MAJOR ARTICLE

Classical and Latent Class Analysis Evaluation of Sputum Polymerase Chain Reaction and Urine Antigen Testing for Diagnosis of Pneumococcal Pneumonia in Adults

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Diagnosis of pneumococcal pneumonia is complicated by the lack of a diagnostic reference standard that is highly sensitive and specific. Latent class analysis (LCA) is a mathematical technique that relates an unobserved ("latent") infection to multiple diagnostic test results by use of a statistical model. We used classical analysis and LCA to evaluate the sensitivity and specificity of blood culture, sputum Gram stain, sputum polymerase chain reaction (PCR), and urine antigen testing for diagnosing pneumococcal pneumonia among 149 adults with community-acquired pneumonia. On the basis of LCA models, sensitivity of autolysin PCR and pneumolysin PCR was 82% and 89%, respectively, but specificity was low, 38% and 27%, respectively. For urine antigen testing, sensitivity was 77%–78%, and specificity was 67%–71%. Results of the LCA models were comparable with those obtained from classical analysis. LCA may be useful for diagnostic test evaluation and for determining the prevalence of pneumococcal infection in epidemiological studies of community-acquired pneumonia and in vaccine efficacy trials.

The diagnosis of pneumococcal pneumonia is challenging. Isolation of *Streptococcus pneumoniae* from normally sterile body sites (e.g., blood and pleural fluid) is highly specific, but sensitivity is low. The utility of sputum Gram stain and culture is variable and is influenced by the following: the ability of the patient to produce a good specimen, laboratory screening practices, and administration of antimicrobial drugs before the collection of specimens. Because of these limitations, new diagnostic tests, such as polymerase chain reaction (PCR) and urine antigen assays for the diagnosis of pneumococcal pneumonia, are being developed and evaluated [1–8].

The limitations of currently available diagnostic tests and the lack of a diagnostic reference standard make evaluation of newer tests difficult. Latent class analysis (LCA) is a mathematical technique that relates an unobserved ("latent") condition to multiple diagnostic test results by use of a statistical model. First developed in the social sciences and psychiatric research [9, 10],

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Informed consent was obtained from each study participant, and the study was conducted in accordance with human experimentation guidelines of the US Department of Health and Human Services and Emory University.

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LCA has been applied to the evaluation of infectious and rheumatologic diseases, in which no tests with perfect sensitivity and specificity are available (i.e., no diagnostic reference standard is available), and the true disease status is "latent" [11–15]. For a group of patients with unknown infection status and for whom at least 3 independent diagnostic test results are available, LCA will model the probability of each combination of test results conditional on the latent class (infected or noninfected). From these probabilities, the prevalence of infection and the sensitivity and specificity of all tests evaluated can be estimated.

We collected results of routine diagnostic tests and obtained specimens for additional testing from patients admitted with community-acquired pneumonia (CAP), to evaluate current and developmental tests for pneumococcal infection using classical methods, to further evaluate selected tests using LCA, and to compare the findings of classical methods with those of LCA.

PATIENTS, MATERIALS, AND METHODS

Enrollment and specimen collection. Patients were recruited from the Emergency Care Center (ECC) of Grady Memorial Hospital in Atlanta from January 1997 through March 1998. Patients with febrile respiratory illnesses were identified by reviewing hospital admission logs for clinical diagnoses suggestive of serious pneumococcal infection (sepsis, CAP, or meningitis) at least daily Monday through Friday. Patients eligible for enrollment were aged ⩾18 years, able to give informed consent, had not taken any antimicrobial drug within 7 days before presentation to the ECC, could be enrolled within 12 h of the first dose of antibiotic given after presentation, and did not have any of the following conditions: human immunodeficiency virus (HIV) infection, acute or chronic renal failure resulting in anuria, an indwelling urinary catheter in place for >24 h, bleeding diathesis, or anatomic abnormality or alteration of the upper respiratory tract (e.g., tracheostomy).

Blood cultures and sputum specimens for culture and Gram stain were collected at the discretion of the attending physician and were processed in the hospital microbiology laboratory. Salivary contamination of sputum specimens was assessed by microscopic examination; samples with >10 squamous epithelial cells/low-power field were rejected. Additional specimens were collected at time of enrollment, including up to 50 mL of urine; 2 nasopharyngeal (NP) swabs using sterile calcium alginate–tipped swabs (Calgiswab Type 1; Harwood Products), and an additional sputum specimen. One NP swab was streaked immediately onto trypticase soy agar plus 5% sheep red blood cells (TSA II; Becton Dickinson) for isolation of *S. pneumoniae.* The other NP swab was immersed in 2 mL of M4 transport medium (Remel) for PCR. The NP swab placed in M4 transport medium and the sputum and urine specimens were placed on cold packs and transported to the Centers for Disease Control and Prevention (CDC) within 24 h. Sputum specimens were streaked onto TSA II plates for isolation of pneumococci, and the remainder was frozen at −70°C for PCR testing. Urine samples were split into aliquots and stored at either 4°C or −70°C. The presence of *S. pneumoniae* in NP swabs and sputum samples was determined by optochin sensitivity (Becton Dickinson) and bile solubility tests, using standard methods described elsewhere [16]. Medical records were reviewed at enrollment and again after discharge, to collect data on basic demographic information, underlying medical conditions, clinical presentation, course of illness, and results of microbiological tests performed in the hospital microbiology laboratory. Discharge *International Classification of Diseases,* 9th Revision, codes were used to identify patients with alcohol abuse (303.0–303.9 and 291.0–291.9) and cocaine use (304.2 and 305.6).

Case definitions and categorization scheme. A case of CAP was defined as an illness occurring in a patient presenting to the ECC with an infiltrate on chest radiography and at least 1 of the following: fever (temperature >38.0°C) or hypothermia (temperature, <35.5°C); history of productive cough noted in the medical record; or complete blood count demonstrating leukocytosis (total leukocyte count $\geqslant 11.0 \times 10^9$ cells/L), leukopenia (total leukocyte count $< 3.0 \times 10^9$ cells/L), or a left shift (band forms accounting for ⩾10% of leukocytes).

A clinical case categorization scheme was used to create mutually exclusive groups for classical analysis. Cases were categorized as "definite pneumococcal pneumonia" if *S. pneumoniae* was recovered from a normally sterile body site and "probable pneumococcal pneumonia" if the chest radiograph demonstrated lobar or multilobar pneumonia and a Gram-stained sputum specimen demonstrated a predominance (>50%) of gram-positive diplococci. All other cases were categorized as "other pneumonia." Patients with other pneumonia were further classified as "colonized" if *S. pneumoniae* was isolated from the NP swab or from sputum in the absence of gram-positive diplococci in the sputum gram stain.

Urine antigen testing. The presence of pneumococcal C polysaccharide in unconcentrated urine was determined using a commercially available immunochromatographic (ICG) assay (NOW *S. pneumoniae;* Binax), according to the manufacturer's specification. Specimens for ICG testing had been frozen at −70°C before testing. No frozen specimen was available for 18 patients, and specimens stored at 4°C were used in these cases.

PCR. The presence of *S. pneumoniae* in sputum specimens and medium inoculated with NP swabs was determined by nested PCR. Pneumococcal DNA was extracted from 200-μL aliquots of patient samples using Qiagen tissue kits, according to the manufacturer's instructions for gram-positive bacteria. All extracted DNA samples were tested within 72 h to minimize negative results due to DNA degradation. Positive control DNA for PCR was extracted from *S. pneumoniae* grown for 18–24 h

on TSA II. Sterile water extracted in parallel with each batch of clinical samples served as the negative control.

Two separate nested PCRs were used. The first detects the pneumococcal autolysin gene by use of previously published primer sets [17], giving an outer PCR product of 395 bp and an inner PCR product of 274 bp. The second detects the pneumolysin gene and also used previously published outer primer sets [18], with inner primers designed in house (sense, 5′-CCCACTCTTCTTGCGGTTGAT-3′; antisense, 5′-CCATGCTGTGAGCCGTTATTT-3′), giving an outer product of 350 bp and an inner product of 217 bp. In brief, 50 μL of outer reaction volumes consisting of 40–45 μL of a solution containing 10 mmol of Tris-HCl (pH 8.8), 75 mmol of KCl, 2.8 mmol of $MgCl_2$, 200 μmol of each dNTP, 0.01% (wt/vol) bovine serum albumin (Sigma), 1.25 U of Taq polymerase (Roche Diagnostics), 0.2 μmol of each outer primer, and 5–10 μL of purified, extracted DNA sample was overlaid with 1 drop of mineral oil. Inner reactions used the same buffer with transfer of 1 μL of outer reaction product transferred into 49 μL of reaction mixture. Both inner and outer PCRs were preceded by a 4 min incubation at 94°C, followed by 30 cycles consisting of 1 min at 94°C, 30 s at 62°C, and 1 min at 72°C, and a final extension of 5 min at 72°C. PCRs for the 2 separate gene targets were run in separate tubes for each patient sample under the same cycling conditions. Positive PCR results were recorded for each sample that yielded a DNA fragment of appropriate size when visualized after electrophoresis in ethidium bromide–stained gels containing 2% agarose (BioRad) in Tris-borate–EDTA buffer (pH 8.4).

Statistical analysis. Sensitivity, specificity, and predictive values for classical analyses were calculated by use of standard methods described elsewhere [19]. Univariate analyses were performed using Epi-Info 2000 (version 1.1; CDC). For comparisons between clinical case categories, the χ^2 or 2-tailed Fisher's exact test were used for categorical variables; analysis of variance or the Kruskal-Wallis test for 2 groups was used for continuous variables. LCA was performed using Latent 1 (version 3) and LEMWIN (1997) software. Selection of tests included in the final LCA model was based on statistical tests (goodness-of-fit χ^2 test) and ease of specimen collection (i.e., sputum collection was considered to be more feasible than obtaining NP swabs in clinical practice).

RESULTS

Overall, 193 patients with suspected pneumonia were enrolled. Of these, 31 were excluded from the analysis because of previously undiagnosed HIV infection ($n = 17$), administration of antibiotics >12 h before collection of specimens ($n = 12$), or because no specimens could be collected ($n = 2$). Of the remaining 162 patients, 149 had illness meeting the case definition of CAP and were included in further analyses. Of these 149, 15 (10%) had definite pneumococcal pneumonia, 26 (17%) had probable pneumococcal pneumonia, and 108 (72%) had other pneumonia. Blood cultures were collected from 124 patients (83%). Pneumococcal infection for patients with definite pneumococcal pneumonia was based on recovery of *S. pneumoniae* from blood specimens of 14 patients and from pleural fluid specimen from 1 patient. Diagnoses among patients with other pneumonia included pulmonary tuberculosis (8 cases), aspiration pneumonia (3 cases), and pneumonia caused by *Haemophilus influenzae* (3 cases), *Klebsiella pneumoniae* (2 cases), and *Staphylococcus aureus* (1 case). The median interval between illness onset and collection of specimens was 4 days, and specimens were collected within 1 week of illness onset for 80% of patients. NP swabs and urine and sputum specimens for PCR were collected before the administration of any antimicrobial drugs for 57 patients (38%). For the remaining 92 patients, these specimens were collected between 30 min and 12 h (mean, 6.7 h) after the first dose of antibiotics.

Patients with definite or probable pneumococcal pneumonia were similar to patients with other pneumonia, except that the patients with definite or probable pneumococcal pneumonia were slightly younger ($P = .04$), less likely to have diabetes mellitus ($P = .009$), and less likely to present with sore throat ($P = .02$; table 1). Results of diagnostic tests for patients in each clinical case category are shown in table 2. Proportions of positive tests for specimens collected before and after the first dose of antibiotics were similar for all tests, including the ICG urine antigen test (48% and 44%, respectively; $P = .6$), the autolysin PCR performed on sputum (68% and 70%, respectively; $P = .8$), and the pneumolysin PCR performed on sputum (72% and 82%, respectively; $P = .2$). ICG urine assays were positive for 44% of 129 patients with a specimen stored at −70°C and for 56% of 18 patients with a sample stored at 4°C ($P = .4$).

By use of classical methods, sensitivity and specificity of the urine ICG assay were both found to be ~60% (table 3). Sensitivities of both PCR assays for sputum were higher than those for NP swabs; specificity of the PCR assays were higher for NP swabs than for sputum.

Of 108 patients with other pneumonia, 31 (29%) were colonized with *S. pneumoniae* (table 4). Either PCR assay on sputum or NP swab was more commonly positive among colonized patients than among noncolonized patients. ICG urine antigen assay was positive for 45% of colonized patients, compared with 36% of noncolonized patients, but this differences was not statistically significant. The proportions of patients with positive ICG urine antigen, sputum pneumolysin PCR, and sputum autolysin PCR tests were similar among patients classified as colonized solely on the basis of a positive NP swab

Table 1. Characteristics of 149 patients presenting with community-acquired pneumonia, by clinical case category.

Characteristic	Pneumonia			All patients (n = 149)
	Pneumococcal			
	Definite (n = 15)	Probable (n = 26)	Other (n = 108)	
Male sex	8 (53)	21 (81)	75 (69)	104 (70)
Age				
Median years (range)	41 (21–82)	42 (23–66)	45 (19–93)	45 (19–93)
⩾65 years	2 (13)	1 (4)	14 (13)	17 (11)
Underlying conditions				
Asthma	3 (20)	4 (15)	17 (16)	24 (16)
COPD	6 (40)	7 (27)	27 (25)	40 (27)
Congestive heart failure	2 (13)	0	6 (6)	8 (5)
Coronary artery disease	1 (7)	0	4 (4)	5 (3)
Diabetes mellitus	1 (7)	0	21 (19)	22 (15)
Hematologic malignancy	0	0	3 (3)	3 (2)
Other malignancy	0	1 (4)	1 (1)	2 (1)
Alcohol abuse	1 (7)	8 (31)	29 (27)	38 (26)
Cocaine use	2 (13)	5 (19)	16 (15)	23 (15)
Pneumonia hospitalization in past 5 years	4 (27)	6 (23)	31 (29)	41 (28)
History of pneumococcal vaccine	0	2 (8)	8 (7)	10 (7)
Findings at presentation				
Fever, ⩾38.0°C	8 (53)	19 (73)	64 (59)	91 (61)
Productive cough	15 (100)	26 (100)	93 (86)	134 (90)
Sore throat	3 (20)	7 (27)	50 (46)	60 (40)
Rhinorrhea	8 (53)	18 (69)	62 (57)	88 (59)
Leukocytosis[a]	11 (73)	15 (58)	66 (61)	92 (62)

NOTE. Data are no. (%) of patients, unless otherwise indicated. COPD, chronic obstructive pulmonary disease or chronic bronchitis.

[a] ⩾11,000 leukocytes/cm^3.

culture, compared with those classified as colonized based on sputum culture and Gram stain findings (data not shown).

An LCA model that included blood culture, sputum Gram stain, ICG urine antigen testing, and sputum autolysin PCR for 109 patients for whom all 4 tests were available (model A), identified 12 (11%) for whom the probability of pneumococcal pneumonia was 1.0 and 26 (23.8%) for whom the probability was >50%. A separate model that included pneumolysin rather than autolysin as the sputum PCR assay for the 108 patients for whom all 4 tests were available (model B) also identified 12 patients with a probability of 1.0, but only 23 (21.3%) had a probability of pneumococcal pneumonia >50%. The models estimated a probability of pneumococcal pneumonia of 1.0 for all patients with definite pneumococcal pneumonia on the basis of the clinical case categorization scheme (table 5).

The LCA models estimated greater sensitivity for ICG urine antigen testing and the sputum PCRs, compared with that for blood culture and sputum Gram stain (table 6). Specificity was low for the PCRs, but greater for ICG urine antigen testing, although slightly less than that of sputum Gram stain. Specificity of blood culture was estimated to be 100%. Estimates of sensitivity and specificity for ICG urine antigen testing and both PCRs from LCA were somewhat higher, compared with those calculated by classical analysis, but 95% confidence intervals included the values from classical analysis (tables 3 and 6). Results of the LCA were not affected by the exclusion of the 31 colonized patients from the analysis (data not shown).

DISCUSSION

The results of our LCA models were plausible and were generally similar to results of our classical analysis. Although LCA provides the option of setting certain properties at predetermined levels, our models found the specificity of blood culture to be 100% without fixing values in the model. An assumption of LCA is that test results are independent of each other within latent classes. We elected to not use a single model with results of both PCR assays because of the high degree of interde-

Table 2. Diagnostic tests results for 149 patients with community-acquired pneumonia, by clinical case category.

	Pneumonia								
	Pneumococcal								
	Definite (n = 15)			Probable (n = 26)			Other (n = 108)		
Test	Positive	Negative	NA	Positive	Negative	NA	Positive	Negative	NA
Blood culture	14 (93)	1 (7)	0	0	26 (100)	0	0	94 (87)	14 (13)
Sputum culture	6 (40)	9 (60)	0	10 (38)	16 (62)	0	26 (24)	81 (75)	1 (1)
Sputum Gram stain	7 (47)	7 (47)	1 (7)	26 (100)	0	0	0	98 (91)	10 (9)
NP culture	5 (33)	10 (67)	0	6 (23)	20 (77)	0	15 (14)	92 (85)	1 (1)
Urine antigen ICG	12 (80)	3 (20)		13 (50)	12 (46)	1 (4)	42 (39)	65 (60)	1 (1)
Pneumolysin PCR									
Sputum	11 (73)	1 (7)	3 (20)	17 (65)	7 (27)	2 (8)	66 (61)	22 (20)	20 (19)
NP swab	12 (80)	3 (20)	0	12 (46)	14 (54)	0	40 (37)	64 (59)	4 (4)
Autolysin PCR									
Sputum	10 (67)	2 (13)	3 (20)	18 (69)	8 (31)	0	58 (54)	30 (28)	20 (19)
NP swab	12 (80)	3 (20)	0	12 (46)	14 (54)	0	40 (37)	64 (59)	4 (4)

NOTE. Data are no. (%) of patients. ICG, immunochromatographic assay (NOW *Streptococcus pneumoniae;* Binax); NA, not available; NP, nasopharyngeal; PCR, polymerase chain reaction.

pendence between the 2 tests. Factors contributing to the high degree of interdependence include use of the same DNA extraction procedure, which makes both assays vulnerable to the same amplification inhibitors and degradation factors. LCA is generally thought to be more accurate than discrepant analysis for determining the sensitivity and specificity of new diagnostic tests. The latter method has been used extensively, particularly in the evaluation of new tests for *Chlamydia trachomatis,* but has been rejected because inherent biases result in inflated estimates of sensitivity and specificity [20–22]. The greatest drawback of LCA is that it assumes a statistical model and that the reference standard is not explicitly defined.

PCR offers a number of potential advantages over other methods of diagnosing pneumococcal pneumonia, including rapid availability of test results and improved sensitivity in patients who are taking antimicrobial drugs [23]. Potential limitations of PCR for the diagnosis of pneumococcal pneumonia include false negative reactions caused by amplification inhibitors in clinical specimens and false positive reactions caused by the presence of other oral streptococcal species (e.g., *S. oralis* and *S. mitus*) that occasionally harbor genes encoding pneumolysin or autolysin [24]. However, inhibitors were not detected in any specimen tested with a PCR assay for the pneumolysin gene in a recent study of 474 adults with CAP [25]. The significance of PCR-targeted sequences in oral streptococci is the subject of ongoing investigations [26]. In our LCA models, PCR of sputum appeared to be a useful adjunct to other tests for rapidly identifying patients with pneumococcal pneumonia; sensitivity of sputum PCR was >80%, with 95% confidence intervals that included 100%. However, specificity was poor. Although patients with other pneumonia who were colonized with *S. pneumoniae* were more likely to have positive results of PCR tests of sputum than were those who were not colonized, exclusion of colonized patients did not improve the estimate of specificity in the LCA models. Specificity of PCR for rapid diagnosis of pneumococcal pneumonia may be greatly improved by use of respiratory secretions obtained by methods that minimize contamination with oropharyngeal organisms, such as bronchoscopy or transthoracic needle aspiration [27, 28]. However, these procedures are not without risk and are not routinely performed on patients with CAP.

Sensitivity of ICG urine antigen testing and the rate of positive ICG tests among persons with *S. pneumoniae* isolated from

Table 3. Sensitivity, specificity, positive predictive value, and negative predictive value by classical analysis, comparing all patients with definite or probable pneumococcal pneumonia (n = 41) with patients with other pneumonia (n = 108).

			Predictive value	
Test	Sensitivity	Specificity	Positive	Negative
Sputum culture	39.0	75.8	38.1	76.4
NP culture	26.8	86.0	42.3	75.4
Urine antigen ICG	62.5	60.7	37.3	81.3
Pneumolysin PCR				
Sputum	77.8	25.0	29.8	73.3
NP swab	58.5	61.5	37.5	79.0
Autolysin PCR				
Sputum	73.4	34.1	32.6	75.0
NP swab	58.5	61.5	37.5	79.0

NOTE. ICG, immunochromatographic assay (NOW *Streptococcus pneumoniae;* Binax); NP, nasopharyngeal; PCR, polymerase chain reaction.

Table 4. Comparison of diagnostic tests results for 108 patients with other pneumonia who were colonized ($n = 31$) and noncolonized ($n = 77$) with *Streptococcus pneumoniae*.

Test	Colonized patients ($n = 31$)			Noncolonized patients ($n = 77$)			P[a]
	Positive	Negative	NA	Positive	Negative	NA	
Urine antigen ICG	14 (45)	16 (52)	1 (3)	28 (36)	49 (64)	0	.33
Pneumolysin PCR							
Sputum	25 (81)	1 (3)	5 (16)	41 (53)	21 (27)	15 (19)	.003
NP swab	23 (74)	7 (23)	1 (3)	17 (22)	57 (74)	3 (4)	<.001
Autolysin PCR							
Sputum	26 (84)	0	5 (16)	32 (42)	30 (39)	15 (19)	<.001
NP swab	23 (74)	7 (23)	1 (3)	17 (22)	57 (74)	3 (4)	<.001

NOTE. Data are no. (%) of patients. Patients for whom results were not available were excluded from the calculations for each test. ICG, immunochromatographic assay (NOW *Streptococcus pneumoniae;* Binax); NA, not available; NP, nasopharyngeal.

[a] Mantel-Haenszel χ^2 or Fisher's exact test, compared with colonized patients.

sterile body sites were similar for our patients, compared with the findings of earlier studies of adults with pneumonia [6, 7, 25, 29]; however, specificity of the ICG urine antigen assay was lower in our analysis. Of patients categorized as having other types of pneumonia, ~40% had positive ICG urine antigen tests. Possible explanations for this finding include true, undiagnosed pneumococcal infection in some of these patients and differences in the characteristics of our patients, compared with those in earlier studies. The slightly higher point estimates of specificity for the ICG urine antigen test in the LCA models in comparison with the classical analysis support the hypothesis that some of these patients may have had true pneumococcal pneumonia. Patients enrolled in our study were quite young, compared with those in most studies of patients with CAP; only 11% were aged ⩾65 years. NP colonization rates among our patients were surprisingly high, and incidental carriage of *S. pneumoniae* could contribute to false-positive urine antigen tests. Although the proportion of colonized patients with other pneumonia who had positive ICG urine antigen tests was not significantly greater than that of patients who were not colonized in our analysis, it has been shown that the urine ICG assay is more likely to be positive among children who are colonized, compared with those who are not colonized. Among healthy children colonized with *S. pneumoniae* in previous studies, 22%–67% had positive ICG urine tests [30–32].

Sputum Gram stain was significantly more specific by LCA than either PCR assay performed on sputum. The point estimates of specificity by LCA were slightly higher for sputum Gram stain, compared with ICG urine antigen testing, but these differences were not statistically significant (table 6). The high specificity of sputum Gram stain depends on appropriate screening to exclude specimens that contain mainly oropharyngeal secretions [33]. In a recent study, the specificity of Gram staining of a good-quality sputum specimen for diagnosis of pneumococcal pneumonia was 97% [34].

PCR assays for the diagnosis of pneumococcal pneumonia are not yet commercially available. An ICG urine antigen assay is commercially available and, on the basis of our LCA models, is more sensitive than blood culture and sputum Gram stain. However, ICG urine antigen testing in the absence of other diagnostic tests may not be prudent, because the specificity of the ICG urine assay was limited in our experience, and the probability of pneumococcal pneumonia for patients with a positive ICG assay and negative blood culture and sputum Gram stain was <0.50. Moreover, cultures of sputum, blood, and other body fluids are needed to evaluate antimicrobial drug susceptibility in areas with high rates of drug-resistant pneumococcal strains. Thus, the greatest utility of the ICG urine antigen assay may be for identifying patients who are unlikely to have pneumococcal pneumonia on the basis of a negative test and who may benefit from additional diagnostic testing.

The prevalence of pneumococcal pneumonia among our pa-

Table 5. Distribution of probabilities of pneumococcal pneumonia by latent class analysis for each clinical case category.

Model, probability	Pneumonia		
	Pneumococcal		
	Definite ($n = 12$)	Probable ($n = 24$)	Other ($n = 60$)
Autolysin PCR			
1.00	12	0	0
0.50–0.99	0	13	1
0.10–0.49	0	11	28
<0.10	0	0	44
Pneumolysin PCR			
1.00	12	0	0
0.50–0.99	0	10	1
0.10–0.49	0	13	28
<0.10	0	0	44

NOTE. PCR, polymerase chain reaction.

Table 6. Latent class analysis models evaluating autolysin polymerase chain reaction (PCR) and pneumolysin PCR of sputum for diagnosis of pneumococcal pneumonia.

Model	Sensitivity (95% CI)	Specificity (95% CI)
A		
Blood culture	29 (0–64)	100 (100–100)
Sputum gram stain	52 (17–86)	84 (69–99)
ICG urine antigen test	77 (55–99)	71 (40–100)
Autolysin PCR	82 (65–100)	38 (20–55)
B		
Blood culture	36 (0–73)	100 (100–100)
Sputum gram stain	56 (27–85)	83 (69–98)
ICG urine antigen test	78 (58–99)	67 (46–87)
Pneumolysin PCR	89 (70–100)	27 (15–39)

NOTE. Model A, goodness-of-fit χ^2, 2.87 ($P = .83$); model B, goodness-of-fit χ^2, 3.82 ($P = .70$). CI, confidence interval; ICG, immunochromatographic assay (NOW *Streptococcus pneumoniae;* Binax).

tients, based on the clinical case categorization scheme, was similar to the prevalence determined by LCA. In most studies of the etiology of CAP among adults, no specific infectious agent is found for a large proportion of patients. Many of these cases of pneumonia of "unknown etiology" have been thought to be caused by undiagnosed pneumococcal infection. Only 1 patient in our study with other pneumonia as defined by the clinical case category scheme had a probability of pneumococcal pneumonia >0.50 by LCA. Nonetheless, the similarity of results between the 2 methods suggests that LCA may be a useful tool for identifying cases of pneumococcal pneumonia for epidemiologic and vaccine evaluation studies. By use of either method, the prevalence of pneumococcal infection among our patients was ~2-fold greater than that found in most large studies that used similar diagnostic methods and categorization schemes to identify the etiology of CAP cases requiring hospitalization among adults in North America [35–38]. The most likely explanation for the discrepancy between our results and these other studies is differing enrollment criteria, which favored patients suspected of having pneumococcal pneumonia at presentation for enrollment into our study, and possibly the younger age of our patients.

Approximately 500,000 adults are hospitalized with CAP each year in the United States [35]. Identifying the microbial cause of CAP may aid in clinical management by permitting selection of optimal antibiotics for the causative agent and use of more narrow-spectrum drugs, thus limiting the selective pressure for drug-resistant organisms. However, to date, no data document that etiologic diagnostic testing can improve outcome or reduce overall medical costs. As a result, recent guidelines on management of patients with CAP differ in their recommendations with regard to the routine collection of specimens for diagnostic testing [39–41]. Because of the limitations of blood culture and sputum Gram stain and culture, this controversy probably will continue until economical, rapid, and accurate diagnostic tests become available.

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