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Rapid urine antigen testing for *Streptococcus pneumoniae* in adults with community-acquired pneumonia: clinical use and barriers

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Abstract

Streptococcus pneumoniae (pneumococcus) is the most common bacterial etiology of community-acquired pneumonia (CAP) in adults, a leading cause of death. The majority of pneumococcal CAP is diagnosed by blood culture, which likely underestimates the burden of disease. The 2007 CAP guidelines recommend routine use of the rapid pneumococcal urinary antigen (UAg) test. To assess the how pneumococcal UAg testing is being used among hospitalized adult CAP patients and what barriers restrict its use, a Web-based survey was distributed in 2013 to 1287 infectious disease physician members of the Emerging Infectious disease Network of the Infectious Disease Society of America. Of 493 eligible responses, 65% use the pneumococcal UAg test. The primary barrier to UAg use was availability (46%). UAg users reported ordering fewer other diagnostic tests and tailoring antibiotic therapy. Increased access to UAg tests could improve pneumonia management and pneumococcal CAP surveillance.

Keywords

Pneumococcus; Community acquired pneumonia; Urine antigen test; Rapid diagnostics

1. Introduction

Streptococcus pneumoniae (pneumococcus) is the most common bacterial etiology of community-acquired pneumonia (CAP) in adults (Klugman et al., 2008), a leading cause of morbidity and mortality in the United States (Kung et al., 2008). In recent years, the incidence of invasive pneumococcal disease, including bacteremic pneumococcal pneumonia in adults, has been declining as a result of routine vaccination of children with pneumococcal conjugate vaccines (Pilishvili et al., 2010). The majority of pneumococcal pneumonia cases are diagnosed by blood culture. However, because only about 25% of pneumococcal pneumonia cases are associated with bacteremia, clinicians miss opportunities for a pathogen-specific CAP diagnosis (Said et al., 2013). In addition, the

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burden of pneumococcal disease and impact of pneumococcal conjugate vaccine are likely underestimated (Said et al., 2013). Culture-independent diagnostic tests could improve clinical care and non-invasive pneumococcal disease surveillance.

The pneumococcal urinary antigen (UAg) test was licensed by the Food and Drug Administration in 1999 and has a reported sensitivity of 50–80% and a specificity of >90% (Mandell et al., 2007). The 2007 IDSA/ATS guidelines for the management of CAP recommend the routine use of the pneumococcal UAg test as an adjunct to blood cultures for hospitalized patients with severe CAP (Mandell et al., 2007). However, physicians do not always follow clinical practice guidelines (Cabana et al., 1999). To understand how the pneumococcal UAg test is being used in clinical practice and what barriers restrict its use, we performed a Web-based survey of practicing infectious disease (ID) physicians regarding their use of the pneumococcal UAg test among hospitalized adult patients with CAP.

2. Materials and methods

We surveyed ID physician members of the Infectious Diseases Society of America (IDSA), Emerging Infections Network (EIN). The EIN is a provider-based emerging infections sentinel network funded by the Centers for Disease Control and Prevention to gather information about clinical aspects of infectious diseases (Pillai et al., 2014). An 11-question survey was distributed via e-mail or facsimile to 1287 EIN members who care for adult patients from the United States, Puerto Rico, and Canada in May 2013. Two reminders were sent to non-responders over 3 weeks.

The physicians were asked how frequently they use the pneumococcal UAg test and reasons why they do or do not use the test. We also inquired about the clinical setting in which the test is used and how results of the pneumococcal UAg test influence clinical decision making. For comparison, the survey also asked about use of blood cultures in CAP patients. Only respondents who reported that they care for adult hospitalized CAP patients were included in the analysis.

A descriptive analysis was performed on completed questions; denominators for certain questions varied, as not all physicians responded to all questions. Comparisons between groups were made by chi-square analysis using SAS version 9.3. (Cary, NC, USA) P values of <0.05 were considered statistically significant.

3. Results

There were 592 (46%) respondents, consistent with other EIN surveys (Gundlapalli et al., 2013). Characteristics of respondents, including patient population, practice setting, and state of residence, did not differ significantly from those of non-respondents. However, respondents were significantly more likely than non-respondents to have at least 15 years of clinical ID experience ($P < 0.001$). Ninety-nine responses were excluded because the physicians reported that they did not treat hospitalized adult patients with CAP, leaving a final sample of 493.

Of these respondents, 319 (65%) use the pneumococcal UAg test, and 485 (98%) use blood cultures in clinical practice. Of the physicians who use the pneumococcal UAg test, 71% had access to the test in their clinical lab, and 29% order it as a send-out to another laboratory. Respondents who do not use the UAg test (N = 174, 35%) provided several reasons for not doing so, including lack of availability (46%), results not available in a timely fashion (33%), a belief that results would not influence clinical decision making (32%), perceived poor reliability (12%), high cost (9%), and inability to obtain susceptibility results (7%).

We observed wide geographic variations in use of the pneumococcal UAg test (Table 1), with highest use in southern regions (range 74–84%) and lower use among northern and western regions of the country (range 48–68%). There were no significant differences in UAg usage with years of experience since completing ID training. There was a non-significant ($P = 0.06$) trend toward differences in UAg usage with community (74%) and Veterans Affairs/Department of Defense (72%) hospitals using the UAg test more than teaching (60%) and city or county hospitals (60%).

Because blood cultures have been a routine diagnostic method among CAP patients for many years, we compared the frequency of UAg testing to blood culture. Among those who do use blood cultures or UAg, blood cultures are used more commonly among all patients with CAP, whereas UAg testing tends to be used only in selected CAP patients (Table 2).

The UAg is recommended to be used for inpatient settings so we asked physicians about the clinical settings in which they use UAg and blood cultures. Of those respondents who use these tests, over 93% of respondents order blood cultures, and over 87% of respondents order the UAg test for inpatients with CAP. Even greater ($P < 0.001$) proportions of respondents indicated use of these tests for intensive care unit (ICU) patients (Table 2).

Over 80% of respondents who use UAg reported that results influenced clinical decision making (Table 2). The most common changes in clinical management related to the ordering of fewer other diagnostic tests, narrowing of antibiotic regimens, and shortening of antibiotic courses for positive UAg results.

Since ID physicians usually see CAP patients after initial evaluation and management, we inquired about respondent's perception of non-ID physicians' use of blood cultures and UAg (Table 2). Non-ID physicians were perceived to use the UAg test some of the time for CAP patients (48%) and blood cultures most of the time or always (69%). Few non-ID physicians were perceived to use the UAg always (3%) or most of the time (17%).

4. Discussion

ID diagnostics are shifting from the traditional culture-based methods to culture-independent methods such as the pneumococcal UAg test. Our survey indicates that 65% of ID physicians use the pneumococcal UAg test routinely; however, they report that <20% of non-ID physicians were perceived to use UAg testing most of the time or always. Importantly, ID physicians alter clinical management in response to a positive UAg test in ways similar to a positive blood culture for *S. pneumoniae*.

Improved CAP diagnostic yield may lead to better clinical practice. The recommended empiric CAP treatment for inpatients is broad, including either a fluoroquinolone or a third-generation cephalosporin plus a macrolide, to cover many possible pneumonia-causing organisms (Bartlett, 2011). Data support use of β-lactams in adult CAP patients with a positive UAg test (Guchev et al., 2005; Stralin et al., 2005), and results from our survey indicate that the majority of ID physicians who use the UAg test narrow therapy in response to a positive test. The main reasons physicians reported for not using the test were lack of ready availability of the UAg test in their clinical settings or lack of timeliness as the test is often sent out for analysis. For send-out testing, the delay in result reporting could be up to a week, which may be too late to alter treatment. Therefore, healthcare centers could improve the quality of care for adult CAP patients with pathogen-directed therapy by making this test more available.

Respondents listed potential reasons in the free-text comments of the survey for why UAg is not available in their clinical setting and included: cost, extra training due to the Clinical Laboratory Improvement Amendments (CLIA), and shelf life of the UAg kit. Regarding cost, the UAg test is estimated to cost between $30 and 40 per test in the United States. An algorithm to determine cost savings of UAg in Europe 2003 showed that patients started empirically on narrow spectrum (less expensive therapy) and used UAg had cost savings of ~ $9.16 compared to those started empirically on broad spectrum (expensive therapy), which had cost excess of ~$27.41 (Oosterheert et al., 2003). However, it is unclear from this study how cost savings would be impacted if patients started on empiric therapy subsequently had therapy tailored toward pneumococcus after a positive test. Unfortunately, while UAg testing is rapid and easy to use, CLIA restricts use to trained technicians in a CLIA-certified laboratory. Lastly, the shelf life of the UAg kit is at least 2 years. We suggest that the UAg test could be integrated into electronic medical order sets to increase clinical use and results of this survey be considered in future CAP clinical guidelines to routinely recommend UAg testing for all CAP patients.

Current pneumococcal surveillance depends on culture-based methods (Williams et al., 2011). Non-bacteremic pneumococcal pneumonia is often not diagnosed with culture-based methods. Therefore, the burden of non-bacteremic pneumococcal pneumonia is difficult to estimate but is clearly larger than the burden of bacteremic pneumococcal pneumonia (Said et al., 2013). Culture-independent tests, such as the pneumococcal UAg test, may be an important tool to incorporate into surveillance systems to better estimate the burden of pneumococcal pneumonia.

Results of the survey should be interpreted with consideration of important limitations. The 46% of individuals who responded to our survey may not be representative of those who did not respond. The EIN is limited to ID physicians who belong to IDSA and is not representative of all physicians. Non-ID clinicians are usually the first to start the evaluation of hospitalized CAP patients and were not surveyed directly. In addition, respondents' reported use of the UAg test may differ from their actual practice.

Inappropriate antibiotic use with cephalosporins and macrolides has contributed to emerging antibiotic resistance for pneumococci (Hicks et al., 2011); thus, pathogen-specific CAP

diagnosis remains critical. While a positive UAg test does not provide susceptibility results, it can reassure clinicians that other pathogens (e.g., *Staphylococcus aureus*) requiring broader-spectrum therapy are less likely to be playing a role in a particular patient's illness. Our survey suggests that physicians with access to the test are using rapid culture-independent diagnostics for hospitalized adult CAP patients more frequently. We suggest that use of the UAg test would improve quality of care by allowing clinicians to use more targeted therapy and may be incorporated into population-based surveillance systems to better estimate the burden of non-bacteremic pneumococcal CAP.

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Table 1

Reported usage and availability of the pneumococcal UAg test by region, clinical experience, and hospital type.

	Total responded, N = 493 (38%)	UAg usage, N = 319 (65%)	UAg available in clinical lab, N = 217 (68%)	UAg available as send-out test, N = 87 (27%)
Region, N (%)				
East South Central	19 (33)	16 (84)	12 (75)	3 (19)
South Atlantic	75 (33)	62 (83)	38 (61)	23 (37)
West South Central	34 (40)	25 (74)	15 (60)	9 (36)
East North Central	76 (40)	52 (68)	43 (83)	8 (15)
Mountain	34 (47)	23 (68)	18 (78)	5 (22)
New England	40 (43)	26 (65)	18 (69)	7 (27)
West North Central	50 (40)	31 (62)	23 (74)	6 (19)
Mid Atlantic	76 (39)	44 (58)	33 (75)	5 (11)
Pacific	80 (36)	38 (48)	16 (42)	22 (58)
Canada	8 (38)	2 (25)	1 (50)	1 (50)
Years since ID fellowship, N (%)				
<5	117 (38)	81 (69)	55 (68)	21 (26)
5–14	112 (29)	75 (67)	50 (67)	21 (28)
15–24	129 (43)	74 (57)	49 (66)	22 (30)
≥25	134 (47)	89 (66)	63 (71)	23 (26)
Primary hospital type, N (%)				
Community	147 (38)	109 (74)	75 (69)	28 (26)
VA/DOD hospital	32 (39)	23 (72)	13 (57)	9 (39)
Non-university teaching	143 (40)	88 (62)	66 (75)	19 (22)
City/county hospital	20 (53)	12 (60)	5 (42)	6 (50)
University	149 (36)	86 (57)	57 (66)	25 (29)
Other	2 (14)	1 (50)	1 (100)	0 (0)

VA = Veterans Affairs; DOD = Department of Defense.

Table 2

Use of blood culture and pneumococcal UAg test for adult patients with CAP.

	Blood culture (%)	UAg test (%)	*P*-value
Do you order blood cultures or the pneumococcal UAg test for patients with CAP in your clinical practice?			
Yes	485 (98)	319 (65)	<0.001
Of those who use the test, where is the test used?[a]			
Outpatient	75 (16)	48 (15)	0.918
Inpatient, non-ICU	445 (93)	271 (87)	0.005
Inpatient, ICU	469 (98)	299 (96)	0.089
Other	17 (4)	13 (4)	0.657
Of those who use the test, which patients are tested?[a]			
All CAP patients	306 (64)	133 (42)	<0.001
The majority of CAP patients	133 (28)	109 (35)	0.034
Only certain CAP patients, i.e., ICU	41 (9)	64 (20)	<0.001
Other	1 (<1)	8 (3)	0.002
How do results influence clinical management for a positive result?[b]			
Narrow antibiotic regimen	433 (90)	262 (84)	0.012
Shorten antibiotic course	117 (24)	88 (28)	0.219
Order fewer diagnostic tests	304 (63)	209 (67)	0.266
No change in clinical management	7 (1)	10 (3)	0.096
Other	32 (7)	6 (2)	0.002
How often do non-ID clinicians use these tests for patients with CAP?[c]			
Always	65 (13)	12 (3)	<0.001
Most of the time	275 (56)	76 (17)	<0.001
Some of the time	142 (29)	213 (48)	<0.001
Not at all	6 (1)	125 (28)	<0.001
Not sure	1 (<1)	14 (3)	<0.001

[a]Responses varied for blood culture (N = 479) and UAg (N = 312).

[b]Responses varied for blood culture (N = 480) and UAg (N = 311).

[c]Responses varied for blood culture (N = 489) and UAg (N = 440).