [PSI] and CURB-65 [scoring by confusion, uremia, respiratory rate, low blood pressure, and age ≥65 years]) and, finally, previous and empirical antimicrobial therapy.

During follow-up we collected data on time to apyrexia, complications (respiratory failure, complicated pleural effusion, septic shock, and intensive care unit [ICU] admission), antimicrobial modifications (including timing and medical reason for these modifications), treatment duration, length of stay, mortality during the first 48 hours after admission, and, finally, 30-day mortality.

MICROBIOLOGICAL PROCEDURES

Diagnostic workup included (1) 2 sets of blood cultures in aerobe and anaerobe medium; (2) sputum sample collected when available (acceptable if it contained >25 polymorphonuclear leukocytes and <10 epithelial cells per high-power field); (3) culture and PCR findings for *S pneumoniae* in pleural fluid in patients requiring a thoracocentesis; (4) serologic determinations to detect *L pneumophila*, *M pneumoniae*, *C pneumoniae*, and *C burnetii* when they were requested by the attending physician; (5) urinary antigen detection for *L pneumophila* performed if there was clinical or epidemiological suspicion and in all cases of severe CAP; and (6) pneumococcal urinary antigen detection performed according to the attending physician.

The immunochromatographic assay BinaxNOW *S pneumoniae* urinary antigen test (Binax Inc, Portland, Maine) was used to detect the C-polysaccharide antigen from the cell wall of *S pneumoniae.* This test, performed in accordance with the manufacturer's instructions, is used in unconcentrated urine samples and gives a result in an average of 15 minutes.

Susceptibility of *S pneumoniae* to penicillin was analyzed according to 2008 Clinical and Laboratory Standards Institute revised breakpoints for infections other than meningitis: susceptible, minimal inhibitory concentration (MIC) = 2 mg/mL or lower; intermediate, MIC = 4 mg/mL; and resistant, MIC = 8 mg/mL or higher.[17]

DIAGNOSTIC ACCURACY OF THE TEST

To evaluate the reliability of pneumococcal urinary antigen detection we calculated its sensitivity and positive and negative predictive values, using 3 different reference groups of patients as the gold standard: (1) in definite pneumococcal pneumonias (CAP with *S pneumoniae* isolated in blood or pleural fluid culture); (2) in probable pneumococcal pneumonias (CAP with *S pneumoniae* as the predominant morphotype on Gram stain or culture of good-quality sputum); and (3) globally in all pneumococcal pneumonias (definite plus probable).

Specificity was calculated using 2 different control groups: (1) exclusively nonpneumococcal pneumonias (CAP with definite or probable microbiological results different from *S pneumoniae,* excluding CAP caused by aspiration; CAP of mixed eti-

Table 1. Baseline Demographic and Clinical Characteristics of 474 Episodes of Community-Acquired Pneumonia

Characteristic	No. (%)
Sex	
Male	317 (66.9)
Female	157 (33.1)
Age, mean (SD), y	64 (19.5)
>80	108 (22.8)
Underlying diseases	327 (69)
COPD	159 (33.5)
Diabetes mellitus	89 (18.8)
Heart failure	81 (17.1)
Active cancer	65 (13.7)
Chronic renal failure	44 (9.3)
Cerebrovascular disease	43 (9.1)
Chronic liver disease or cirrhosis	27 (5.7)
Immunosuppressive conditions	96 (20.3)
Chronic steroids consumption	33 (6.9)
Hematological malignant disease	22 (4.6)
HIV infection	21 (4.4)
Chemotherapy for solid tumor	17 (3.5)
Solid organ transplantation	11 (2.3)
Bone marrow transplantation	2 (0.4)
Severity-of-illness scores	
PSI high mortality risk classes (IV and V)	276 (58.2)
CURB-65 high mortality risk group (≥3 points)	104 (21.9)
Respiratory failure	211 (44.5)
Septic shock	74 (15.6)
ICU admission	41 (8.6)

Abbreviations: COPD, chronic obstructive pulmonary disease; CURB-65, scoring by confusion, uremia, respiratory rate, low blood pressure, and age 65 years or older; HIV, human immunodeficiency virus; ICU intensive care unit; PSI, Pneumonia Severity Index.

Table 2. Etiology of Community-Acquired Pneumonia

Microorganism	No. (%)
Streptococcus pneumoniae	171 (36.1)
Legionella pneumophila	15 (3.2)
Haemophilus influenzae	13 (2.7)
Gram-negative enteric bacilli (non–*Pseudomonas* species)	11 (2.3)
Pseudomonas aeruginosa	10 (2.1)
Staphylococcus aureus	4 (0.8)
Chlamydophila pneumoniae	3 (0.6)
Mycoplasma pneumoniae	3 (0.6)
Anaerobes	2 (0.4)
Mixed infections	9 (1.9)
Other microorganisms[a]	6 (1.3)
Aspiration	22 (4.6)
Unknown	205 (43.2)

[a] *Streptococcus* species (other than pneumococcus), *Moraxella* species, *Nocardia* species, and *Coxiella burnetii.*

ology in which pneumococcus was isolated; and CAP with unknown etiology) and (2) all patients without a diagnosis of pneumococcal pneumonia, including those with aspiration pneumonia and pneumonia of unknown etiology. We also calculated positive and negative likelihood ratios (LRs) as a measure of the extent to which the pretest odds were altered by the test results; low negative LR (<0.1) and high positive LR (>10) are considered useful for ruling out and ruling in decisions, respectively.[18]

Table 3. Diagnosis of Pneumococcal Pneumonia

Microbiological Test	No. (%)
Definite diagnosis	
By blood culture	53 (30.9)
By pleural fluid culture (2) or PCR (3)	5 (2.9)
Probable diagnosis	
By sputum Gram stain and culture	38 (22.2)
Exclusively by urinary antigen test	75 (43.8)
Total	**171**

Abbreviation: PCR, polymerase chain reaction.

CLINICAL USEFULNESS OF PNEUMOCOCCAL URINARY ANTIGEN TEST

We collected the modifications of antimicrobial therapy according to the pneumococcal urinary antigen results and classified this modification as (1) optimal: narrowing the antimicrobial spectrum to intravenous penicillin or ampicillin or switch to oral route with amoxicillin; (2) improved: withdrawal of the macrolide in patients empirically treated with β-lactam and macrolide combination or partial reduction of antimicrobial spectrum (eg, changing from piperacillin-tazobactam to amoxicillin-clavulanate or ceftriaxone instead of to penicillin or ampicillin); (3) inappropriate therapy modifications; or (4) no changes in empirical therapy. We considered that the change in antibiotic treatment was due to the pneumococcal urinary antigen result when it was specifically recorded in the clinical chart of the patient and confirmed by the attending physician.

Finally, clinical outcomes of patients who received treatment adjustments according to urinary antigen test results were assessed. Statistical calculations were performed using SPSS software (version 15.0 for Windows; SPSS Inc, Chicago, Illinois).

RESULTS

A total of 474 episodes of CAP in 464 patients were included. There were 317 men (66.9%) and 157 women (33.1%), with a mean (SD) age of 64 (19.5) years. Baseline demographic and clinical characteristics of patients are summarized in **Table 1**. Forty-nine patients (10.3%) died during follow-up, 15 of whom (30.6%) died during the first 48 hours after admission.

Blood cultures were performed in 382 patients (80.6%) and in 68 cases (17.8%) a microorganism was isolated. A culture of pleural fluid was analyzed in 47 patients (9.9%), and in 10 cases the findings were positive. *Legionella pneumophila* urinary antigen test was performed in 386 cases (81.4%) with 14 positive results. Finally, in 45 patients (9.5%), paired serum samples were tested for atypical microorganisms with positive results in 10 cases.

Causal microorganisms are detailed in **Table 2**. Diagnosis of pneumococcal pneumonia was performed in 171 cases (36.1%). In 75 cases, diagnosis was made only by positive pneumoccoccal urinary antigen detection. Microbiological tests that provide the diagnosis of pneumococcal pneumonia are detailed in **Table 3**.

Susceptibility to antibiotics was available for 78 isolates of *S pneumoniae*, 50 of them from blood samples and 28 from sputum cultures. There was not any strain resistant to penicillin or cephalosporins.

Table 4. Calculation of Sensitivity, Specificity, Positive and Negative Predictive Value, and Positive and Negative Likelihood Ratio According to Different Pneumococcal Pneumonias Reference Group

Reference Group	No.	AgP Positive, (AgP Performed)	(95% CI)					
			Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+	LR–
Patients With a Diagnosis of Nonpneumococcal Pneumonias[a]								
Definite diagnosis[b]	58	39 (50)	78.0 (64.0-88.4)[c]	96.0 (86.5-99.5)	95.1 (83.4-99.4)	81.6 (69.5-90.4)	19.9 (5.1-77.9)	0.23 (0.13-0.38)
Probable diagnosis[d]	38	16 (28)	57.1 (37.0-75.5)	96.0 (86.5-99.5)	88.8 (65.3-98.6)	80.3 (68.1-89.4)	14.6 (3.6-58.8)	0.44 (0.29-0.68)
Globally[e]	96	55 (78)	70.5 (59.0-80.3)	96.0 (86.5-99.5)	96.5 (87.9-99.5)	68.0 (56.0-78.5)	17.9 (4.6-70.5)	0.31 (0.22-0.43)
All Patients Without a Diagnosis of Pneumococcal Pneumonia[f]								
Definite diagnosis[b]	58	39 (50)	78.0 (64.0-88.4)[c]	98.6 (96.0-99.7)	92.8 (80.5-98.5)	95.3 (91.7-97.6)	58.5 (18.8-181.7)	0.22 (0.13-0.37)
Probable diagnosis[d]	38	16 (28)	57.1 (37.0-75.5)	98.6 (96.0-99.7)	84.2 (60.4-96.6)	94.8 (91.2-97.3)	42.8 (13.3-137.9)	0.44 (0.28-0.66)
Globally[e]	96	55 (78)	70.5 (59.0-80.3)	98.6 (96.0-99.7)	94.8 (85.6-98.9)	90.6 (86.2-93.9)	52.9 (17.0-164.2)	0.30 (0.21-0.42)

Abbreviations: AgP, pneumococcal urinary antigen detection; CAP, community-acquired pneumonia; CI, confidence interval; LR+, positive likelihood ratio; LR–, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

[a] Community-acquired pneumonia with definite or probable microbiological results different from *Streptococcus pneumoniae* excluding CAP due to aspiration, CAP of mixed etiology in which pneumococcus was isolated, and CAP with unknown etiology.

[b] Isolation of *S pneumoniae* from blood or pleural fluid.

[c] If we consider only patients with bacteremia, the sensitivity was even higher; 38 tested positive of 47 available (80.8%; 95% CI, 66.7-90.8).

[d] Isolation of *S pneumoniae* as predominant microorganism in a culture of a good-quality sputum sample with a concordant morphotype on Gram stain.

[e] Both definite and probable diagnosis added.

[f] Including those with aspiration pneumonia and pneumonia of unknown etiology.

CURRENT USE OF PNEUMOCOCCAL URINARY ANTIGEN DETECTION

Pneumococcal urinary antigen assay was performed in 383 cases of CAP (80.8%), and findings were positive in 136 (35.5%). The test was performed in 153 of 171 patients (89.5%) with pneumococcal pneumonia, and it was positive in 130 (85.0%). The other 6 positive results were found in the following situations: 3 positive results in mixed infections in which pneumococcus was isolated, 1 in aspiration pneumonia and the remaining 2 in pneumonias due to *Escherichia coli*. These diagnosis of pneumonia caused by *E coli* were based on isolation in blood culture in 1 case and isolation of *E coli* as the only bacterial isolation in a good-quality sputum sample in the other. Both patients were severely immunosuppressed, 1 with an extensive lung cancer in chemotherapy and the other with AIDS. The result of pneumococcal antigen test was considered false positive in both cases.

DIAGNOSTIC ACCURACY OF THE TEST AND ITS CONTRIBUTION TO ETIOLOGIC DIAGNOSIS OF CAP

In the group with definite pneumococccal pneumonias, the pneumococcal urinary antigen test was performed in 50 cases, and it was positive in 39. In the group with probable pneumococcal pneumonias, the antigen test was performed in 28 cases and was positive in 16. Taking into account both groups together, the pneumococcal urinary antigen test was performed in 78 cases, and its result was positive in 55. In the nonpneumococcal pneumonias group, the test was performed in 51, and the findings were positive in 2 cases, which were considered to be false-positive results. Calculations of sensitivity, specificity, positive and negative predictive values, and positive and negative LRs by the different methods described are shown in **Table 4**.

The test allowed the diagnosis of pneumococcal pneumonia in 75 additional cases (43.8% of pneumococcal pneumonias). In consequence, the number of patients with CAP in whom an etiologic diagnosis was achieved increased from 194 (40.9%) to 269 (56.7%).

OPTIMIZATION OF ANTIMICROBIAL THERAPY ACCORDING TO THE ANTIGEN TEST RESULTS

Positive results from the pneumococcal antigen test led the clinicians to reduce the spectrum of antibiotic treatment in 41 patients (8.6%). These reductions consisted in improved modification of empirical therapy in 18 cases and optimal modification of empirical therapy in 23. The median time to these modifications was 1 day (interquartile range [IQR], 1 day) in the improved adjustments group and 3 days (IQR, 3 days) in the optimal group. Globally, the median time to a treatment optimization due to the pneumococcal urinary antigen test result was 2 days (IQR, 2.5 days).

Five of these 41 patients (12.2%) were admitted to an ICU setting, 24 (58.5%) had 1 or more underlying disease, and 20 (48.8%) were classified as having a high mortality risk according to the PSI. Community-acquired pneumonia was cured in all of them. Just 1 patient died of progression of an underlying oncologic disease in the 18th day of admission. In this patient, the antibiotics modification was from piperacillin-tazobactam plus azithromycin to amoxicillin-clavulanate due to the positive antigen test result.

There were no cases of inappropriate adjustment of antimicrobial therapy. Despite the positive result of urinary antigen, in the remaining 89 cases the treatment was not modified.

COMMENT

The urinary detection of pneumococcal antigen was widely used in our setting for the etiologic diagnosis of CAP.

Sensitivity of the test varied according to the reference group used as the gold standard. It changed from 78.0% in pneumococcal pneumonias with definite diagnosis to 57.1% in the group of probable pneumococcal pneumonias. Taken together, the sensitivity of the test was 70.5%. These results are similar to those reported in previous studies.[8-13]

It is known that in the pediatric population specificity is below 70% because children have high rates of nasopharyngeal colonization.[19] In contrast, the number of false-positive test results in adults is lower even in patients with COPD, those with respiratory infections different from pneumonia, patients infected with HIV, and those with bacteremias caused by *Streptococcus* species different from pneumococcus.[9-11,13,20] We attempted to analyze this parameter using patients with nonpneumococcal pneumonia as the control group. Specificity was high and reached 96%, findings similar to those of other studies.[9-11] According to this specificity, the high positive predictive value and the high positive LR obtained in all reference groups, we think that the test, when the findings are positive, has a great value for the diagnosis of pneumococcal pneumonia. There were 2 patients with a urinary antigen test classified as false positive. They could have had a polymicrobial pneumonia in which *S pneumoniae* was involved as we documented in 3 other mixed infections with isolation of pneumococcus. Mixed infections represent approximately 5% to 10% of CAP in several studies.[21,22] Most coinfective pathogens in these cases are viral agents that do not usually require specific antimicrobial therapy. These microorganisms are not routinely investigated, but the underestimation of its role in CAP seems to have little importance in therapeutic matters.[22,23]

We also calculated the diagnostic accuracy of the test using all patients without a diagnosis of pneumococcal pneumonia, including those with aspiration pneumonia and pneumonia of unknown etiology. With this method, the specificity, negative predictive value, and positive LR are even higher. Nevertheless, it is possible that some cases of aspiration pneumonia or CAP of unknown etiology could be caused by an undiagnosed *S pneumoniae*. In addition, if we include all patients with CAP of unknown etiology, because they had a negative result in the pneumococcal urinary antigen detection, the number of cases with a negative test result is higher, so it increases, maybe erroneously, the specificity, the negative predictive value, and positive LR of the test, causing an overestimation in its accuracy. For these reasons, we think that evaluating the accuracy using only the nonpneumococcal pneumonias as a control group is a more reliable approach.

Few studies reflect the usefulness of the pneumococcal urinary antigen detection in the current clinical practice. In a recent open-labeled controlled trial[14] in immunocompetent young outpatients with positive pneumococcal urinary antigen test results, the results of a targeted therapy with amoxicillin were as effective as therapy with broader spectrum antibiotics.

In hospitalized patients, there is scarce information about pneumococcal urinary antigen-guided therapy. In these patients this test would allow physicians to use therapy directed against pneumococcus (pneumococcus-directed therapy if the test results are positive) and would enable them to switch to the oral route with amoxicillin when clinical stability would be achieved.

In a study of 59 patients with CAP, positive results of this test did not involve any modification in the empirical treatment; however, only 9 patients with a positive test result were included.[24] Kobashi et al[25] evaluated prospectively the use of the test in 168 patients admitted with CAP to a university hospital. Empirical treatment was modified in the 44 patients in whom the test results were positive, and they had acceptable outcomes. However, just 10 received a targeted antipneumococcal antibiotic like ampicillin. The remaining patients received broader spectrum antibiotics, such as carbapenems and respiratory quinolones, which makes it difficult to evaluate the usefulness of targeted therapy. The only randomized trial that tried to focus on this question failed to demonstrate a clinical benefit of targeted therapy based on urinary antigen test results. This study was designed to compare an empirical vs a targeted treatment on the basis of urine antigen results in hospitalized patients with CAP. The authors[15] did not find differences between these 2 strategies in terms of clinical outcomes or economic benefits. Moreover, they observed some clinical relapse in patients who received a targeted therapy that might be due to uncovered agents in some potential mixed infections. However, the main limitations of this study were the low number of patients with positive pneumococcal antigen test results included (25 patients in the targeted treatment arm) and the 2 to 6 days of broad spectrum antibiotic therapy given before the targeted therapy that makes it difficult to assess the effect of this strategy.[16]

In our study, patients started the targeted therapy during the first to third day after admission, and the good clinical outcomes assessed in the 41 patients who received a favorable adjusted therapy suggest that a targeted therapy for pneumoccoccus is a valid strategy to treat inpatients with CAP. We also did not observe any relapse in the 23 patients with an optimal adjustment.

Taking into account that current usefulness of the pneumoccoccal antigen test allowed the clinicians to use a narrow antimicrobial spectrum with good clinical outcomes, potentially the antimicrobial optimization could have been possible in the 75 patients diagnosed exclusively by the pneumococcal urinary antigen test. Moreover, the adjustment could have also been performed in all 130 patients with pneumococcal pneumonia in whom the test results were positive because it provides results faster than conventional microbiological methods.

Patients with immunosuppressive conditions are often excluded from studies of adult CAP. In our study we included all patients with CAP, even those with immunosuppressive conditions (20.3% of the total population). Because of the high proportion of these patients, we think that our results could also be applicable to this high-risk population.

Our study had some limitations. We did not study the duration of test positivity after pneumococcal infection. Previous studies have shown that 50% to 70% of patients have positive test results 4 to 6 weeks after the pneumonia episode.[10-20] In our cohort, this matter could have little relevance because there were just 10 patients who experienced more than 1 episode of CAP, and the time

between episodes was over 3 months in all cases. Another possible limitation of our study is that specific diagnostic tests were performed according to the attending physician, and consequently we did not have complete microbiological data for all patients included in the study. Because patients with missing data are not included in the analysis of the accuracy of the pneumococcal urinary antigen test and urinary antigen detection for *S pneumoniae* was performed in a very high proportion of the patients (80.8%), we think that the possible bias should not significantly affect the final results of our study. Although our study was not designed as a randomized clinical trial, the prospective analysis of an important number of patients with CAP allows us, in our opinion, to suggest the clinical effectiveness of the pneumococcal urinary antigen detection.

In conclusion, because of its high specificity, positive predictive value, and positive LR, we think that the urinary detection of pneumococcal antigen is a useful tool in the treatment of adult inpatients with CAP. When findings are positive, it allows clinicians to optimize antimicrobial therapy with good clinical outcomes. In our opinion, this test should be incorporated into clinical guidelines at the same level as classic microbiological studies because it can supplement, but not replace, their results.

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INVITED COMMENTARY

A Clinical Solution to Antimicrobial Resistance in Community-Acquired Pneumonia

Narrowing the Spectrum of Antimicrobial Therapy

For several generations, infectious disease specialists have sounded a clarion warning of impending antimicrobial agent resistance. That forewarning has been fulfilled for community-acquired pneumonia (CAP). *Streptococcus pneumoniae*, the leading pathogen in CAP, has become resistant to the penicillins (in vitro), macrolides, and quinolones. The well-publicized nonavailability of new antimicrobial agents aggravates this ominous trend. The pharmaceutical industry has been reluctant to invest large sums of money to overcome the hurdles of academic institutional review boards and the US Food and Drug Administration (FDA).

But a solution is at hand. Instead of developing new antimicrobial agents, we should halt the widespread practice of antibiotic empiricism. Fortuitously, the age of innovative technology and molecular laboratory testing has also arrived.[1-3] The application of new clinical microbiology tests to identify the offending pathogen may allow administration of narrow spectrum antibiotic therapy.

In the article by Sordé et al in this issue of the *Archives*, the pneumococcal urinary antigen was shown to be effective in identifying *S pneumoniae*,[4] and for 75% of patients diagnosed as having pneumococcal pneumonia, it was the only test result that was positive. This is pertinent given the practical difficulties of obtaining adequate sputum for culture and Gram stain. Rapid turnaround time allows the clinician to use targeted rather than empirical therapy for the pneumoccoccus shortly after examining the patient. Add the Gram stain of sputum, another rapid test, and the clinician has 2 potent diagnostic tests that should allow the use of penicillin for pneumococcal pneumonia rather than the oft-used regimen of either a quinolone or a combination of third-generation cephalosporin plus a macrolide.

THE SOLUTION

I suggest that the general prescribing community (internists, emergency department physicians, hospitalists, and critical care specialists) should now use point-of-care (POC) tests to apply narrow spectrum rather than broad spectrum antibiotic therapy for pneumococcal pneumonia. Ironically, effective narrow spectrum therapy is penicillin (or amoxicillin for ambulatory patients).[4] Breakpoints for in vitro sensitivity of pneumococci to penicillin have been raised by FDA such that pneumococci once considered "nonsusceptible" are now correctly labeled as "susceptible." Moreover, the pneumococci that are resistant in vitro by current FDA breakpoints rarely cause bacteremic pneumonia (the fitness hypothesis), which is the strongest risk factor for mortality in pneumococcal pneumonia.

Increasing use of a penicillin compound could lead to a dramatic decline in the use of empirical quinolones and macrolides for a notable segment of patients with CAP, while minimizing the emergence of antimicrobial resistance of 2 valuable classes of antibiotics. The diagnosis of pneumococcal pneumonia has plummeted from 60% to 81% of CAP prior to the late 1970s to only 8% to 12%. One reason for this precipitous decline is, as Bartlett concludes, "diagnostic microbiology is disappearing as a component of quality care."[5] In the study by Sordé et al, *S pneumoniae* comprised 36.1% of the patients with CAP.

Urinary antigen was not performed for almost 20% of the patients in the study by Sordé et al; exclusion of these patients might bias evaluation of the accuracy of the test. However, their results parallel those of other studies. Unfortunately, only a small number of physicians exploited a positive test result for decision making; only 8.6% of the physicians availed themselves of the opportunity to narrow the spectrum of therapy. Other studies have also used the pneumococcal urinary antigen as a decision-making tool.[6-8] Once again, the physicians at these hospitals failed to initiate the most narrow spectrum therapy at the POC despite positive test results. This underscores 2 points: (1) physician education is necessary to encourage prescription of narrow spectrum antibiotics, and (2) the urinary antigen test (and other rapid tests) should be obtained as soon as possible when pneumonia is suspected, given the guidelines requiring 6-hour response time for antibiotic administration.

POINT-OF-CARE MICROBIOLOGY

It is now logical and feasible for physicians to adopt the policy of administering narrow spectrum therapy when the etiologic agent has been defined. Urinary antigen tests (both the pneumococcal and Legionella urinary antigen) and the Gram stain should become standard in-house tests of pneumonia at the POC in the clinic, emer-