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Original Article

Diagnostic value of the Binax NOW assay for identifying a pneumococcal etiology in patients with respiratory tract infection

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Background and Purpose: *Streptococcus pneumoniae* is a common pathogen in respiratory tract infections which is usually underestimated with conventional tests, largely due to the fragility of the bacteria. This study assessed the diagnostic value of a rapid test (Binax NOW) for the detection of the pneumococcal antigen in urine.
Methods: Unconcentrated urine samples from 1243 adults and 91 children hospitalized with respiratory tract infections were tested.
Results: In all adults with respiratory tract infections, the diagnostic results were as follows: sensitivity, 29 (60%) of 48; specificity, 748 (92.2%) of 811; negative predictive value, 748 (97.5%) of 767; false-positive rate, 63 (68%) of 92. The diagnostic results were similar in adults with lower respiratory tract infections: sensitivity, 21 (64%) of 33; specificity, 658 (92.2%) of 714; negative predictive value, 658 (98.2%) of 670; false-positive rate, 56 (73%) of 77. In children with respiratory tract infections, the diagnostic results were: sensitivity, 4 of 4; specificity 18 (64%) of 28; negative predictive value, 18 of 18; false-positive rate, 10 of 14. The low specificity of the test in children may be due to frequent pneumococcal nasopharyngeal colonization.
Conclusions: High negative predictive values and high false-positive rates were found in both adults and children, indicating that a negative result may be more useful than a positive one in clinical practice. The high specificity of this test in adults indicates its potential value in the choice of initial antibiotic treatment by eliminating pneumococcal infection as a likely cause of respiratory tract infection in a proportion of patients.

Key words: Bacterial antigens, diagnostic reagent kits, predictive value of tests, sensitivity and specificity, *Streptococcus pneumoniae*

Introduction

Respiratory tract infections (RTIs) are common among hospitalized patients. Conventional tests used to identify the etiology of these infections include Gram stain of sputum, sputum cultures and blood cultures; however, the difficulty in obtaining sputum samples from seriously ill patients leads to more extensive use of empirical antibiotics in these patients.

Among hospitalized patients with RTIs, *Streptococcus pneumoniae* is a common pathogen, but microbial diagnosis remains problematic. Tests for pneumococcal capsular antigens, such as latex agglutination or counterimmunoelectrophoresis, have insufficient sensitivity and specificity [1-6]. Therefore, they are not widely accepted as useful diagnostic techniques in clinical practice.

An immunochromatographic membrane assay (ICT; Binax NOW® *S. pneumoniae* Urinary Antigen Test; Binax, Portland, ME, USA) has been recently approved by the US FDA to detect the pneumococcal antigen in the urine. ICT detects the pneumococcal C-polysaccharide which is found in the cell wall and is common to all serotypes [7]. In this study, we evaluated the sensitivity and specificity of ICT for the diagnosis of pneumococcal infections in adults and children with RTIs.

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Methods

During a 2-year period from February 2003 through February 2005, 1334 patients with RTIs were hospitalized at Taichung Veterans Hospital, a 1512-bed tertiary care facility in Taiwan, and were included in this retrospective study. There were 1243 adults (≥15 years old) and 91 children. All of these patients met the study criteria for RTI, including fever (>38°C) and at least 1 of following conditions: cough, sore throat, otalgia, and radiological signs of pulmonary involvement. A series of chest films was reviewed in each patient. Based on the radiological signs of new pulmonary involvement, patients were classified as having lower RTI (LRTI). Patients without radiological signs of pulmonary involvement were considered to have upper RTI (URTI). A third category of patients with chronic pulmonary infiltrations without radiological signs of new pulmonary involvement were classified as having chronic RTI.

Cultures of blood, sputum, pleural effusion and nasopharyngeal samples were performed according to standard microbiological methods [8]. Adult patients with *S. pneumoniae* identified from cultures of blood, pleural effusion or sputum which met the standard criteria for qualified sputum samples were classified as having pneumococcal infection (presence of >25 WBC and <10 squamous cells per low-power magnification field [× 10]). However, the study definition of pneumococcal infection in pediatric patients required a positive *S. pneumoniae* culture result from blood or pleural effusion. Patients with bacterial pathogens other than *S. pneumoniae* identified from samples of blood, sputum and pleural effusion were defined as having non-pneumococcal bacterial infections. Conversely, patients without bacterial pathogen identified from samples of blood, sputum and pleural effusion were not classified as having an unknown etiology.

Unconcentrated urine was used for ICT according to the manufacturer's instructions. The test used a rabbit anti-*S. pneumoniae*-conjugated antibody to bind any soluble pneumococcal antigen (C-polysaccharide) present in the urine sample, and the resulting antigen-antibody complexes were captured by immobilized anti-*S. pneumoniae* antibodies, forming the sample line. Immobilized goat anti-rabbit immunoglobulin G captured excess visualizing conjugate, forming the control line. 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. Color on both the sample and control lines indicated a positive antigen test. Color on the control line alone indicated a negative test. Absence of color on the control line indicated an invalid test.

Table 1. Biostatistics of disease status by test results[a]

Disease status	Test result		Total
	Positive	Negative	
Presence	*a*	*b*	*a* + *b*
Absence	*c*	*d*	*c* + *d*
Total	*a* + *c*	*b* + *d*	*a* + *b* + *c* + *d*

[a]The sensitivity of a test is the probability of a positive result given that the person has the disease (*a*/[*a* + *b*]). The specificity of a test is the probability of a negative result given that the person does not have the disease (*d*/[*c* + *d*]). Positive predictive value is the probability of disease given a positive test result (*a*/[*a* + *c*]). Negative predictive value is the probability of no disease given a negative test result (*d*/[*b* + *d*]). False-negative is a negative test result in a person who is actually positive (*b*/[*b* + *d*]). False-positive is a positive test result in a person who is actually negative (*c*/[*a* + *c*]).

The sensitivity and the specificity of ICT to diagnose a pneumococcal etiology of RTI were calculated according to standard formulae (Table 1). The statistical precision was determined by calculating the 95% confidence interval (CI). Fisher's exact test was used to compare proportions of qualitative variables. A 2-tailed *p* value of 0.05 was considered statistically significant.

Results

ICT was positive in 129 (10.4%) of 1243 adult patients with RTIs (Table 2). *S. pneumoniae* was identified microbiologically in 48 adult patients (3.9%). Among these patients, *S. pneumoniae* was identified from blood in 9 and from qualified sputum in 39. There were 811 adult cases (65.2%) with non-pneumococcal bacterial etiology. No bacterial pathogen was identified in the remaining 384 adult cases (30.9%), which were excluded from the calculation of sensitivity and specificity to avoid possible bias. The ICT results were more frequently positive for patients infected by *S. pneumoniae* (29 [60%] of 48 patients) than in those who were infected by non-pneumococcal bacterial pathogens (63 [7.8%] of 811 patients; $p<0.0001$). Based on these data, the following diagnostic values were obtained for ICT in pneumococcal infection in adults (Table 2): sensitivity, 29 (60%; 95% CI, 46-73) of 48; specificity, 748 (92.2%; 95% CI, 90.3-94.1) of 811; positive predictive value, 29 (32%; 95% CI, 23-42) of

Table 2. Detection of pneumococcal infection by immunochromatographic membrane assay (ICT)

Pathogen	Sample	Adult patients ICT test result		Total	Pediatric patients ICT test result		Total
		Positive	Negative		Positive	Negative	
Streptococcus pneumoniae	Blood	7	2	9	3	0	3
	Pleural effusion	0	0	0	1	0	1
	Sputum	22	17	39	2	1	3
	Throat swab	-	-	-	4	0	4
Non-pneumococcal bacteria		63	748	811	10	18	28
No bacteria identified		37	347	384	15	37	52
Total		129	1114	1243	35	56	91

92; negative predictive value, 748 (97.5%; 95% CI, 96.2-98.4) of 767; false-positive rate, 63 (68%; 95% CI, 58-77) of 92; false-negative rate, 19 (2.5%; 95% CI, 1.6-3.9) of 767.

In pediatric patients with RTIs, the ICT-positive rate was 38% (35 of 91 patients) [Table 2]. Samples from 11 patients (12%) yielded *S. pneumoniae*, and non-pneumococcal bacterial pathogens were identified in 28 patients (31%); conversely, no bacterial pathogen was identified in the other 52 patients (57%). Among the 11 patients, *S. pneumoniae* was identified from throat swab in 4, blood in 3, sputum in 3 and pleural effusion in 1. Children have a high nasopharyngeal carriage rate of pneumococci [9-14] and we thus excluded children with sputum and throat swab samples from the analysis to avoid possible bias. Patients without a bacterial pathogen identified were also excluded. Thus, the ICT was more frequently positive for children infected by *S. pneumoniae* (4 of 4 patients; Table 2) than in those infected by non-pneumococcal bacterial pathogens (10 [36%] of 28 patients; p=0.0278). The diagnostic values for pneumococcal infection in children by ICT were as follows: sensitivity, 4 of 4; specificity, 18 (64%; 95% CI, 45-84) of 28; positive predictive value, 4 of 14; negative predictive value, 18 of 18; false-positive rate, 10 of 14; false-negative rate, 0 of 18.

The sample size of patients with URTI was too small to evaluate statistically (Table 3). Most of the patients in this study, including adults and children, had LRTI. Patients with chronic infiltrations for whom RTI could not be classified as either URTI or LRTI were excluded from the analyses for lower RTIs to avoid possible bias. Patients without a bacterial pathogen identified were also excluded from these analyses.

Among the 747 adult patients with LRTIs (Table 3), *S. pneumoniae* was identified in 33 patients and non-pneumococcal bacterial pathogens in the other 714 patients. ICT was positive in a higher percentage of patients infected by *S. pneumoniae* (21 [64%] of 33 patients) than in those infected by non-pneumococcal bacterial pathogens (56 [7.8%] of 714 patients; p<0.0001). The diagnostic values of ICT for lower respiratory tract pneumococcal infection were as follows: sensitivity, 21 (64%; 95% CI, 47-78) of 33; specificity, 658 (92.2%; 95% CI, 89.9-93.9) of 714; positive predictive value, 21 (27%; 95% CI, 19-38) of 77; negative predictive value, 658 (98.2%; 95% CI, 96.9-99.0) of 670; false-positive rate, 56 (73%; 95% CI, 62-82) of 77; false-negative rate, 12 (1.8%; 95% CI, 1.0-3.2) of 670.

Among the children with LRTIs, 3 had definite pneumococcal infections, and non-pneumococcal bacterial pathogens were identified in 26 (Table 3). ICT

Table 3. Immunochromatographic membrane assay (ICT) results in patients with upper respiratory tract infections (URTIs) and lower respiratory tract infections (LRTIs)

Category of respiratory tract infection	Pathogen	Adult patients ICT result		Pediatric patients ICT result	
		Positive	Negative	Positive	Negative
URTIs	Pneumococcal bacteria	0	1	1	0
	Non-pneumococcal bacteria	1	4	0	0
LRTIs	Pneumococcal bacteria	21	12	3	0
	Non-pneumococcal bacteria	56	658	10	16
Indistinguishable between	Pneumococcal bacteria	8	6	0	0
URTIs and LRTIs	Non-pneumococcal bacteria	6	86	0	2

was positive in a higher percentage of children with *S. pneumoniae* infection (3 of 3 patients) than in those infected with non-pneumococcal bacterial pathogens (10 [38%] of 26 patients). The diagnostic values for detection of pneumococcal infection by ICT in children with LRTIs were as follows: sensitivity, 3 of 3; specificity, 16 (62%; 95% CI, 43-78) of 26; positive predictive value, 3 of 13; negative predictive value, 16 of 16; false-positive rate, 10 of 13; false-negative rate, 0 of 16. However, there was no significant association between the ICT results and the presence of LRTIs (p=0.0783).

Discussion

This study showed that the Binax NOW immunochromatographic test for the detection of *S. pneumoniae* is useful for the rapid diagnosis of pneumococcal infections in adult patients with all RTIs as well as in adults with LRTIs. In this study, the sensitivity of the test was 60% (95% CI, 46-73) and the specificity was 92.2% (95% CI, 90.3-94.1) in hospitalized adult patients with all RTIs. The sensitivity of this ICT was 64% (95% CI, 47-78) and the specificity was 92.2% (95% CI, 89.9-93.9) in adult patients with LRTIs. These findings are similar to previous studies which used this test in adult patients [15-21] and found variable results, with sensitivities ranging from 57% to 80.4% and specificities ranging from 89.7% to 98.8% (Table 4).

In this study, most patients had LRTIs (Table 3) and the sample size of patients with URTIs was very small. This may explain why the sensitivity, specificity, positive predictive value, negative predictive value, false-positive rate and false-negative rate of ICT in patients with all RTIs were very similar to those in patients with LRTIs.

The specificity (92.2%) and negative predictive value (97.5%) of ICT in adults with all RTIs were very high. The specificity (92.2%) and negative predictive value (98.2%) of ICT in adults with LRTIs were also very high. These results indicate that the likelihood of pneumococcal infections in adult patients is low when ICT is negative. However, the sensitivity (60%) of ICT in adults with all RTIs and the sensitivity (64%) of ICT in adults with LRTIs were not high enough to screen for a pneumococcal etiology. In a previous study, ICT results were more frequently positive with concentrated urine (87.1%) than unconcentrated urine (42.5%) from pediatric pneumococcal pharyngeal carriers [10]. Thus, concentration of urine samples for ICT might increase the sensitivity of the assay. The high false-positive rates both in adults with all RTIs (68%) and in adults with LRTIs (73%) in this study indicate that a negative result of ICT is more useful than a positive one in clinical practice for possible etiology.

The sensitivity (18 [85.7%] of 21) of ICT was higher in a previous study of bacteremic patients reported by Honore et al [16]. Dominguez et al also found a similar tendency that the sensitivity (23 [82%] of 28) of ICT was higher in bacteremic cases [21]. In our adult patients with RTIs (Table 2), the ICT results were more frequently positive for patients with *S. pneumoniae* bacteremia (7 of 9) than for those with *S. pneumoniae* identified from sputum samples (22 [56%] of 39 patients). However, this difference was not significant (p=0.2864).

Hedlund et al reported that the nasopharyngeal colonization rate of *S. pneumoniae* was very low (4 [2.9%] of 140 patients) in adult patients with non-pneumococcal community-acquired pneumonia but the nasopharyngeal swab culture rate of *S. pneumoniae* was higher in definite pneumococcal pneumonia patients (33 [27.3%] of 121; p<0.0001) [22]. Regev Yohay et al reported that the pneumococcal nasopharyngeal colonization rate of adults (4%) was much lower than children in the community [12]. Therefore, in the study, we did not consider the finding of 39 *S. pneumoniae* colonies identified from qualified sputum samples in adult patients with all RTIs as indicating nasopharyngeal contamination (Table 2).

Adegbola et al reported that the nasopharyngeal carriage rate of pneumococci was very high (89 [87.3%] of 102) in healthy Gambian children [9]. Pneumococcal antigen was present in urine from 49 (48.0%) of the 102 healthy children in their study. Dominguez et al reported a similar finding that pneumococcal antigen was present in 42.5% of unconcentrated urine and 87.1% of

Table 4. Sensitivity and specificity of immunochromatographic membrane assay for identifying a pneumococcal etiology in adult patients with respiratory tract infections in different studies

Sensitivity	Specificity	Number	Author
63	92.2	1243	Present study
64.9	97.7	313	Watanuki et al [15]
71.4	98.3	146	Honore et al [16]
70.4	89.7	452	Gutierrez et al [17]
57	91.6	163	Payeras Cifre et al [18]
72	94	379	Sato et al [19]
77.7	98.8	104	Farina et al [20]
80.4	97.2	157	Dominguez et al [21]

concentrated urine samples from nasopharyngeal carriers in children from United States [10]. A previous study in Taiwan found nasopharyngeal carriage of pneumococci in 611 (21.0%) of 2905 children in southern Taiwan [13] and 95 (19.9%) of 478 in northern Taiwan [14]. Thus, we excluded sputum and throat swab samples from children to avoid possible bias. Even though patients without bacterial pathogens identified were excluded, RTIs in children had a lower specificity (64%; p=0.0278) and higher false-positive rate (10 of 14) of ICT (Table 2). After excluding URTIs, we also found a tendency for lower specificity (62%; p=0.0783) and higher false-positive rate (10 of 13) of ICT in children with LRTIs (Table 3). The lower specificity and higher false-positive rate in children may be due to a higher pneumococcal nasopharyngeal colonization rate in children with non-pneumococcal bacterial pathogens. In addition, the ICT cannot distinguish pneumococcal infection from nasopharyngeal pneumococcal carriage in children [10,23,24]. For these reasons, this ICT appears to be of no value as a diagnostic tool in children with all RTIs or in children with LRTIs. The negative predictive value of this ICT in children with all RTIs was higher (18 of 18; p=0.0278) than the false-positive rate (10 of 14) of ICT (Table 2), and a tendency of higher negative predictive value (16 of 16; p=0.0783) than false-positive rate (10 of 13) was also found in children with LRTIs (Table 3). Thus, pneumococcal infection and nasopharyngeal colonization may be excluded in children with negative urinary ICT.

In summary, this study has demonstrated that a negative ICT result is useful in excluding the possibility of pneumococcal infections in adults or children with RTIs. This test may thus be helpful in the selection of antibiotic therapy. The false-positive rates of ICT were high in both adults and children, suggesting that the value of a positive ICT result in etiology determination may be limited. Further research is needed to delineate the time course of urinary antigen positivity and the possible interference of antibiotic administration before sampling on the results of testing, due to the possible effects of these factors on the false-positive rate.

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