Do clinicians consider the results of the BinaxNOW *Streptococcus pneumoniae* urinary antigen test when adapting antibiotic regimens for pneumonia patients?

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Abstract

The BinaxNOW *Streptococcus pneumoniae* urinary antigen test is a rapid and reliable immunochromatographic test (ICT) for the identification of a pneumococcal aetiology of pneumonia. The aim of this study was to evaluate the attitude of clinicians in their everyday practice towards prescription of the ICT and the impact of its results on the adaptation of the antibiotic therapy when pneumonia is suspected. From October 2007 to March 2008, we prospectively evaluated 541 consecutive inpatients for whom the ICT was performed in our institution. Of the 541 patients evaluated, only 233 (43%) were suspected by the treating physicians to have a pneumonia, 58 of whom had a positive ICT result. Among these 58 patients, four (7%) and 26 (45%), respectively, were treated with amoxycillin monotherapy before and after the ICT result had been obtained ($p < 10^{-4}$). Although a positive ICT result led to a rise in the proportion of patients treated with amoxycillin alone, a large number continued to be treated with broader-spectrum antibiotics. These results suggest that prescription monitoring of the ICT should be implemented along with encouragement to adhere more strictly to treatment guidelines.

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Introduction

Streptococcus pneumoniae is recognized as the most common microorganism responsible for community-acquired pneumonia [1] and, in most cases, it is still susceptible to aminopenicillin. Therefore, US and French guidelines recommend, respectively, penicillin or amoxycillin [2] and amoxycillin [3] as the drugs of choice for pneumococcal pneumonia, as opposed to community-acquired pneumonia without aetiological identification, for which several broad-spectrum antibiotics, alone or in combination, are used [2]. However, microbiological identification of *S. pneumoniae* remains problematic. Blood cultures are specific but have a sensitivity of less than 25% [4]. The sensitivities of Gram staining and culture of sputum have been estimated to be 57% and 79%, respectively [5], but only if adequate specimens (more than ten white blood cells per epithelial cell at a magnification of ×400) are included in the analysis. As not all patients can produce an adequate specimen, the overall sensitivity is, in fact, much lower, i.e. <10% [6]. Furthermore, the results of blood and sputum culture are not available before 24–48 h, and can become rapidly negative after antibiotic treatment, thereby limiting their usefulness.

In contrast to these microbiological methods, cell wall polysaccharide antigen detection in fresh, urines can lead to a result in 15 min.

The BinaxNOW *S. pneumoniae* urinary antigen test (Binax Inc., Portland, ME, USA) is a commercially available immuno-

chromatographic test (ICT) that has a sensitivity of approximately 65% [7–9] and a specificity of more than 90% in cases of pneumonia [8–10]. This test may remain positive for several months after an infectious episode [11,12]. The main interest of the ICT in cases of positivity is to allow the rapid adaptation of the antibiotic regimen, so that aminopenicillin rather than broader-spectrum antibiotics is used. This kind of antibiotic switch is beneficial, as amoxycillin may have a less detrimental effect on microbial ecology than broader-spectrum antibiotics [13], and is also less expensive. Thus, the ICT appears to be a useful tool for the establishment of an aetiological diagnosis of pneumonia and for the rapid adaptation of antibiotic therapy.

The objectives of this study were, first, to describe clinical signs that prompt clinicians to prescribe the ICT, and second, to evaluate the effect of a positive ICT result on antibiotic adaptation, an issue that has not been previously evaluated.

Materials and Methods

Patients and setting

From October 2007 to March 2008, we conducted an observational prospective study on all inpatients of the Hopital Européen Georges Pompidou, a French 800-bed university hospital of the Assistance Publique—Hôpitaux de Paris. All inpatients with a presumed diagnosis of pneumonia for whom an ICT was performed during the study period were included. The ICT was performed whenever the attending physician thought that it was necessary. Patients were excluded in the case of discharge from the hospital before the result of the ICT was available to the treating physician. If, for a patient, the ICT was repeated several times for the same episode of illness, only the result of the first test was taken into account. Patients could be included multiple times in cases of different illnesses only if the previous ICT results were negative. Any subsequent positive ICT result was excluded. The distinction between different episodes of illness was based on the appreciation of the treating physician.

Antigen tests

Fresh, unconcentrated urines were tested using the Binax-NOW *S. pneumoniae* urinary antigen test, which was performed and interpreted according to the manufacturer's instructions.

Data collection

When an ICT was interpreted, we recorded which medical department prescribed the test and then reviewed the medical chart of the patient, irrespective of the ICT result. Data were collected concerning the medical history, the clinical course of the disease and the results of clinical, biological and radiological examinations. The treating physician was interviewed for the first time before receipt of the ICT result and asked to give his (her) diagnosis according to one of the following categories: pneumonia, other respiratory tract infection, other pulmonary disease, other infectious disease, cardiac disease and other disease. The physician did not have to justify the reason for this choice. Antibiotic regimens were also recorded. We gave no advice as to antibiotic use, although local recommendations for the management of pneumonia were available in electronic form. During the second interview, after receipt of the ICT result, every change in the antibiotic regimen was recorded. As the epidemiological data of the National Reference Laboratory showed that the MICs for 99% of *S. pneumoniae* isolates were <2 mg/L in France at the time when the study was undertaken (http://www.invs.sante.fr/surveillance), an antibiotic switch was considered to be appropriate if monotherapy with parenteral or oral amoxycillin was used, except in cases of allergy, where alternative treatments included cefotaxime (in cases of non-type I allergy) or levofloxacin.

Statistical analysis

Continuous variables are presented as median (range), and categorical variables as *N* (%). Fisher's exact test was used to compare categorical variables. All tests were two-sided at the 0.05 significance level. We analysed the impact of the ICT results on the antibiotic regimen in the group of patients diagnosed with pneumonia by their treating physician. Statistical analyses were performed with the R 2.4.0 statistical package (R Development Core Team; R Foundation for Statistical Computing, Vienna, Austria (http://www.R-project.org)).

Results

Indications for ICT prescription

Seven hundred and two ICTs were performed during the study period (Fig. 1). Of these, 103 were not included, because they were performed for outpatients, and 57 were excluded because they were repeat ICTs during a single episode of illness in the same patient. One ICT was excluded because the patient had had a previous positive ICT. Therefore, 541 patients were evaluated. Pneumonia was diagnosed in 233 patients ('pneumonia' group) (Table 1). Three hundred and eight patients had other diagnoses: 79 were 'other respiratory infections', 83 'other infectious diseases', 47

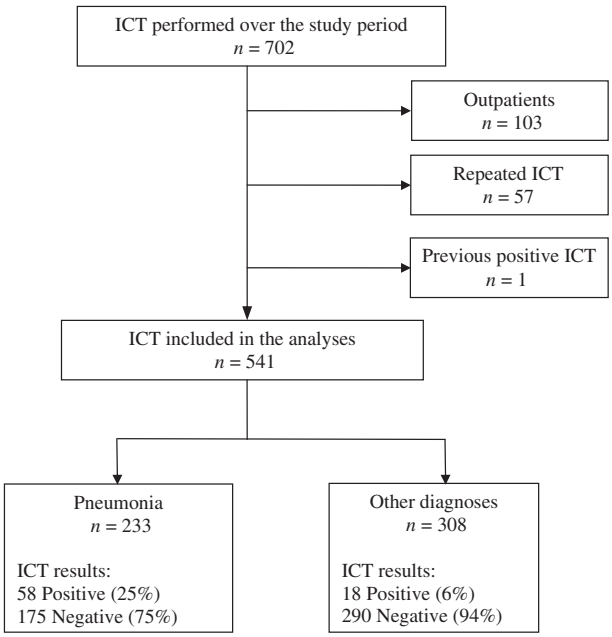

FIG. 1. Flow chart of the study, showing the number of patients included and results of the immunochromatographic test (ICT). Numbers refer to the numbers of patients.

TABLE 1. Clinical and paraclinical features of the 233 patients studied (percentage of total in parentheses unless otherwise stated)

Patient characteristics	Pneumonia group N = 233
Comorbidities	
Cardiac insufficiency	34 (15)
Chronic respiratory disease	44 (19)
Diabetes	21 (9)
Immunosuppression	43 (18)
History of neoplasia	50 (21)
Clinical findings	
Chills	49 (21)
Cough	160 (69)
Fever	164 (70)
Expectoration	108 (46)
Dyspnoea	145 (62)
Desaturation	146 (63)
Crackles	156 (67)
Paraclinical findings	
WBC count (mean ± SD)	13 300 ± 11 520
Abnormal chest X-ray	218 (94)
Alveolar condensation	197 (85)
Interstitial infiltrate	9 (4)
Pleural effusion	10 (4)
Other radiological image	12 (5)
Chest X-ray not performed	0 (0)
Blood culture drawn	184 (79)
Positive blood culture[a]	5 (2)
Respiratory sample	144 (62)
Positive respiratory sample[a]	26 (18)

SD, standard deviation; WBC, white blood cell.
[a]Positive blood cultures and positive respiratory samples refer to the number of cultures positive for *Streptococcus pneumoniae* only.

'non-infectious pulmonary diseases', 44 'cardiac deficiencies' and 55 'other diseases'; they were not included in the analysis.

ICT results

In the group of patients with pneumonia, 58 of 233 ICT results (25%) were positive (Fig. 1). Among the 58 patients with positive ICT results, 17 patients had both a positive ICT result and *S. pneumoniae* present in a clinically relevant microbiological sample (cultures were negative in 35 cases and not performed in six).

Adaptation of antibiotherapy in the pneumonia group

We reviewed how treating physicians adapted antibiotic regimens after receiving the ICT results in the group of patients diagnosed with pneumonia (*N* = 233). Before receipt of the ICT results (Table 2), amoxycillin–clavulanic acid alone was the most frequently prescribed antibiotic (81 patients, 35%), followed by combinations of a macrolide or a fluoroquinolone with a β-lactam (54 patients, 23%). Cefotaxime or amoxycillin alone were less frequently used.

Twenty-eight patients (12%) did not receive any antibiotics. After communication of the ICT results, antibiotic prescription was similar, except that the proportion of patients treated with amoxycillin rose from 5% to 15% ($p < 0.001$). The proportion of non-treated patients decreased to 3% ($p < 0.001$) (Table 2).

As a positive ICT result should contribute to the adaptation of antibiotic prescription, we further analysed the changes in the antibiotic regimen in the subgroup of patients with a positive ICT result (Table 2). Before knowledge of the ICT results, patients were mostly treated with amoxycillin–clavulanic acid, a combination therapy or cefotaxime. Four patients received amoxycillin, and nine were not

TABLE 2: Antibiotic regimen before and after the results of the immunochromatographic test (ICT), in the group of patients diagnosed with pneumonia (*n* = 233, percentage in parentheses)

Antibiotic regimen	Number of patients: Before ICT result	Number of patients: After ICT results	p[a]
All patients (*N* = 233)			
AMC	81 (35)	82 (35)	1
Combined[b]	54 (23)	43 (18)	0.25
Cefotaxime	31 (13)	36(15)	0.60
Amoxycillin	11 (5)	35 (15)	<0.001
Other[c]	28 (12)	29(12)	1
No antibiotic	28 (12)	8 (3)	<0.001
Patients with positive ICT result (*N* = 58)			
AMC	19 (33)	9 (16)	0.05
Combined[b]	13 (22)	3 (5)	0.01
Cefotaxime	9 (16)	16 (28)	0.17
Amoxycillin	4 (7)	26 (45)	<0.0001
Other[c]	4 (7)	4 (7)	1
No antibiotic	9 (16)	0 (0)	0.003

AMC, amoxycillin–clavulanic acid.
[a]p-values calculated using Fisher's exact tests.

treated with antibiotics. After receipt of the ICT results, all patients were treated with antibiotics. Twenty-six received amoxycillin and 16 received cefotaxime (Table 2). In both cases, the increase in the number of patients treated with amoxycillin after a positive ICT result was statistically significant, as was the decrease in the number of patients treated with amoxycillin–clavulanic acid or combined therapy.

In summary, 233 patients were diagnosed with pneumonia. In this group (Table 3), after knowledge of the ICT result, the antibiotic regimen was not changed for 161 patients, the regimen was adapted in 22 of 58 cases and changed to amoxycillin after a positive ICT result, and six of 175 patients were treated with broader-range regimens after a negative ICT result.

Discussion

The impact of the ICT result on the aetiological diagnosis of pneumonia is well documented [14]. The sensitivity and specificity of the test are sufficient to allow a confident switch from a broad-spectrum to a more specific antibiotic regimen against *S. pneumoniae* [7,10]. Although urinary antigen detection has been found to be useless for the diagnosis of pneumonia [10], it is true that this test is often misused for this purpose in clinical practice.

Distinguishing pneumonia from other pneumological afflictions is sometimes challenging, especially in elderly patients. In the absence of a unique diagnostic reference criterion, physicians tend to rely on a number of criteria to establish the diagnosis [15]. We deliberately chose to use the clinician's diagnosis as the standard for the identification of patients with pneumonia, rather than an independent review, as we were attempting to analyse physicians' behaviour. In our study, more than half of the ICTs were performed for patients who were not considered, by the prescriber, to have pneumonia. This finding can be explained by the fact that some physicians probably use the ICT as a means to diagnose pneumonia rather than the aetiology of the pneumonia.

TABLE 3. Impact of immunochromatographic test (ICT) results on the antibiotic regimen in the pneumonia group (*n* = 233, percentage in parentheses)

Impact on the antibiotic regimen	Number (%) of patients
ICT positive (*N* = 58)	
Change adapted[a]	22 (9)
Change not adapted	14 (6)
No change	20 (9)
ICT negative (*N* = 175)[b]	
Initiation of therapy	11 (5)
Step-down[c]	8 (3)
Broader-range therapy[d]	6 (3)
Other change	9 (4)
No change	141 (61)

[a]In cases of positive ICT results, a change was considered to be adapted if antibiotic therapy was switched to amoxycillin or, in cases of allergy, to cefotaxime or levofloxacin (see Materials and Methods).
[b]In cases of negative ICT results, a BinaxNOW urinary *Legionella* test was performed immediately, which could explain some step-downs.
[c]Switching from a combination regimen to a monotherapy.
[d]Adding a quinolone or a macrolide to the antibiotic regimen.

Another striking element is the relatively high rate of multiple ICTs prescribed for the same patient (8%) (data not shown). One explanation is the presence of multiple care-takers (interns, fellows and seniors), who might prescribe it repeatedly. Another explanation is that the patient often does not stay in the emergency department but is transferred to a general ward; it can then sometimes be difficult to view the computerized prescription made at the emergency department. A third explanation is that the physician wants to repeat the ICT in order to increase the sensitivity, although this possibility has not been demonstrated. This excess of ICT prescriptions comes with an economic cost. One ICT kit costs €20 and an additional €7 of labour costs. In our hospital, more than 1300 ICTs are performed each year. Taking duplicate and unnecessary ICTs into account (8% and 57%, respectively), we estimated a surplus cost of€22 000 per year.

The ICT allowed the aetiological diagnosis in an additional 17% of the patients who had pneumonia with no *S. pneumoniae*-positive cultures. This number is comparable to that obtained in other studies [14,16].

There are differences in the adherence to guidelines as reported in published studies [17–19]. In the pneumonia group of this study, although a positive ICT result led to a greater proportion of patients being treated with amoxycillin (45% vs. 7%, p <0.01), there was still fairly poor adherence to the national guidelines for the management of pneumonia, which advocate the use of amoxycillin in pneumococcal pneumonia [2,3].

Overall, the impact of an ICT on changing the antibiotic regimen appeared to be low in this study (Table 3), because a positive ICT result did not lead to the use of a narrow-spectrum antibiotic such as amoxycillin. Other reports have found that blood culture results have a limited impact on changing the antibiotic regimen in cases of pneumonia, even when they are positive [20,21]. These findings raise the question of the usefulness of microbiological examinations in non-severe pneumonia [2], as there is limited impact on the adaptation of therapy. This can be explained by the reluctance of physicians to prescribe narrow-spectrum antibiotics and to change a 'winning team' [22]. However, this habit could lead to the alteration of the human bacterial flora and the selection of resistant microorganisms.

This study has several limitations. First, it was conducted in one single centre, and generalization could therefore be

problematic, as prescription habits could be different elsewhere. Second, during the study, we established direct contact with the physicians in charge of the patients soon after receipt of the ICT result. Therefore, even in the absence of any therapeutic advice, an influence on antibiotic prescription practices was possible, and the effect of the ICT in clinical practice could actually be much lower. Another potential limitation was that the majority of the patients were from the emergency department, and diagnosing pneumonia could be a way of justifying hospitalization or antibiotic use. However, we did not find any difference in the percentages of pneumonia patients between the emergency department (118 of 308, 38%) and overall (77 of 203, 38%).

Finally, we did not evaluate the clinical impact of any antibiotic regimen modification in terms of mortality, morbidity or length of hospital stay. Therefore, no conclusions can be drawn concerning the safety of the adaptation of the antibiotic regimen and the true clinical implications of a positive ICT result.

In summary, although the ICT has a good sensitivity and specificity, it is misused in our institution, with more than 50% of the tests being performed in patients without pneumonia. Although a positive ICT result led to a rise in the proportion of patients treated with amoxycillin and a decrease in the proportion of patients treated with combination therapy, insufficient adherence to treatment guidelines for pneumonia when an ICT result is positive contributes to limiting its impact. For this reason, we recommend that prescription monitoring of the ICT should be implemented, along with encouragement to adhere more strictly to treatment guidelines.

Transparency Declaration

All authors declare no financial support and no conflict of interest.

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