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ORIGINAL ARTICLE

Severe community-acquired pneumonia and positive urinary antigen test for *S. pneumoniae*: amoxicillin is associated with a favourable outcome

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Abstract Positive urinary antigen tests (UAT) for pneumococcal infection in community-acquired pneumonia (CAP) may lead to targeted antibiotic therapy. We report an audit aimed at defining the link between mortality and targeted therapy. We conducted a retrospective multicentre audit of patients with severe CAP for whom a UAT was positive for *S. pneumoniae*. Patients admitted from January 2010 to December 2013 to 8 medical centres (from A to H) were included. Co-morbidities were defined by the specific treatment administered before hospital care, or if the diagnosis was newly established during the hospital stay. We used the Pneumonia Severity Index (PSI) to assess disease severity. Only patients with PSI>90 were included. Antibiotic treatments and the PSI were extracted from patients' charts. Amoxicillin had to be prescribed as a targeted antibiotic treatment or at the time of antibiotic reassessment. A total of 389 patients were included. The mean (±STD) PSI score was 128±29; 38.9 % of the patients had a class 5 PSI score. Intensive care was required for 36.6 % of the patients. Amoxicillin was initially prescribed in 47 cases (12.1 %) and in 34 cases after reassessment (8.7 %). In logistic regression analysis, we found three parameters associated with mortality: being hospitalised in institution D, class 5 PSI score, and metastatic cancer. In contrast, three antibiotic regimens were protective factors, including targeted therapy: OR=0.09, $p<0.001$. In the context of severe CAP with positive UAT for *S. pneumoniae*, targeted therapy was associated with a reduction in mortality.

Introduction

Community-acquired pneumonia (CAP) is a common and sometimes severe illness associated with significant morbidity and an estimated 30 day-mortality rate of over 20 % [1, 2]. The establishment of clinical and therapeutic strategies aimed at the reduction of mortality have been published as guidelines

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across the world [3–6]. The favourable impact of these guidelines has been reported, with a lower duration of hospital stay, a lower requirement for intensive care and a reduction in mortality [7–9].

However, differences exist between strategies, particularly regarding microbial investigations [3–6, 10]. Nearly all guidelines recommend performing blood cultures, but the clinical benefit of urinary antigen tests (UATs) for *S. pneumoniae*, the main pathogen to be considered when providing care to patients with severe CAP, is more controversial. In brief, in France [5], an *S. pneumonia* UAT is proposed for CAP requiring intensive care admission. In US guidelines [3], some comorbidities are indications for the *S. pneumoniae* UAT for in-patient management, regardless of the severity of the disease, while in Japan, this test is advised for all hospitalised patients [6].

Previous studies on the utilisation of the *S. pneumonia* UAT in clinical practice indicated that it is widely prescribed, but with a low rate of antibiotic reassessment (<25 %) [11–13]. The absence of consensual consideration of the UAT may come from variable interpretations of the sensitivity, specificity and predictive values [13–16]. Finally, there are few studies on the clinical impact of targeted therapy, suggesting overall that the outcome was not altered in the case of non-severe CAP [17–21].

In the era of rising bacterial resistance to antibiotics, targeted therapy without prognosis alteration is a major goal [22, 23]. Also, antibiotic reassessment, narrowing the antibacterial spectrum, is a cornerstone of antimicrobial stewardship worldwide [24, 25]. Therefore, our aim was to determine the impact of targeted therapy after a positive *S. pneumonia* UAT on the mortality of severe CAP.

Materials and methods

Population and study design

This was a retrospective multicentre study including all adult patients with positive UAT for *S. pneumoniae* between January 2010 and December 2013. The study profile is shown in Fig. 1.

Participating institutions work in a professional multidisciplinary network for antibiotic stewardship, objectives being practice homogenisation, audits and clinical research [26, 27].

Positive UATs were selected from a computerised database from relevant laboratories. All participating laboratories used the Binax-NOW *S. pneumoniae* urinary antigen test, which was performed and interpreted according to the manufacturer's instructions.

Included were adult patients with a primary discharge diagnosis of CAP for whom a UAT was performed during the study period. Exclusion criteria were nosocomial infection defined by a diagnosis established≥48 h after hospital admission, acute bronchitis, exacerbation of chronic obstructive pulmonary disease, and meningitis for which *Pneumococcus* UAT might be positive.

All clinical data, therapeutic means and outcome were collected from patient' charts. Co-morbidities were defined by the prescription of the specific treatment before hospital care, or if the diagnosis was newly established during the hospital stay. In all co-morbid conditions, the most severe forms were listed: for cardio-vascular diseases: chronic heart failure and/or infarction; for diabetes, the knowledge of any vascular complications; neurological diseases: loss of autonomy related to dementia and/or stroke with sequelae; for pulmonary diseases: chronic obstructive pulmonary disease and/or lung fibrosis; for cancer: the knowledge of a metastatic disease; for liver diseases: the knowledge of cirrhosis; for renal diseases: the end-stage of chronic renal failure or dialysis. Community-acquired pneumonia severity was evaluated using the Pneumonia Severity Index (PSI). An unfavourable outcome was defined by the death of the patient during the hospital stay.

Depending on the health-care organisation, and varying from one hospital to another, a positive UAT may have different impacts on antibiotic treatment. If their results were immediately available, targeted therapy, e.g. amoxicillin, may be the first course of antibiotics. If the UAT result was available after the prescription of the first course of antibiotics, reassessment may lead to amoxicillin prescription.

Antibiotic simplification was defined by antibiotic reassessment leading to a narrower antibacterial spectrum (for example, from a combination therapy to a single therapy).

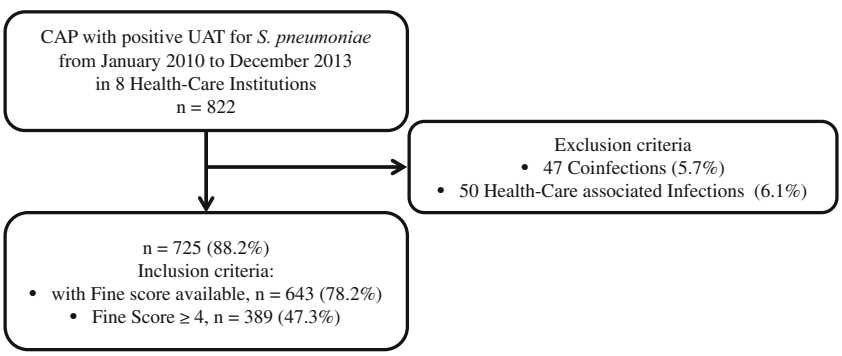

Fig. 1 Study profile

Table 1 Comparability of the groups, depending on the simplified antibiotic therapy for community-acquired pneumonia with a positive urinary antigen test for *S. pneumoniae*. Univariate analysis

	Simplified therapy, *n*=81 (20.8)	No simplified therapy, *n*=308 (79.2)	*p*	Total, *n* (%)
Hospital				
A	4 (4.9)	55 (17.8)	0.004	4/59 (6.8)
B	11 (13.6)	38 (12.3)	0.764	11/49 (22.4)
C	20 (24.7)	19 (6.2)	<0.001	20/49 (51.3)
D	5 (6.2)	37 (12.0)	0.132	5/42 (11.9)
E	0 (0.0)	14 (4.55)	0.051	0/14
F	5 (6.2)	65 (21.1)	0.002	5/70 (5.1)
G	26 (32.1)	40 (13.0)	<0.001	26/66 (39.4)
H	10 (12.3)	27 (8.8)	0.328	10/37 (27.0)
Age (years, mean±STD deviation)	75±15	79±13	0.046	78±13
Sex ratio (male/female)	1.08	1.23	0.591	1.19
ICU admissions	25 (30.9)	111 (36.0)	0.384	136 (34.9)
Comorbid conditions				
Allergy to penicillin	1 (1.2)	5 (1.6)	0.800	6 (1.5)
Cardio-vascular	39 (48.1)	186 (60.4)	0.047	225 (57.8)
Pulmonary	28 (34.6)	120 (39.0)	0.469	148 (38.0)
Neurological and/or psychiatric	18 (22.2)	89 (28.9)	0.231	107 (27.5)
Cancer	11 (13.6)	69 (22.4)	0.080	80 (20.6)
Diabetes	11 (13.6)	45 (14.6)	0.814	56 (14.4)
Chronic renal diseases	8 (9.9)	28 (9.1)	0.828	36 (9.2)
Alcoholism	6 (7.4)	25 (8.1)	0.834	31 (8.0)
Liver diseases	4 (4.9)	26 (8.4)	0.293	30 (7.7)
PSI score	123±27	129±29	0.073	128±29
PSI 4	55 (67.9)	184 (59.7)	0.179	239 (61.4)
PSI 5	26 (32.1)	124 (40.3)	0.179	150 (38.6)
Microbial data				
S. pneumoniae isolated	19 (23.5)	53 (17.2)	0.197	72 (18.5)
Blood culture performed	61 (75.0)	220 (71.4)	0.488	281 (72.2)
Positive for *S. pneumoniae*	10 (12.4)	36 (11.7)	0.172	46 (16.4)
Death	3 (3.7)	76 (24.7)	<0.001	79 (20.3)

Antibiotic reassessment from ceftriaxone to amoxicillin+ clavulanic acid or from levofloxacin to amoxicillin+ clavulanic acid was not considered to be a narrower spectrum. Antibiotic strengthening was defined by the prescription of a higher spectrum antibiotic or a combination therapy at the time of antibiotic reassessment. Exclusion criteria were extra-pulmonary co-infection and/or a health-care associated infection (HCAI) defined by its occurrence≥48 h after hospital admission.

Microbial investigations

Commercial products for *S. pneumoniae* UAT were used in all participating centres. Specific manufacturer's recommendations were followed. All other bacteriological investigations were systematically included, more specifically blood cultures, respiratory specimens, whatever the technique used (sputum, broncho-alveolar lavages, bronchial aspirations), but also other microbiological samples that indicate co-infection or HCAI.

Statistical analysis

Data were analysed using Statview software version 4.5 and statistical significance was established at $\alpha=0.05$. Continuous variables were compared using the Mann–Whitney non-parametric test and qualitative variables were compared using the Chi-squared or Fisher's exact test when appropriate. Logistic regression was used for the multivariate analysis of the impact of antibiotic simplification on all-cause in-hospital mortality and results are presented as adjusted odds ratios (AORs) with their 95 % confidence intervals (CIs). Variables

Table 2 Risk factors associated with mortality. Only the main antibiotic modalities are indicated for a better understanding

	Favourable outcome, 310 (79.7)	Unfavourable outcome, 79 (20.3)	*p*	Multivariate analysis AOR (95 % CI), *p* value
Hospitals				
A	53 (17.1)	6 (7.6)	0.035	
B	42 (13.5)	7 (8.9)	0.262	
C	35 (11.3)	4 (5.1)	0.100	
D	22 (7.1)	20 (25.3)	<0.001	6.68 [2.84–15.72], < 0.001
E	7 (2.6)	7 (8.9)	0.005	
F	52 (16.8)	18 (22.8)	0.214	
G	54 (17.4)	12 (15.2)	0.637	
H	34 (11.0)	3 (3.8)	0.052	
Age (years, mean±STD deviation)	78±14	77±12	0.098	
Sex ratio (male/female)	1.20	1.19	0.522	
Intensive care admission	92 (29.7)	44 (55.7)	<0.001	
Comorbid conditions				
Any comorbid conditions	302 (97.4)	76 (96.2)	0.560	
Cardio-vascular	182 (58.7)	43 (54.4)	0.492	
Chronic heart failure and/or infarction[a]	24 (7.7)	10 (12.6)	0.167	
Diabetes	48 (15.5)	8 (10.1)	0.226	
With vascular complications	12 (3.9)	4 (5.1)	0.634	
Neurological and/or psychiatric	80 (25.8)	27 (34.2)	0.137	
Loss of autonomy	49 (15.8)	17 (21.5)	0.227	
Pulmonary	116 (37.4)	32 (40.5)	0.614	
COPD	71 (22.9)	18 (22.8)	0.982	
Active smoking	44 (14.2)	12 (15.2)	0.822	
Cancers	54 (17.4)	26 (22.9)	0.002	
With metastasis	12 (3.9)	12 (15.2)	0.002	4.50 [1.65–12.28], 0.003
Alcoholism	21 (6.8)	10 (12.6)	0.085	
Liver diseases	23 (7.4)	7 (8.9)	0.668	
With cirrhosis	3 (1.0)	3 (3.8)	0.069	
Chronic renal failure	30 (9.7)	6 (7.6)	0.567	
With end-stage disease or dialysis	22 (7.1)	4 (5.1)	0.518	
At least one end-stage disease	120 (38.7)	45 (57.0)	0.003	
PSI 5	93 (30.0)	57 (72.2)	<0.001	5.97 [3.22–11.04], < 0.001
Microbial data				
Bacteraemia	34 (11.0)	12 (15.2)	0.296	
Streptococcus pneumoniae isolated	51 (16.5)	21 (26.6)	0.038	
Other bacteria from respiratory sample[b]	31 (10.1)	12 (15.2)	0.199	
Antibiotic therapy				
Targeted antibiotic regimen	78 (25.7)	3 (3.8)	<0.001	0.09 [0.02–0.27], < 0.001
Main other unchanged regimens				
Amoxicillin+clavulanic acid	8 (10.1)	72 (23.2)	0.010	0.24 [0.10–0.59], 0.001
Third generation cephalosporin (Ceph-3)	7 (8.9)	21 (6.7)	0.521	
Levofloxacin	4 (5.0)	14 (5.5)	0.882	
Antibiotic combinations	41 (13.2)	26 (32.9)	<0.001	
Ceph-3+levofloxacin	10 (6.1)	19 (12.6)	0.048	
Ceph-3+macrolide[c]	3 (<1)	6 (7.6)	<0.001	
Two courses of antibiotics	90 (29.0)	24 (30.4)	0.814	
With antibacterial spectrum reduction	20 (6.4)	1 (1.3)	0.068	0.89 [0.01–0.73], 0.024
With antibiotic strengthening	14 (4.5)	10 (12.6)	0.007	

Table 2 (continued)

	Favourable outcome, 310 (79.7)	Unfavourable outcome, 79 (20.3)	*p*	Multivariate analysis AOR (95 % CI), *p* value
Three or more courses of antibiotics	8 (10.1)	19 (6.1)	0.212	

[a] Previous myocardial infarction declared by the patient and/or by the general physician

[b] Including polymicrobial samples, the diagnosis being based on standard isolation procedures (analysis of sputum, broncho-alveolar lavages, bronchial aspirations)

[c] Among erythromycin, roxithromycin, clarithromycin

were selected as candidates for the multivariate analysis on the basis of the level of significance of the univariate association with in-hospital mortality ($P<0.1$). Models were built up sequentially, starting with the variable most strongly associated with the outcome and continuing until no other variable reached significance or altered the odds ratios of variables already in the model. When the final model was reached, each variable was dropped in turn to assess its effect.

Results

Eight health-care institutions contributed to the study: 1 tertiary-care teaching hospital, 6 general hospitals and 1 private clinic. Overall, 32 clinical departments participated including 17 medical departments, 8 intensive care units, 2 infectious disease departments and 5 pneumology departments.

A total of 822 patients with positive UAT were included; 97 patients were excluded, while in 97 other patients PSI score was not determined. Considering a PSI score≥4 only, 389 patients were finally analysed (Table 1).

Targeted antibiotic therapy was prescribed in 47 cases (12.0 %). Antibiotic reassessment leading to the prescription of a targeted therapy was observed in 34 cases (8.7 %). Thus, a total of 81 patients benefited from a targeted antibiotic therapy (20.8 %) according to UAT results (group 1), while 308 patients did not (group 2).

The main clinical characteristics of these patients are listed in Table 1. The main difference between the two groups was the clinical outcome, with significantly more deaths in the second group: 24.7 % compared with 3.7 %, $p<0.001$. Interestingly, the mean age of the patients benefiting from targeted therapy was higher than those benefiting from antibiotic reassessment leading to targeted therapy: 78±14 *versus* 71± 16 years-old, p=0.048, the PSI score was nearly equal (122 vs 123) and there was no difference in terms of comorbid condition frequency. Accordingly, 2 out of 47 patients with a targeted therapy died, as well as 1 out of 34 patients who had an antibiotic reassessment leading to targeted therapy.

As targeted therapy appeared to be associated with a better outcome, we wanted to characterise the patients who died (Table 2). To to carry out this analysis, we determined end-stage comorbid conditions that might have a specific impact on the prognosis in addition to detailing antibiotic treatment modalities. In univariate analysis, several factors including hospital sites, comorbid conditions, CAP severity and antibiotic regimens were associated with mortality. However, in the multivariate analysis, we found three risk factors associated with mortality: hospital D (OR 6.68, $p<0.001$), a PSI score 5 (OR 5.97, $p<0.001$), metastatic cancer OR 4.50, $p=0.003$. In contrast, antibiotic simplification was protective: targeted antibiotic treatment (OR 0.09, $p<0.001$), use of amoxicillin/clavulanate acid alone (OR 0.24, $p=0.001$) or antibiotic simplification (OR 0.89, $p=0.024$).

It should be noted that the favourable impact on survival of targeted antibiotics was still obvious when we focused on patients requiring intensive care or when we included only the patients with end-stage co-morbid conditions as described in the Materials and methods section ($n=165$). In this latter analysis, the rate of death was 27.3 % and the higher risk factor for death was the PSI score V (OR 7.32 [3.02–17.71], $p<0.001$), while the targeted antibiotic therapy was still protective (OR 0.11 [0.01–1.00], $p=0.050$).

Discussion

Our study shows that targeted therapy in severe CAP, on the basis of positive UAT for *S. pneumonia*, is associated with a lower rate of mortality, compared with patients for whom the result of the UAT was not taken into account. Importantly, the significant statistical association between the targeted therapy and survival was observed whatever the selected population, including the most severe patients, i.e. those requiring intensive care or with at least one end-stage co-morbid condition.

To our knowledge, our multicentre study is the largest one currently published that focuses on the clinical impact of targeted antibiotic therapy on the basis of positive UAT for *S. pneumonia* in CAP [10, 18–21].

The possibility of obtain the UAT results in a few hours and therefore the opportunity to prescribe the targeted therapy with only a short delay are among the limitations in studying the

impact of UAT in clinical practice. In fact, few studies aimed to establish the clinical impact of targeted therapy on the basis of a positive UAT, and their methodologies reflected these limitations. In a prospective study including 219 patients with non-severe CAP, 48 had positive UAT and were treated by amoxicillin, with a rapid favourable outcome in 92 % [18]. In another prospective randomised study, Falguera et al. concluded that UAT for *S. pneumoniae* did not carry substantial therapeutic benefit [19]. However, their antibiotic consensus included at least 2 days of intra-venous large-spectrum antibiotic therapy before targeted treatment; moreover, only 25 out of 194 patients had a positive UAT. Also, we published a retrospective monocentric study including 152 patients presenting with positive UAT for *S. pneumonia* or *L. pneumophila* who benefited from targeted therapy in both our infectious diseases department and intensive care unit. Despite the high PSI score, the percentage of unfavourable outcomes was very low [20]. However, there was no comparison group in this study. In another prospective study including 474 CAP, *S. pneumonia* was the causative agent in 171 cases and UAT was positive in 75 cases, leading eventually to a lower spectrum of antibiotics in only 41 patients [21]. Owing to the limited number of patients with simplified antibiotic therapy, it was not possible to draw any conclusion on the clinical impact of these urinary tests. Last, a recent study showed that positive UAT for *S. pneumonia* was associated with a poorer clinical outcome than those without positive UAT; however, the antibiotic treatment was not clearly altered, and the majority of the patients were being treated with respiratory fluoroquinolones [28].

Among factors associated with mortality, some are obvious, such as PSI score V and disseminated cancer, but we also observed that one hospital site was associated with a poorer outcome. It should be not a surprise as both antibiotic prescriptions in CAP are known to be extremely diverse and inappropriate therapeutic choices are a source of an unfavourable outcome [25–29]. We have recently reported in our professional network that differences between institutions in the care for patients with prosthetic bone infection were also associated with variable outcomes [27].

Considering our results, the main question is why simplified antibiotic therapy in CAP is associated with a better survival rate? The deleterious impact of an excess of antibiotic therapy was observed in the univariate analysis (Table 2). The excess of antibiotic therapy may be also detrimental through increased antibiotic adverse effects and/or the preservation of intra-venous administration and its potential complications [30]. Also, targeted therapy may reflect the better standard of care, as it was associated with a trend towards more successful microbial investigations (see Tables 1 and 2). In accordance with this hypothesis, Meehan et al. described a better prognosis in patients with CAP when blood cultures were performed [31].

Our study has some limitations: first, being retrospective in nature, we cannot exclude drawback; second, we did not specifically study the duration of antibiotic combinations before antibiotic reassessment leading to targeted therapy, which may have had an impact on the outcome; third, we did not study the duration of parenteral therapy before the switch to an enteral route of antibiotic treatment.

In conclusion, our study shows that targeted therapy because of a positive UAT for *S. pneumoniae* in severe CAP is associated with survival. Owing to this major outcome, a prospective study is needed to confirm this large series of patients. Because of the burden of CAP, simplified therapy will be a major tool in fighting the tide of multi-drug resistant bacteria.

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Compliance with ethical standards

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