MAJOR ARTICLE

Contribution of a Urinary Antigen Assay (Binax NOW) to the Early Diagnosis of Pneumococcal Pneumonia

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We evaluated the usefulness of a rapid urinary antigen test (Binax NOW; Binax) to detect *Streptococcus pneumoniae* for the early diagnosis of community-acquired pneumococcal pneumonia (PP) in 220 nonseverely immunosuppressed adults. We compared results of this test with those of sputum Gram staining. The rapid urinary antigen test showed limited sensitivity (65.9%; 95% confidence interval [CI], 51.4–80.4) but high specificity (100%; 95% CI, 99.7–100) for diagnosing PP. The test was more sensitive for patients with versus those without high-risk pneumonia (94% vs. 63%; $P < .001$) and for patients without versus those with demonstrative results of a sputum Gram stain (97% vs. 55%; $P < .001$), and it tended to be more sensitive for patients with versus those without bacteremic PP (92% vs. 74%; $P =$ NS). Rapid urinary antigen testing permitted early diagnosis of PP in 26% more patients than did Gram staining but missed 22% of the rapid diagnoses initially identified by Gram staining. On the basis of our results, a sequential approach is proposed, with reservation of urinary antigen testing for high-risk patients for whom demonstrative results of a sputum Gram stain are unavailable.

There is increasing interest in improving the rapid etiological diagnosis of community-acquired pneumonia (CAP) to provide initial appropriate pathogen-oriented therapy [1, 2]. *Streptococcus pneumoniae* is the most commonly identified pathogen in cases of CAP and is probably the leading cause of pneumonia of unknown etiology [3]. Until recently, rapid, noninvasive presumptive diagnosis of pneumococcal pneumonia was almost exclusively based on results of a sputum Gram stain [1, 4]. In our experience, sputum Gram staining is a highly specific test and a useful tool in the early presumptive diagnosis of pneumococcal pneumonia. However, a good-quality sputum sample cannot be obtained from >50% of patients with CAP [4].

The recently developed rapid urinary antigen tests that detect *S. pneumoniae* present practical and theoretical advantages over sputum tests. The sample can be easily collected from most patients, and the results, which can be made available within 15 min, are unaffected by the previous use of antibiotics [5]. However, recent CAP guidelines do not specify when these tests should be performed [1, 6, 7]. In fact, there is little information in the literature regarding the usefulness of the *S. pneumoniae* urinary antigen test as a rapid diagnostic technique in daily clinical practice. Specifically, no previous study has compared the performance of this technique with that of sputum Gram staining in the presumptive early diagnosis of pneumococcal pneumonia. The aims of this study were to evaluate the sensitivity and specificity of the *S. pneumoniae* urinary

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antigen test in the diagnosis of pneumococcal pneumonia in adult patients with CAP and to define its usefulness, compared with that of sputum Gram staining, in the early diagnosis of pneumococcal pneumonia.

PATIENTS AND METHODS

The study was performed in a 1000-bed university hospital for adults in Barcelona, Spain. We included all patients from a prospective cohort of nonseverely immunosuppressed adult patients with CAP who were recruited from June 2000 through April 2002 and from whom urine samples were obtained and tested once for *S. pneumoniae* antigen. Patients with neutropenia and AIDS, transplant recipients, and those who had received pneumococcal vaccination within 1 week before the diagnosis of CAP were excluded. We also tested urinary samples obtained from 40 control subjects, 20 of whom who were healthy volunteers (11 men; mean age, 64 years; range, 48–79 years) and 20 of whom who were patients without pneumonia hospitalized for acute exacerbation of chronic bronchitis (15 men; mean age, 71 years; range, 60–85 years).

CAP was defined as an acute respiratory illness, with evidence of the presence of a new infiltrate on a chest radiograph. Baseline risk was calculated using the pneumonia severity index, as described elsewhere [8]. Diagnostic workup included 2 sets of blood cultures, Gram staining and culture of a sputum sample obtained before antibiotic therapy, and serological testing of paired serum samples obtained at an interval of 3–8 weeks. Other diagnostic tests, including a test for detection of *Legionella pneumophila* urinary antigen, were performed as indicated by the attending physician.

The presence of pathogens in blood, normally sterile fluids, sputum, and other samples was assessed by conventional procedures, as described elsewhere [9]. Sputum Gram staining was performed on a purulent portion of each sample. Samples were considered to be of good quality when >25 polymorphonuclear cells and <10 squamous cells were observed under low-power (i.e., $\times$10) magnification. Good-quality specimens were then screened for a predominant bacterial morphotype by oil-immersion microscopy (magnification, $\times$100). A single morphotype that accounted for >75% of the organisms seen was considered to be predominant [4].

Unconcentrated urine samples were tested using the immunochromatographic assay Binax NOW *S. pneumoniae* antigen (Binax). This test detects the C-polysaccharide antigen from the cell wall of *S. pneumoniae* that is believed to be specific for all pneumococcal serotypes. The test was performed in accordance with the manufacturer's instructions. A swab was dipped into the urine sample and then inserted into the test device. A buffer solution was added, and the device was closed, bringing the sample into contact with the test strip. The test was read at 15 min and was interpreted by noting the presence or absence of visually detectable pink lines. A positive test result was indicated by the detection of both sample and control lines, and a negative result was indicated by the detection of a control line only.

To evaluate the yield of the *S. pneumoniae* urinary antigen test, etiologic diagnosis of CAP was established in accordance with the following conventional criteria: recovery of a respiratory pathogen from culture of a specimen with normally sterile culture results; recovery of *L. pneumophila* from a sputum sample; a positive result of a urinary antigen test for detection of *L. pneumophila* (*Legionella* Urinary Antigen, Binax); a 4-fold increase in the antibody titer for *Mycoplasma pneumoniae* (as determined by indirect agglutination), *Chlamydia psittaci* (immunofluorescence [IF]), *Chlamydia pneumoniae* using microimmunofluorescence), *Coxiella burnetii* (IF), and *L. pneumophila* (serogroups 1–6; EIA); and high yield of a respiratory pathogen in a culture of a good-quality sputum sample with a predominant morphotype on Gram stain. Aspiration pneumonia was diagnosed on a clinical and radiological basis for patients who had a predisposing cause of aspiration (compromised consciousness, altered gag reflex, or dysphagia) and radiographic evidence of involvement of a dependent pulmonary segment. The yield of the *S. pneumoniae* urinary antigen was calculated in terms of sensitivity, specificity, and positive and negative predictive values.

To examine the usefulness of the urinary antigen assay in the early diagnosis of pneumococcal pneumonia, the results were compared with those of a sputum Gram stain. An early diagnosis of pneumococcal pneumonia was obtained for all patients with either positive results of a urinary antigen test or a positive sputum sample (i.e., a sputum Gram stain that showed gram-positive diplococci). For the purposes of calculation, the lack of a sputum sample, poor-quality samples, and/or samples in which other predominant morphotypes were detected were considered to be negative sputum samples. Comparison between results of *S. pneumoniae* urinary antigen testing and sputum Gram staining was performed using McNemar statistics with Yates correction. The magnitude of the difference was calculated in exact limits, when appropriate. $P < .05$ was considered to be significant.

RESULTS

The *S. pneumoniae* urinary antigen test was performed for 220 adults with CAP. Demographic and clinical characteristics of these patients are summarized in table 1. There were 157 men and 63 women, with a mean age of 66 years (range, 19–94 years). One or more underlying diseases were identified in 167 patients (76%), and 40 patients (18%) had received previous antibiotic therapy. Fifty patients (23%) were treated as out-

Table 1. Baseline demographic and clinical characteristics of 220 patients with community-acquired pneumonia from whom a urine sample was obtained and tested for *Streptococcus pneumoniae* urinary antigen.

Characteristic	Value
Age, mean years (range)	66 (19–94)
Male sex	157 (71)
Underlying disease	167 (76)
COPD	60 (27)
Congestive heart failure	50 (23)
Diabetes	36 (16)
Neoplasm	14 (6)
Pneumococcal vaccination within previous 5 years	42 (19)
Previous antibiotic therapy	40 (18)
β-Lactams	21 (10)
Macrolides	8 (4)
Quinolones	4 (2)
Unknown	7 (3)
Site of care	
Outpatient	50 (23)
Inpatient	170 (77)
Intensive care unit	12 (5)
High risk class (IV and V; PSI, >90)	78 (35)

NOTE. Data are no. (%) of patients, unless otherwise indicated. COPD, chronic obstructive pulmonary disease; PSI, pneumonia severity index.

patients, and 170 (77%) were hospitalized, 12 of whom required admission to the intensive care unit. Diagnostic workup included blood cultures for 214 patients (97%), Gram staining and culture of a good-quality sputum sample for 80 patients (36%), *Legionella* urinary antigen testing for 157 patients (71%), and 2 paired serum samples for serological testing for 143 patients (65%).

When considering only conventional microbiological procedures, 67 patients (30%) received an etiological diagnosis of CAP, and 1 additional patient received a diagnosis of aspiration pneumonia. Forty-one patients (19%) received a diagnosis of pneumococcal pneumonia, on the basis of positive results of blood cultures (12 patients), pleural fluid cultures (1 patient), and sputum cultures (27 patients). Results of urinary antigen testing were positive for *S. pneumoniae* for 27 of these 41 patients (sensitivity, 65.9%; 95% CI, 51.4–80.4). Of the 27 remaining patients (12%), *Legionella pneumophila* was recovered from 10, *Haemophilus influenzae* was recovered from 6, atypical agents were recovered from 7, *Moraxella catarrhalis* was recovered from 2, *Escherichia coli* was recovered from 1, and aspiration pneumonia was diagnosed for 1. No positive results of urinary antigen testing were observed for any of these 27 patients (specificity, 100%; 95% CI, 99.7–100). Positive and negative predictive values were 100% (95% CI, 99.7–100) and 65.9% (95% CI, 51.4–80.4), respectively. Only 1 of 20 healthy adults and 0 of 20 patients with chronic bronchitis had a positive result of a urinary antigen test. With regard to Gram stain results, a good-quality sputum sample was obtained from 80 patients. Of these, Gram staining revealed gram-positive diplococci for 45 patients, gram-negative coccobacilli for 8, gram-negative bacilli for 4, and gram-negative diplococci for 2. Pleomorphisms were found for 18 patients, and no morphotype was observed for 3 patients.

As shown in figure 1, when we used both sputum Gram stains and urinary antigen tests, there were 88 early diagnoses of pneumococcal pneumonia. These diagnoses were later confirmed by culture in 40 of these cases. All but 1 patient (who received a final diagnosis of pneumococcal pneumonia on the basis of conventional criteria) had positive results for one or both tests (40 of 41 patients), yielding an overall sensitivity of the combination of the 2 techniques of 97%. No positive results of *S. pneumoniae* urinary antigen testing or Gram staining were observed in patients with other known etiologies of CAP that were diagnosed by conventional microbiological procedures. The techniques were concordant for the early diagnosis of pneumococcal pneumonia ($P < .001$), but urinary antigen testing detected 26% more cases than did sputum Gram staining (76% vs. 50%; 95% CI of the difference, +9% to +42%; $P < .01$). This difference was greater among the 12 patients with pneumococcal bacteremia for whom results of urinary antigen testing were positive in 11 cases (92%) and results of sputum Gram staining were positive in 3 (25%).

S. pneumoniae urinary antigen testing was more sensitive for patients with high-risk pneumonia (pneumonia severity index, >90; classes IV and V) than for those with less-severe cases (36 [95%] of 38 vs. 32 [63%] of 51; $P < .001$), and it tended to be more sensitive for bacteremic than for nonbacteremic patients (11 [92%] of 12 vs. 57 [74%] of 77; $P = .18$). Among patients without a demonstrative result of sputum Gram staining, results of urinary antigen testing were positive for 98% (43 of 44), compared with 55% (25 of 45) for those with demonstrative results of sputum Gram staining ($P < .001$). Differences in the sensitivity of the urinary antigen assay between patients who had and those who had not received previous antibiotic therapy did not reach statistical significance (54% vs. 79%; $P = .261$).

DISCUSSION

There is little information on the contribution of *S. pneumoniae* urinary antigen testing to the rapid diagnosis of pneumococcal pneumonia. In the present study, we evaluated the performance of a rapid *S. pneumoniae* urinary antigen assay and compared it with that of sputum Gram staining, mirroring the daily clinical situation in which both techniques are rapidly available. This approach may provide a more practical understanding of the clinical value of the assay, but, to our knowledge, a study

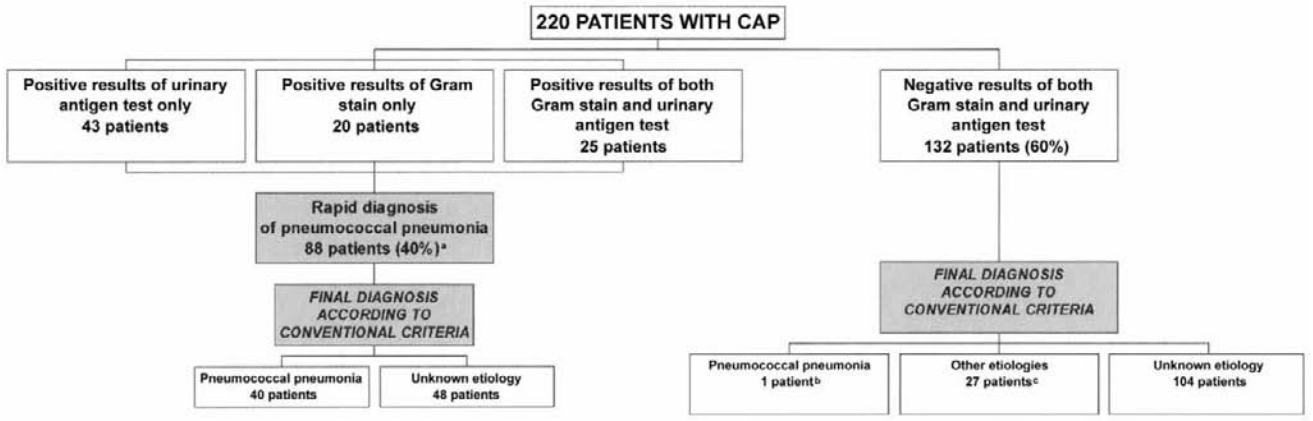

Figure 1. Flow chart illustrating early and final diagnosis of community-acquired pneumonia (CAP) for 220 nonseverely immunosuppressed adult patients who received their diagnosis on the basis of results of rapid *Streptococcus pneumoniae* urinary antigen testing and sputum Gram staining and conventional criteria. [a]Diagnoses for 30 (67%) of 45 patients with predominant gram-positive diplococci on a sputum Gram stain and for 27 (40%) of 68 patients with positive results of urinary antigen testing were later confirmed by culture. The overall sensitivities of blood and sputum cultures were 12 (13%) of 89 and 27 (30%) of 89, respectively. [b]This patient had pneumococcal bacteremia, with negative results of urinary antigen testing and a poor-quality sputum sample. [c]Other etiological agents identified were *Legionella pneumophila* in 10 patients; *Haemophilus influenzae* in 6; atypical agents in 7, including *Mycoplasma pneumoniae* (4 patients), *Coxiella burnetii* (1), *Chlamydia psittaci* (1), and *Chlamydia pneumoniae* (1); *Moraxella catarrhalis* (2); and *Escherichia coli* (1). One patient had aspiration pneumonia.

comparing both rapid techniques has not previously been reported.

The urinary antigen test has proved to be a sensitive and highly specific tool for the early diagnosis of pneumococcal pneumonia, particularly for patients for whom results of sputum Gram staining are not conclusive and for those with high-risk pneumonia. Even so, the overall sensitivity of the *S. pneumoniae* urinary antigen test was <80%; it was >90% only for patients with pneumococcal bacteremia and for those with high-risk pneumonia. These data concord with results of previous studies, and they emphasize the current limitation of the assay, because a number of pneumococcal pneumonia diagnoses (including those for bacteremic patients) were missed [10–12]. With regard to specificity, previous studies have suggested that the detection of pneumococcal antigen in urine is not useful for distinguishing children with pneumococcal pneumonia from those who had merely nasopharyngeal colonization [1, 13, 14]. However, it has been reported that rates of false-positive findings decrease substantially with age, as do rates of pneumococcal carriage [14]. In our adult population, we found a very low rate of false-positive results among both healthy patients (1 of 20), control patients with chronic bronchitis (0 of 20), and patients with CAP (0 of 27) with another identified etiology. In fact, the specificity of the urinary antigen assay in adult patients with CAP was >95% in most previous studies of adult patients with CAP [10, 11]. Therefore, pneumococcal antigen detection should be used only as a tool to determine the causative organism after the diagnosis of pneumonia has been made on the basis of clinical and radiological criteria.

In our study, both sputum Gram staining and urinary antigen testing were concordant for the diagnosis of pneumococcal pneumonia, but the urinary antigen assay detected up to one-fourth more cases than did Gram staining. As shown in figure 1, the diagnoses for only one-half of the patients for whom pneumococcal pneumonia was initially diagnosed were later confirmed by culture. The high specificity of the assay shown by our results and others suggests that most of these cases were, in fact, caused by *S. pneumoniae*. It should be noted, however, that without the consideration of results of sputum Gram staining, 20 (22%) of 88 diagnoses of pneumococcal pneumonia would have been missed, and, in 27 cases, no strain would have been available for susceptibility testing. These results provide further support to the rationale for performing sputum studies in cases of CAP, which result in increases in the number of etiological diagnoses of both pneumococcal pneumonia and infection with antibiotic-resistant pneumococci and increased identification of other common or epidemiologically important respiratory pathogens [1, 15].

It should also be emphasized that, when both urinary antigen detection and sputum Gram staining were used, we were able to rapidly provide diagnoses to >90% of patients with pneumococcal pneumonia. However, this strategy may be expensive and time-consuming in daily clinical practice. *S. pneumoniae* urinary antigen testing has been shown to be particularly useful for those patients without conclusive results of sputum Gram staining and for those with high-risk pneumonia. Thus, in our opinion, a sequential approach—reserving urinary techniques for patients with high-risk pneumonia for whom demonstrative

results of sputum Gram staining are not available—would be a more reasonable strategy.

In conclusion, the *S. pneumoniae* urinary antigen test is a sensitive and highly specific assay for the diagnosis of pneumococcal pneumonia. It permitted early recognition of 26% more cases than did sputum Gram straining and may be particularly useful as an initial diagnostic tool for patients with high-risk CAP for whom demonstrative results of Gram staining are not available.

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