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Comparison of Two Urinary Antigen Tests for Establishment of Pneumococcal Etiology of Adult Community-Acquired Pneumonia

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The Binax NOW immunochromatographic test (ICT) detecting the pneumococcal C polysaccharide and a serotype-specific latex agglutination (LA) test detecting 23 pneumococcal capsular antigens were evaluated for establishing pneumococcal etiology in community-acquired pneumonia (CAP) by use of nonconcentrated urine. ICT was considered to be strongly positive for result lines at least as intense as the control line and weakly positive for less intense result lines. When 215 adult CAP patients were tested, strong ICT, weak ICT, and LA positivity were found in 28, 24, and 16 patients, respectively; of these patients, 13 (46%), 6 (25%), and 13 (81%), respectively, had pneumococcal bacteremia and 27 (96%), 17 (71%), and 15 (94%), respectively, had *Streptococcus pneumoniae* isolated from blood, sputum, and/or nasopharynx. Among 108 controls tested, 2 (1.9%) were weakly ICT positive. When weak positivity was considered negative, the sensitivity of ICT decreased from 79% (19 of 24) to 54% (13 of 24), while the specificity increased from 83% (158 of 191) to 92% (176 of 191); no controls were false positive. The sensitivity and specificity of LA were 54% (13 of 24) and 98% (188 of 191), respectively. Eight of nine LA serotypes corresponded to culture serotypes. In conclusion, using nonconcentrated urine and dividing ICT-positive results into strongly and weakly positive results is a suitable way of performing ICT. While weak ICT positivity should be interpreted with caution, strong ICT positivity and LA positivity should be considered supportive of pneumococcal etiology in adult CAP. As such, these assays might have implications for antibiotic use in CAP. LA has promising potential for pneumococcal serotyping, although further evaluation is required.

Streptococcus pneumoniae is the leading cause of community-acquired pneumonia (CAP) worldwide (9). Because of emerging resistance in *S. pneumoniae* and other respiratory pathogens, an independent, multinational, and interdisciplinary group recently recommended strategies for appropriate antibiotic use, including optimization of etiological diagnosis (1). For this purpose, the development of tests that can rapidly and reliably identify the causative agent in CAP has been encouraged (2, 9).

Urine is a suitable medium for microbiological assays aimed at respiratory pathogens, as it is not influenced by respiratory flora and can be collected easily from most patients. Although specific methods have been available since 1917 (4), the detection of pneumococcal capsular antigens in urine has not been used in routine clinical practice because of insufficient sensitivity, lack of robustness, and expense (8). A major reason for the low sensitivity is the large number of pneumococcal serotypes present, since the detection of several serotypes per reaction has been shown to be inferior to the detection of one serotype per reaction (27).

In the Streptococcus Unit at Statens Serum Institut, Copenhagen, Denmark, an in-house serotype-specific latex agglutination (LA) test comprising 22 solution reagents for 23 different serotypes has been developed. It was constructed for a fast reaction on a microscopic slide, so that it would be quicker and more easily processed than previous serotype-specific LA assays (27, 30) and other techniques, such as the counterimmunoelectrophoresis assay (26) and the enzyme-linked immunosorbent assay (16).

The pneumococcal C polysaccharide can be detected in urine by the commercial Binax NOW immunochromatographic test (ICT) for *S. pneumoniae* (Binax, Portland, Maine). This quick test was recently recommended for diagnostic use by the Infectious Diseases Society of America (19). However, it has not yet been clarified how ICT should be used and interpreted. Dominguez et al. (6) suggested that the specificity of the test could be enhanced if result lines weaker than the control line were considered negative. Gutierrez et al. (12) interpreted the results of the test in this way, but they used concentrated urine and encountered specificity problems. So far, no prospective study with nonconcentrated urine has evaluated the clinical utility of dividing visible ICT result lines according to color intensity.

The aim of the present study was to compare the performances of the LA test and ICT, with visible ICT result lines being divided into two groups according to color intensity, by use of nonconcentrated urine samples from adult CAP patients and controls.

MATERIALS AND METHODS

Population. During a 2.5-year period from November 1999 through April 2002, 294 patients hospitalized for suspected CAP at the Department of Infectious Diseases, a 35-bed clinic at the 600-bed Örebro University Hospital, were enrolled in a prospective study. A total of 235 patients met our criteria for CAP, i.e., acute illness, radiological signs of pulmonary consolidation, at least two of

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five signs and symptoms (fever of >38°C, dyspnea, cough, pleuritic chest pain, and abnormal lung auscultation), and nonhospitalization during the preceding month. The scoring system of Fine et al. (11) was used for calculating pneumonia severity. In total, 215 CAP patients (91%) had a urine sample collected during the first 2 days of hospitalization and were included in the present study. Urine samples were collected on admission and during the study period from 108 patients hospitalized for skin infections ($n = 12$), urinary tract infections ($n = 13$), arthritis or spondylitis ($n = 6$), or planned orthopedic or urological surgery ($n = 77$) (controls). None of the controls had been hospitalized for any reason during the preceding month or had received any antibiotic treatment during the preceding week. On admission, respiratory symptoms were absent in all controls, but four of these patients (4%) developed such symptoms during the hospital stay.

Microbiological investigations. Samples from blood, nasopharyngeal swabs, and nasopharyngeal aspirates were taken from all of the controls and from 215 (100%), 213 (99%), and 201 (93%) of the CAP patients, respectively; 105 (49%) of the CAP patients also had representative sputum samples available, i.e., samples with >5 neutrophils per squamous epithelial cell. Culturing of blood, sputum, nasopharyngeal, and urine samples was performed according to standard microbiological methods (24). The Binax NOW ICT for *Legionella pneumophila* (Binax) applied to all urine samples and *Legionella* culturing of all sputum samples were used for the identification of *L. pneumophila*. For 198 CAP patients (92%) and 89 controls (82%), serological tests of paired sera were performed with the microimmunofluorescence test for *Chlamydia pneumoniae* and *Chlamydia psittaci* and the complement fixation test for *Mycoplasma pneumoniae*, influenza viruses A and B, respiratory syncytial virus, and adenovirus.

Urine samples. After being cultured, the urine samples were kept frozen at −70°C for up to 3 years until tested with the ICT at the Department of Clinical Microbiology, Örebro University Hospital, Örebro, Sweden, and by LA at the Streptococcus Unit, Division of Microbiology and Diagnostics, Statens Serum Institut, Copenhagen, Denmark. Both ICT and LA were performed and interpreted under blind conditions.

Binax NOW ICT. Nonconcentrated urine was used for ICT according to the instructions of the manufacturer. The result was read visually after 15 min and was interpreted on the basis of the presence or absence of detectable pink to purple lines. Result lines with a color intensity at least as intense as that of the control line were considered strongly positive, while result lines with weaker intensity were considered weakly positive.

LA. For each of 21 different pneumococcal serotypes and 2 serotypes in combination (9N and 9V), a 1% latex suspension in glycine buffer was produced by coating with type-specific pneumococcal antisera raised in rabbits as previously described (31). The 22-suspension assay was constructed for identification of the serotypes included in the 23-valent pneumococcal polysaccharide vaccine (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F). It was developed from the counterimmunoelectrophoresis assay previously constructed at the Statens Serum Institut (26).

An aliquot of 10 μl of nonconcentrated urine, boiled in a water bath for 10 min, was mixed with 10 μl of a 1% latex suspension coated with type-specific pneumococcal antisera on a microscope slide. The slide was hand rocked for 5 to 8 s. A positive reaction was observed when the milky solution became fluffy and no similar reaction was observed for the remaining 21 latex suspensions or the negative control, in which the latex suspension was mixed with tap water. A positive reaction was verified by testing the urine in another batch of the homotype antiserum. During production at the Statens Serum Institute, each one of the type-specific pneumococcal antisera had been absorbed with all of the other 89 serotypes to rule out cross-reactivity (18). Before use, every new batch of latex suspension was tested with polysaccharides of the 23 serotypes included in the assay. During routine use in the Streptococcus Unit, all 22 latex suspensions represented in the assay have yielded positive results (data not shown).

Serotyping of pneumococcal strains. The pneumococcal strains isolated from the blood, sputum, and nasopharyx were serotyped at the Statens Serum Institut. The capsular reaction test was performed according to the instructions of the manufacturer (Statens Serum Institut) by using type-specific pneumococcal rabbit antisera (33).

Statistical analyses. Pearson's chi-square test and Fisher's exact test were used for comparisons of proportions. A P value of <0.05 was regarded as significant.

RESULTS

The characteristics of the 215 CAP patients and the 108 controls are shown in Table 1. According to the scoring system of Fine et al. (11), the CAP patients were divided into the following risk classes: I, $n = 16$ (7.4%); II, $n = 62$ (29%); III, $n = 53$ (25%); IV, $n = 70$ (33%); and V, $n = 14$ (6.5%). A total of 37 CAP patients (17%) had been treated with antibiotics before hospital admission, while an additional 20 were treated with antibiotics after admission, at least 8 h before urine collection.

S. pneumoniae was isolated from blood in 24 CAP patients (11%) and from any culture site (blood, sputum, and/or nasopharynx) in 82 patients (38%); the culture serotypes were included in LA for 22 (92%) and 73 (89%) of these patients, respectively. The relationship among positive results for blood cultures, LA, and ICT is shown in Table 1, while Table 2 demonstrates the performance of the urine antigen tests with blood cultures and any cultures as references. If patients with culture serotypes not included in LA were not counted, then the sensitivity of LA compared with blood cultures and any cultures would be 55% (12 of 22) and 19% (14 of 73), respectively.

With blood cultures used as a reference, the sensitivity of ICT tended to be higher for high-risk patients (severity risk classes IV and V) than for lower-risk patients—8 (73%) of 11 versus 5 (38%) of 13 ($P = 0.12$) when weak positivity was considered negative and 10 (91%) of 11 versus 9 (69%) of 13 ($P = 0.33$) when weak positivity was considered positive. With cultures from blood and sputum or blood, sputum, and nasopharynx used as a reference, no tendency for different sensitivities according to severity risk classes was found for ICT. For LA, no difference in sensitivity was seen between high-risk patients and lower-risk patients when blood cultures were used as a reference—5 (45%) of 11 versus 8 (62%) of 13 ($P = 0.68$)—or when sputum or sputum and nasopharynx cultures were used as a reference.

For 34 patients found positive for *S. pneumoniae* in sputum, LA-positive, strongly ICT-positive, and weakly ICT-positive results were found for 5 (15%), 9 (26%), and 7 (21%) of these patients, respectively. In total, pneumococcal urine antigen was detected by LA or ICT in 47 (57%) of the 82 patients found culture positive for *S. pneumoniae* in blood, sputum, and/or nasopharynx. Of the 133 patients found culture negative for *S. pneumoniae*, 1 was LA positive, 1 was strongly ICT positive, and 7 were weakly ICT positive. None of these nine patients had been treated with antibiotics before blood or respiratory culturing.

For 57 patients with ongoing antibiotic treatment and 158 without prior antibiotic treatment, LA was positive in 8.8 and 7.0%, respectively ($P = 0.77$), and ICT was positive (strongly or weakly) in 12 and 28%, respectively ($P = 0.014$). For patients found positive for *S. pneumoniae* in any culture, 10 were being treated with antibiotics at urine sampling and 72 were not. For these patients, LA was positive in 50 and 14%, respectively ($P = 0.016$), and ICT was positive (strongly or weakly) in 60 and 53%, respectively ($P = 0.74$).

Of 191 CAP patients without pneumococcal bacteremia, 37 (19%) had positive urine cultures, i.e., any bacteria at a concentration of $\geq 10^4$ CFU ml^{-1}; LA-positive, strongly ICT-positive, and weakly ICT-positive results were found for 1 (2.7%), 3 (8.1%), and 10 (27%) of these patients, respectively. The frequency of urine culture positivity was significantly higher for weakly ICT-positive samples (56%) than for negative ICT samples (15%) ($P < 0.001$). Five of the 10 weakly ICT-positive

TABLE 1. Main characteristics of 215 CAP patients and 108 controls found to be positive or negative for *S. pneumoniae* by blood culturing, LA, and Binax NOW ICT

Characteristic	Value[a] for the following patients:						
	Total (n = 215)	*S. pneumoniae* in blood culture (n = 24)[b]	LA positive (n = 16)	Strongly ICT positive (n = 28)	Weakly ICT positive (n = 24)	Negative blood culture, LA, and ICT (n = 157)	Control (n = 108)
Age, median (range) yr	71 (18–96)	69.5 (31–91)	67.5 (23–91)	70.5 (23–91)	67.5 (31–92)	72 (18–96)	68 (33–93)
Age of ≥65 yr	133 (62)	16 (67)	10 (62)	19 (68)	13 (54)	97 (62)	65 (60)
Female sex	102 (47)	15 (62)	9 (56)	14 (50)	16 (67)	68 (43)	44 (40)
Score, from Fine et al. (11), median (range)	83 (18–191)	84 (31–191)	82 (31–191)	88 (53–191)	81 (31–149)	83 (18–179)	—
Risk classes IV and V	84 (39)	11 (46)	7 (44)	12 (43)	8 (33)	62 (39)	—
Length of hospital stay, median (range) days	4 (1–52)	5 (1–52)	5 (1–52)	5 (1–52)	4 (1–33)	4 (1–44)	—
Admission to intensive care unit	10 (4.7)	3 (12)	3 (19)	3 (11)	2 (8.3)	5 (3.2)	—
30-day mortality	5 (2.3)	1 (4.2)	1 (6.2)	1 (3.6)	0	4 (2.5)	—
6-mo mortality	20 (9.3)	2 (8.3)	2 (12)	2 (7.1)	1 (4.2)	17 (11)	—
Duration of symptoms before urine collection, median (range) days	3 (0–35)	3.5 (0–7)	4.5 (2–12)	3 (0–35)	2.5 (0–10)	4 (0–30)	—
Antibiotic therapy before urine collection	57 (27)	7 (29)	5 (31)	5 (18)	2 (8.3)	48 (31)	0
Positive urine culture (≥10^4 CFU ml^{-1})	38 (18)	1 (4.2)	2[c] (12)	4[d] (14)	10[e] (42)	23 (15)	35[f] (32)
S. pneumoniae in any culture	82[g] (38)	bd	15[h] (94)	27[i] (96)	17[j] (71)	33[k] (21)	5[l] (4.6)
S. pneumoniae in blood	24 (11)	bd	13 (81)	13 (46)	6 (25)	—	0
S. pneumoniae in sputum	34 (16)	7 (29)	5 (31)	9 (32)	7 (29)	17 (11)	—
S. pneumoniae in nasopharynx	70 (33)	17 (71)	11 (69)	23 (82)	15 (62)	29 (18)	5 (4.6)
LA positive	16 (7.4)	13 (54)	bd	11 (39)	1 (4.2)	—	0
Strongly ICT positive	28 (13)	13 (54)	11 (69)	bd	—	—	0
Weakly ICT positive	24 (11)	6 (25)	1 (6.2)	—	bd	—	2 (1.9)

[a] Values are numbers (percentages) of patients, unless otherwise indicated. —, not investigated or by definition 0; bd, by definition, 100%.
[b] Serotypes represented: 1, 3, 7F, 9V, 12F, 14, 16F, 19A, 19F, 22F, 23F, and 33A.
[c] *Escherichia coli* (n = 1) and *Enterococcus faecalis* (n = 1).
[d] *E. coli* (n = 1), *Klebsiella* species (n = 1), *E. faecalis* (n = 1), and *Streptococcus agalactiae* (n = 1).
[e] *E. coli* (n = 6), *Proteus* species (n = 1), *Enterobacter* species (n = 1), mixed *Enterobacteriaceae* (n = 1), and *Staphylococcus aureus* (n = 1).
[f] Eleven were treated for urinary tract infections.
[g] Serotypes represented: 1, 3, 4, 6B, 7F, 9N, 9V, 11A, 12F, 14, 16F, 18C, 19A, 19F, 21, 22F, 23F, 31, 33A, 35A, 35B, 38, and 42.
[h] Serotypes represented: 1, 3, 7F, 9V, 14, 19A, 19F, 22F, 23F, and 33A.
[i] Serotypes represented: 1, 3, 6B, 7F, 9N, 9V, 11A, 12F, 14, 19A, 19F, 22F, 23F, 35A, 35B, and 42.
[j] Serotypes represented: 1, 3, 4, 7F, 9N, 9V, 11A, 14, 16F, 18C, and 23F.
[k] Serotypes represented: 3, 4, 7F, 9N, 9V, 11A, 14, 16F, 18C, 19A, 19F, 21, 22F, 23F, 31, and 38.
[l] Serotypes represented: 3, 6B, 11A, 19F, and 23A.

TABLE 2. Performance of LA and ICT for diagnosis of pneumococccal pneumonia in 215 CAP patients

Test and result	Reference culture	Sensitivity[a]	Specificity[a]
LA	Blood	54 (13/24)	98 (188/191)
	Blood, sputum, and/or nasopharynx	18 (15/82)	99 (132/133)
ICT[b]			
Considered negative	Blood	54 (13/24)	92 (176/191)
	Blood, sputum, and/or nasopharynx	33 (27/82)	99 (132/133)
Considered positive	Blood	79 (19/24)	83 (158/191)
	Blood, sputum, and/or nasopharynx	54 (44/82)	94 (125/133)

[a] Reported as percentage (number of positive samples/number of samples tested).
[b] ICT results were weakly positive but were considered to be negative or positive as indicated.

patients had sputum or nasopharyngeal cultures that were positive for *S. pneumoniae*. Of the 35 controls with positive urine cultures, 1 was weakly ICT positive and none was LA or strongly ICT positive.

Pneumococcal serotyping was performed for all 24 blood isolates, for 31 of 34 sputum isolates, and for at least 1 nasopharyngeal isolate from 70 CAP patients with positive cultures. Serotyping was performed for strains from two or more different samples from 50 CAP patients, and different serotypes in different samples from the same individual were found for 3 patients (6%).

Of 16 LA-positive patients, 13 with eight different serotypes (3, 7F, 9V, 14, 19A, 19F, 22F, and 23F) had the same pneumococcal serotypes identified by LA and culturing; 11 of these patients had pneumococcal bacteremia. The three patients without a correlation between LA and culturing were LA positive for serotype 12F. Two of them were blood culture positive for other serotypes (1 and 33A), and one was blood and nasopharyngeal culture negative. Of 11 serotypes found in blood cultures and included in LA, 2 (serotypes 12F and 14) yielded no LA-positive results.

Of 33 CAP patients with LA and/or strong ICT positivity, respiratory syncytial virus infection and influenza virus infection were found in 2 and 4 of these patients, respectively. Of 24 patients with weak ICT positivity, *H. influenzae* was isolated from sputum in 3 patients, while 2 patients had influenza virus infection. *L. pneumophila*, *M. pneumoniae*, *C. pneumoniae*, or *C. psittaci* was not identified in patients with LA and/or ICT positivity.

Of the five pneumococcal carriers in the control group, one was weakly ICT positive. One additional control, who was culture negative for *S. pneumoniae*, was weakly ICT positive. This patient had stable elevated influenza virus A titers of 1:160 in paired sera and a urine culture positive for *Escherichia coli*.

DISCUSSION

In the present study of adults with CAP and controls, both LA and ICT (weak positivity considered negative) showed low sensitivities but high specificities. When weak positivity was considered positive, the sensitivity of ICT was still lower than those reported in a few previous studies (29, 32) but was similar to those reported in a few other studies (6, 7), in which nonconcentrated urine was used.

In order to estimate predictive values for LA and ICT in a CAP population, the sensitivities and specificities of the present study could be applied to the results from the well-designed study of CAP incidence and etiology performed by Jokinen et al. (14). For LA, ICT (weak positivity considered negative), and ICT (weak positivity considered positive), the positive predictive values would be 96, 83, and 76%, respectively, compared with blood cultures and 94, 97, and 86%, respectively, compared with any cultures. The negative predictive values would be 75, 74, and 85%, respectively, compared with blood cultures and 63, 68, and 74%, respectively, compared with any cultures.

Because of low specificity, weakly ICT-positive results appear to be unreliable for diagnostic use. The low negative predictive values of LA and ICT discourage their use in order to rule out pneumococcal etiology in CAP.

However, the present study shows that LA and strong ICT positivity can be used to establish pneumococcal etiology in adult CAP. This finding makes both assays interesting for the management of CAP. There is increasing evidence that penicillin and cephalosporins seem to be clinically effective in treating CAP caused by *S. pneumoniae* with reduced in vitro susceptibility to penicillin (10, 28, 35). Accordingly, an LA-positive or strongly ICT-positive CAP patient can probably be treated safely with narrow-spectrum β-lactam antibiotics, at least in geographic areas with a low frequency of pneumococcal resistance (MIC, ≥2.0 μg/ml). Although neither ICT nor LA provides any information about antibiotic susceptibility, most highly resistant clones of *S. pneumoniae* belong to a limited number of serotypes (6B, 9V, 14, 19A, 19F, and 23F) (21), all detectable by LA. In areas with a higher frequency of pneumococcal resistance, patients may be treated with narrow-spectrum β-lactam antibiotics if they are LA positive for a serotype other than the six serotypes with a higher likelihood of resistance.

This approach might enable a reduction of the current extensive use of fluoroquinolones, which has been associated with the development of resistance in both *S. pneumoniae* (3) and other bacteria (25).

The potential impact on antibiotic use and resistance emergence advocates the broad use of the commercially available ICT. We believe that the ICT should not be reserved for high-risk patients (severity risk classes IV and V), as was recently suggested by Roson et al. (29), who demonstrated a higher sensitivity in high-risk patients than in lower-risk patients. In the present study, we could not find any clear correlation between the severity of disease and the sensitivity of either ICT or LA.

Because of the speed and ease with which it can be performed, ICT can be used for bedside examination, as was recently shown by Roson et al. (29). Therefore, first-line antibiotic therapy can be influenced by ICT. This approach would be obstructed by a urine concentration step prior to testing. Although prior urine concentration yielded a high ICT sensitivity in a study by Marcos et al. (20), it was associated with a low specificity in a study by Gutierrez et al. (12). In the present study, when the two weakly ICT-positive control urine samples were concentrated 30-fold prior to testing, both became

strongly ICT positive (data not shown). Because of the specificity problems and practical disadvantages associated with urine concentration, we suggest that nonconcentrated urine be used for ICT.

In addition, in children, the specificity of ICT has been shown to be higher for nonconcentrated urine than for concentrated urine (5). A correlation between nasopharyngeal pneumococcal carriage and ICT positivity has been shown for children (13), but it has not yet been demonstrated whether the intensity of the result line is different during pneumococcal infection and carriage. Although pneumococcal carriage in adults was not associated with ICT positivity in eight patients tested by Marcos et al. (20), one of five carriers showed weakly positive results in the present study. Thus, pneumococcal carriage may be a reason for false-positive ICT results in adults. However, there are probably other reasons, such as cross-reactions with antigens from nonpneumococcal organisms.

Alpha-hemolytic streptococci, such as *Streptococcus mitis* and *Streptococcus oralis*, have been shown to yield false-positive ICT results in vitro (D. R. Murdoch and L. B. Reller, Letter, J. Clin. Microbiol. **41:**2271, 2003), as they contain cell wall components similar to the pneumococcal C polysaccharide. Furthermore, when ICT was tested with bacterial strains (including both gram-positive and gram-negative strains) isolated from patients with urinary tract infections, 9% were ICT positive (according to the ICT product manual). In the present study, weak ICT positivity was suspected to be associated with urine culture positivity when CAP patients were tested. However, the results for the control group indicate that there is no obvious association. Pneumococcal capsular polysaccharides can also cross-react with gram-negative strains (18). When LA was tested in the present study with strains of *E. coli* ($n = 10$), *Klebsiella* species ($n = 10$), and *Neisseria meningitidis* ($n = 8$), 4 *Klebsiella* strains yielded false-positive LA results for serotypes 4, 5, 20, and 23F (data not shown). However, there was no association between urine culture positivity and LA positivity in the present study.

After pneumococcal pneumonia, long persistence in urine of both capsular antigens and C polysaccharide has been demonstrated (20, 23, 34). Thus, positivity due to a previous pneumococcal infection should always be considered in urine antigen-positive patients. Recent vaccination with pneumococcal polysaccharide vaccine might also be a reason for pneumococcal antigen present in urine.

In the present study, prior antibiotic treatment was associated with LA positivity in patients culture positive for *S. pneumoniae*. For ICT, positive results were more frequent in nontreated CAP patients than in antibiotic-treated CAP patients, as shown in previous studies (12, 17), when single urine samples were used. However, when Smith et al. (32) tested repeat urine samples from patients who had pneumococcal bacteremia and who were initially ICT positive, ICT was still positive in 29 of 35 patients (83%) on treatment day 3 and in 18 of 20 patients (90%) on treatment day 7. Thus, both LA and ICT appear to be particularly useful in antibiotic-treated patients.

For the promising ongoing development of pneumococcal polysaccharide vaccines (15), serotype monitoring is crucial. The correlation between LA and culture serotypes in the present study, along with the high diagnostic specificity, the large number of included serotypes, the simplicity, and the speed of performance, shows that LA has promising potential for epidemiological use in order to determine which pneumococcal serotypes are causing CAP. LA could be particularly useful for both etiological establishment and serotyping in communities with limited laboratory facilities, where blood culturing and serotyping of bacterial strains are difficult to perform for practical reasons (27, 30).

Because there is a lack of reliable diagnostic tests for pneumonia in children (22), the use of LA with urine from children is an important topic for future research.

The clinical usefulness of LA may be limited by low sensitivity, as shown in the present study when nonconcentrated urine was used. A concentration step prior to testing would not be a disadvantage for the practical use of LA, as it cannot be performed as a bedside assay. If concentrated urine were used, LA sensitivity would probably be enhanced, although the specificity of such a practice would have to be carefully evaluated.

In the present study, two patients with pneumococcal serotypes 1 and 33A in blood cultures were LA positive for serotype 12F. A preliminary in vitro study indicated that cross-reactivity does occur. The LA reagent for serotype 12F was positive for one out of three serotype 1 pneumococcal isolates but negative for two serotype 33A isolates and negative for polysaccharides from serotype 1 and 33A isolates. The capacity of LA for identifying pneumococcal serotypes in urine deserves further exploration, and further cross-reactivity must be carefully investigated. Mixed infections with two serotypes could be an additional explanation for noncorrespondence between serotypes of cultures and LA.

The performance of both ICT and LA in the present study might have been affected by the 2.5- to 3-year period of freezing prior to examination, although it is generally accepted that polysaccharides are relatively stable substances. According to the ICT product manual, a freezing period of 14 days is accepted, but to our knowledge, the effect of storage for longer periods has not been studied for either ICT or methods detecting pneumococcal capsular antigens.

We have tested LA with serum samples with a sensitivity much lower than that of urine (data not shown). To our knowledge, ICT has not been tested with serum samples.

In conclusion, ICT appears to be a promising supplement to blood culturing for the establishment of pneumococcal etiology in adult CAP. Using nonconcentrated urine and dividing ICT-positive results into strong and weak positivity are suitable methods for performing the test. While weak ICT positivity should be interpreted with caution, strong ICT positivity and LA positivity should be considered supportive of pneumococcal etiology in adult CAP. As such, these assays can have implications for the choice of first-line antibiotic therapy in CAP. ICT can be applied for diagnostic use in adult CAP patients at any inpatient or outpatient clinic, and LA can be used for pneumococcal antigen detection and perhaps, in the future, for serotype monitoring in microbiological laboratories.

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