Clinical Usefulness of Streptococcus pneumoniae Urinary Antigen in Patients Hospitalized with Non-Nosocomial Pneumonia

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Citation: J.P. Ferreira, M.A. Abreu, P. Rodrigues, J.M. Maia, P. Leuschner, J.A. Correia: Clinical Usefulness of Streptococcus pneumoniae Urinary Antigen in Patients Hospitalized with Non-Nosocomial Pneumonia. *The Internet Journal of Internal Medicine*. 2012 Volume 9 Number 2. DOI: 10.5580/2bd6

Keywords: pneumonia, Streptococcus pneumoniae urinary antigen, clinical usefulness

Abstract

Introduction **:** Community acquired pneumonia (CAP) is a major cause of hospital admissions and mortality in developed countries. Nevertheless, in about half of the cases a microbial etiology can`t be determined. The need to improve the diagnostic tools of this disease has led to the development of new techniques, such as *Streptococcus pneumoniae* urinary antigen. ***Objectives*** : To analyse the usefulness of the urinary antigen in determining the etiologic diagnosis of pneumonias and its influence in the antibiotherapy modification. ***Methods*** **:** Retrospective analysis of hospitalized patients in 2010 with CAP (n=226) and healthcare associated pneumonia (HCAP) [n=64] diagnosis whose urinary pneumococcal antigen has been analyzed. ***Results:*** Median age was significantly greater in HCAP. HCAP patients had more co-morbidities and higher severity scores. Twenty-one patients in the CAP group and 4 patients in the HCAP group had positive pneumococcal antigen. The sensibility of urinary antigen in determining pneumococcal pneumonias was 36% and the specificity 89%. Almost one quarter of the 25 patients with positive urinary antigen had appropriate reductions in antimicrobial spectra, which was not statistically significant when compared with the group with negative urinary antigen. There was a significant relation between a positive urinary antigen and pneumonia severity. ***Conclusions:*** Considering its high specificity, the urinary antigen is useful to confirm the presence of pneumococcal pneumonia.

Potentially urinary antigen can help to avoid unnecessary treatments in hospitalized patients with CAP.

Introduction

Community acquired pneumonia (CAP) is a common disease and represents the main cause of hospital admissions and mortality by infectious diseases in developed countries[1]. The most frequent etiologic agent of CAP is Streptococcus pneumoniae (S. pneumoniae), responsible for 30-40% of CAP whose etiology is determined. However, the etiology of CAP remains unknown in about 50% of the cases[2].

Recent studies suggest that S. pneumoniae may be underdiagnosed and it can, actually, represent a third of CAP of undetermined etiology[2].

The urge to improve the diagnosis of CAP is clearly justified by its high morbidity and mortality, excessive use of broad-spectrum antibiotics and the emergence of multiresistant strains[1].

According to the current recommendations of the Infectious Diseases Society of America (IDSA), it is good practice to investigate the etiologic agent responsible for the pneumonia, because it allows a significant change in the treatment, promotes the rational use of antibiotics, reduces costs, adverse effects and resistance[2,3].

In clinical practice, there are multiple obstacles to the diagnosis: 1) the sputum culture is limited by the difficulty of getting valid samples and adequate specimens; 2) frequent S. pneumoniae nasopharyngeal colonization in healthy individuals (causing uncertainty about the validity of the results); 3) identification of S. Pneumoniae in the blood or pleural fluid, which is the gold standard, has a low sensitivity (positive in only 15-30% of the cases); 4) beginning antibiotics before hospital admission (in about 30% if patients) decreases the sensitivity of the diagnostic tools[4,5].

Even though some invasive techniques (e.g., bronchoalveolar lavage) offer better samples, they aren't routinely used, for they require specific training and may bring potential complications.

With the objective of increasing the number of diagnosis, an immunochromatographic test was developed (BinaxNow® Streptococcus pneumoniae), that detects S. pneumoniae C polysaccharide (PnC) in urine samples. This test increases the number of etiological diagnosis, has proven to be fast, relatively sensitive and rather specific in the diagnosis of S. pneumoniae pneumonia in adults (the sensitivity is between 50-80% in patients without bacteraemia and

75-85% in those with bacteraemia; the specificity is approximately 95%); the use of concentrated urine by selective ultrafiltration slightly increases the sensitivity of the test[6].
The airway colonization by S. pneumoniae or other streptococcal strains doesn't seem to be related with false positives in adults, even in patients with chronic bronchitis (that is related with higher colonization rates)[7].
The excretion of antigens may last for several weeks (more than 3 months) after specific antibiotics[6-11].
The clinical usefulness of the pneumococcal urinary antigen (PUatg) is not totally established; therefore, the current recommendations don't clearly define the situations in which the test should be obtained[12-14].
For example, according to the British Thoracic Society (BTS) and the IDSA, all the patients with moderate to severe CAP should do, at least, blood cultures, sputum cultures and urinary antigens for S. Pneumoniae[15].
In what concerns the use of PUatg in Healthcare Associated Pneumonias (HCAP), the evidence in literature is scarce, its usefulness in this context is controversial and the main societies don't recommend it[15-17]. However, in clinical practice, the test is frequently requested, so we decided to include these patients to clarify the role of the PUatg in this population.

Objectives

This work evaluates the use of PUatg in a central hospital and has three main objectives: 1) to characterize the patients hospitalized with non-nosocomial pneumonia; 2) to evaluate the contribution of PUatg to the etiologic diagnosis of CAP and HCAP and 3) to analyze the antimicrobial therapy modifications according to microbiological results.

Methods

We conducted a retrospective study of the patients with the diagnosis of Pneumonia (code ICD9 480 till 488) from January to December 2010.

We used the definition of Pneumonia by the World Health Organization (WHO)[18].
The patients with CAP and HCAP in whom the pneumococcal urinary antigens had been processed were enrolled in the study. The patients with Nosocomial Pneumonia (NP), Ventilator Associated Pneumonia (VAP), Aspiration Pneumonia/Pneumonitis (AspP) and patients without pneumococcal urinary antigen records were excluded.

HCAP comprehends the pneumonias that were acquired before hospital admission or during the first 48h after admission, in patients that have at least one of the risk factors: 1) received antibiotics or chemotherapy in the previous 30 days; 2) with wounds that were treated in that period; 3) hospital stay for 2 or more days in the last 90 days; 4) dialysis in the last 30 days; 5) live in a institution; 6) have a close relative with a multi resistant organism. We therefore excluded nosocomial pneumonias that appear more than 8h after hospital admission or that are acquired in the hospital.

For each patient, the comorbidities, scores of disease severity (Pneumonia Severity Index [PSI] and CURB-65), antibiotics, duration of the hospitalization, complications and 30 day mortality were recorded.

In order to evaluate diagnostic accuracy of the test, we used two reference groups:
1) *definitive pneumococcal CAP* – S. pneumoniae isolated in blood cultures (BC) or pleural fluid and 2) *probable pneumococcal CAP* – isolation of S. pneumoniae in the culture of bronchial secretions (BS). The BS that were considered valid consisted of sputum with less than 25 squamous epithelial cells in the Gram stain examination.
We recorded the therapeutic changes based on the results of the urinary antigens and classified the changes as: 1) optimal – narrowing of the antibiotic spectrum to Penicillin iv, Ampicillin iv or oral Amoxicillin; 2) appropriate – suspension of the macrolide, maintaining the beta-lactam antibiotic; 3) absent – without narrowing of the antibiotic spectrum or without treatment changes.

The outcomes of the patients who received therapeutic changes according to the urinary antigens were also recorded.

The data were inserted in Excel® and the statistical analysis was performed with the SPSS 19® software. We used chi-square or Fischer tests for proportions and means were compared using paramentric or non-parametric tests depending on the verified assumptions. A p value of ≤0,05 was considered statistically significant.

For the calculations of sensitivity, specificity, positive and negative predictive values, we considered true-positives the positive results of pneumococcal urinary antigen test in patients with definitive and probable pneumococcal pneumonia. We considered false-positives patients with positive PUatg and other agents in BC/BS.

Results

Of the 780 cases analysed after searching the ICD-9 codes in the database of the hospital, 290 fulfilled the inclusion criteria. Of those, 77,9% (n=226) corresponded to CAP and 22,1% (n=64) to HCAP. The other 490 excluded pneumonias corresponded to NP (n=149), VAP (n=91), AspP (n=178) and patients without pneumococcal urinary antigen records (n=72).

The demographic and clinical characteristics of the studied population are summarized in Table I.

The mean hospital length of stay (and standard deviation) was 9,7 (7,4) days in CAP and 9,3 (7,5) days in HCAP. There were not statistically significant differences in the mean hospital length of stay between CAP and HCAP (p=0,5).

In the vast majority of patients (94,5%; n=274) BC were collected. A microorganism was isolated in 5,3% (n=12) of the patients with CAP and 9,4% (n=6) of the patients with HCAP. In a great amount of patients (62,4%; n=181), BS were collected. However, in 12,2% (n=22) of the samples the product was considered inappropriate by the microbiology laboratory (>25 squamous epithelial cells). Those cases were excluded, leaving 120 samples in CAP and 39 in HCAP. An agent was isolated in 26,7% (n=32) of the patients with CAP and 25,6% (n=10) of the patients with HCAP. No agents were isolated in pleural effusions. Culture results are detailed in Table II.

Streptococcus pneumoniae was isolated in 2 (0,9%) BC, and in the BS of 4,9% (n=11) patients with CAP and 1,6% (n=1) patient with HCAP. S. pneumoniae pneumonia was diagnosed exclusively by PUatg in 8,4% (n=19) patients with CAP and 4,7% (n=3) patients with HCAP. All S. pneumoniae isolates were penicillin-sensitive.

In 3 of the patients with positive PUatg, other agents were isolated in the BC (Escherichia coli, Pseudomonas aeruginosa and Staphylococcus hominis). In another 2 positive cases, other agents (Haemophillus influenzae and Klebsiella pneumoniae) were isolated in BS.

Crosstabulation between PUatg and BS/BC in presented in Table III. The results for sensitivity, specificity, positive and negative predictive values are presented in Table IV., and the relative frequencies of empirical therapy are described in Table V.

Positive results from the PUatg test (n=25) led the clinicians to reduce the spectrum of antibiotic treatment in 6 (22,2%) patients. Noteworthy, the spectrum was reduced in 25 (10,4%) patients with negative PUatg. In 19 (70,4%) patients with positive PUatg the treatment wasn`t modified. No statistically significant differences were found (p=0,054).

In all cases (n=31) considered to have appropriate reductions, that was translated into a macrolide suspension. No optimal reductions were found. The median time to modification of empirical therapy was 3 days (IQR, 2 days) in patients with negative PUatg. In patients with positive PUatg, median time was 3,5 days (IQR, 2,25 days).

In the group with positive PUatg (n=25), 5 patients (20,0%) were admitted to the ICU (p=0,05), 4 (16,0%) had COPD (p=0,137), 20 (80,0%) had high mortality risk in PSI index score (p=0,994), and 17 (68,0%) in CURB-65 score (p=0,035), 6 (24,0%) had pneumonia related complications (p=0,777).

No deaths were directly related to pneumonia. No positive PUatg were found in the previous 3 months.

Characteristic	CAP % (nº)	HCAP % (nº)	P
Sex			
Male	61,9% (n=140)	50% (n=32)	0,086
Female	38,1% (n=86)	50% (n=32)	0,086
Age, mean (SD)	69,5 (17,7)	78,8 (12,8)	<0,001*
≥ 65 years	66,8% (n=151)	89,0% (n=57)	0,289
Underlying diseases			
Alcohol abuse	9,3% (n=21)	n=0	N/A
Active smoking	27,2% (n=61)	10,9% (n=7)	0.007**
COPD	71,2% (n=161)	79,7% (n=51)	0,178
Bronchiectasis	4,0% (n=9)	3,1% (n=2)	0,751
Diabetes *mellitus*	29,2% (n=66)	21,9% (n=14)	0,247
Systolic heart failure	10,2% (n=23)	15,6% (n=10)	0.226
Active neoplasm	8,4% (n=19)	18,8% (n=12)	0.019**
Chronic renal failure	14,2% (n=32)	14,1% (n=9)	0,984
Neurologic disabling disease	25,0% (n=56)	53,1% (n=34)	<0,001**
Chronic liver disease	4,1% (n=9)	0	N/A
Imunossupressive conditions			
Chronic steroids consumption	4,0% (n=9)	7,9% (n=5)	0,201
Chemotherapy	1,8% (n=4)	7,8% (n=5)	0,027**
Organ transplantation	1,8% (n=4)	1,6% (n=1)	1,000
HIV infection	2,2% (n=5)	1,6% (n=1)	1,000
Severity scores			
PSI – high risk	69,0% (n=156)	92,2% (n=59)	<0,001**
CURB-65 – high risk	39,4% (n=89)	59,4% (n=38)	0,004**
Respiratory failure	82,3% (n=186)	88,9% (n=56)	0,210
Septic shock	8,8% (n=20)	9,4% (n=6)	0,897
ICU admission	8,8% (n=20)	4,7% (n=3)	0,277

Table I. Baseline demographic and clinical characteristics of studied population.

*non-parametric Mann-Whitney test

**chi-square or Fisher exact test

Microorganism	CAP		HCAP	
	BC (nº and %) (n=212)	BS (nº and %) (n=120)	BC (nº and %) (n=62)	BS (nº and %) (n=39)
Streptococcus pneumoniae	2 (0,9%)	11 (9,2%)	0	1 (2,6%)
Haemophilus influenzae	0	10 (8,3%)	0	0
Moraxella catarrhalis	0	1 (0,8%)	0	0
Gram-negative enteric bacilli (non-*Pseudomonas*)	1 (0,5%)	4 (3,3%)	1 (1,6%)	1(2,6%)
Pseudomonas aeruginosa	0	1 (0,8%)	1 (1,6%)	4 (10,3%)
MRSA	1 (0,5%)	0	1 (1,6%)	3 (7,7%)
Other	8 (3,8%)	5 (4,2%)	3 (4,8%)	1 (2,6%)
Unknown	200 (94,3%)	88 (73,3%)	56 (90,3%)	29 (74,4%)

Table II. Etiologic profile

Abbreviation: MRSA, methicilin resistant Staphylococcus aureus; BC, blood culture; BS, bronchial secretion.

	Urinary antigen test		
	Positive (n and %)	Negative (n and %)	p
Positive BS (n=12)	4 (33,3%)	8 (66,7%)	0,034
Positive blood cultures (n=2)	1 (50,0%)	1 (50,0%)	0,172

Table III. Relation between microbiological identification of Streptococcus pneumonia in bronchial secretions (BS) or blood and the result of the urinary antigen test, using Pearson's Chi-square Test.

			(CI 95%)			
Group	nº	PUatg +	Ss, %	Sp, %	PPV, %	NPV, %
PP	14	5	35,7 (10-62)	88,9 (80-98)	50,0 (19-81)	81,6 (72-92)

Table IV. Calculation of sensitivity, specificity, positive and negative predictive values for urinary antigen test.

Abbreviation: PP, pneumococcal pneumonia; Ss, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; CI95%, 95% confidence interval; PUatg +, positive S. pneumoniae urinary antigen.

Initial antibiotherapy	CAP (nº and %) (n=222)	HCAP (nº and %) (n=57)
Amoxicilin Clavulanate	33 (14,9%)	5 (8,8%)
Amoxiciline Clavulanate+Macrolide	62 (27,9%)	6 (10,5%)
3G cephalosporin	3 (1,4%)	2 (3,5%)
3G cephalosporine+Macrolide	56 (25,2%)	6 (10,5%)
Quinolone	38 (17,1%)	5 (8,8%)
Piperaciline Tazobactam	14 (6,3%)	23 (40,4%)
Piperaciline Tazobactam+Macrolide	8 (3,6%)	3 (5,3%)
Carbapenem	5 (2,3%)	5 (8,8%)
Other	3 (1,4%)	1 (1,8%)

Table V. Relative frequencies of initial antibiotherapy.

Discussion

As we expected, the mean age was greater in HCAP than in CAP ($p < 0,001$). However, there wasn't a significant difference in the length of stay in the hospital between HCAP and CAP ($p=0,5$).

Patients with HCAP had more co-morbidities, such as active cancer (p=0,019), cerebrovascular disease (p<0,001) and chemotherapy (p=0,027). They had also higher severity scores - PSI-PORT and CURB-65 (p <0,001 and p=0,004, respectively).

In our setting, the conventional diagnostic tests had low rentability. The described data are inferior to those previously described in the literature[2]. These results may be due to low quality products collected in the emergency department and inclusion of non-septic patients. The PUatg is widely used and increases the number of etiologic diagnosis[14,15,16]. In our setting the sensitivity was 36% ($CI_{95\%}$ 10-62), conferring the test low precision in diagnosis. Small sample size (few true-positives) implies great limitations in these calculations. The urine samples weren't ultra-filtrated, possibly contributing to the low sensitivity found [17]. Even though these numbers are inferior to the published data, sensitivity varies widely between series[1,13,14].

The specificity was high – 89% ($IC_{95\%}$ 80-98), which is also consistent with the data previously described[10,11]. Based on these results, we can state that determining PUatg is useful to confirm the S. pneumoniae etiology.

The number of false positives (FP) doesn't seem to be increased in the patients with COPD (p=0,137), which is concordant to what was published in the literature before[18].

There were 3 cases considered FP. However, we can't exclude the possibility of mixed infections or a previous exposure to S. pneumoniae (in the last 3 months)[19].

Until this date, few studies have confirmed the utility of PUatg in clinical practice. A study evaluated prospectively the use of PUatg in 168 patients admitted with CAP. Having a positive PUatg caused a change in antibiotics in 44 cases, without any significant change in the prognosis[13]. The only prospective randomized study that compared empirical treatment versus targeted treatment on the basis of the urine antigen results in hospitalised patients with CAP [20] did not show any benefits (economic- or prognostic-wise) in choosing antibiotics according to the results of PUatg. Moreover, the patients that received a microorganism-directed antibiotic had more recurrences and complications. According to the authors, those recurrences and complications could be due to co-infection with agents not covered by those antibiotics.

In our study, none of the patients with positive PUatg received antibiotics directed specifically to S. pneumoniae (optimal alteration). Six (24%) of the 25 patients with positive PUatg had a narrowing in the antibiotic spectrum considered appropriate (discontinuation of the macrolide). However, in spite of having a positive PUatg, the treatment wasn't modified in 19 (76%) of the patients. We have to point out that the macrolide was also suspended in 25

(10,4%) of the patients with negative PUatg, with a borderline correlation between a positive PUatg result and the suspension of the macrolide (p=0,054).

Surprisingly, the time interval until there was a change in the antibiotics was longer in the patients with positive PUatg (median - 3,5 days and IQR - 2,25 days). However, this time interval is difficult to determine in a retrospective study, because the reductions may be related to other microbiological results (blood or BS cultures).

These data suggest that the physicians may not give much importance to the PUatg results. Perhaps doctors don't trust the PUatg results enough to narrow the spectrum of antibiotics. This leads to a low clinical utility of PUatg.

Our study suggests that the PUatg, because of its high specificity, can be useful to confirm the disease. However, the benefit can only be effective if the PUatg result determines a change in the therapeutic approach – such as a narrowing of the antibiotics spectrum – which was not the case in this series.

In HCAP, the PUatg seems to be less important. This may be due to a lower preponderance of a S. pneumoniae etiology, a higher risk of false positives (by previous infections), and a selection of the agents caused by the frequent use of antibiotics. In this group, we didn`t find any utility in performing PUatg test.

Our study has several limitations, most importantly it`s a retrospective study limiting the ability to calculate precisely antibiotherapy duration, antibiotherapy modification timing, microbiological results, clinical data and outcomes. In addition many patients (n=72) were excluded because PUatg test was not performed during hospitalization.

Conclusions

Considering its high specificity, the urinary antigen is useful to confirm the presence of S. pneumoniae pneumonia. Potentially urinary antigen can help to avoid unnecessary treatments in hospitalized patients with CAP. However, in HCAP the urinary antigen does not seem to be useful.

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