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Invasive Disease vs Urinary Antigen-Confirmed Pneumococcal Community-Acquired Pneumonia

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BACKGROUND: The burden of pneumococcal disease is measured only through patients with invasive pneumococcal disease. The urinary antigen test (UAT) for pneumococcus has exhibited high sensitivity and specificity. We aimed to compare the pneumococcal pneumonias diagnosed as invasive disease with pneumococcal pneumonias defined by UAT results.

METHODS: A prospective observational study of consecutive nonimmunosuppressed patients with community-acquired pneumonia was performed from January 2000 to December 2014. Patients were stratified into two groups: invasive pneumococcal pneumonia (IPP) defined as a positive blood culture or pleural fluid culture result and noninvasive pneumococcal pneumonia (NIPP) defined as a positive UAT result with negative blood or pleural fluid culture result.

RESULTS: We analyzed 779 patients (15%) of 5,132, where 361 (46%) had IPP and 418 (54%) had NIPP. Compared with the patients with IPP, those with NIPP presented more frequent chronic pulmonary disease and received previous antibiotics more frequently. Patients with IPP presented more severe community-acquired pneumonia, higher levels of inflammatory markers, and worse oxygenation at admission; more pulmonary complications; greater extrapulmonary complications; longer time to clinical stability; and longer length of hospital stay compared with the NIPP group. Age, chronic liver disease, mechanical ventilation, and acute renal failure were independent risk factors for 30-day crude mortality. Neither IPP nor NIPP was an independent risk factor for 30-day mortality.

CONCLUSIONS: A high percentage of confirmed pneumococcal pneumonia is diagnosed by UAT. Despite differences in clinical characteristics and outcomes, IPP is not an independent risk factor for 30-day mortality compared with NIPP, reinforcing the importance of NIPP for pneumococcal pneumonia. CHEST 2017; 151(6):1311-1319

KEY WORDS: burden of pneumococcal disease; community-acquired pneumonia; diagnosis; *Streptococcus pneumoniae*; urinary antigen test

ABBREVIATIONS: ATS/IDSA = American Thoracic Society/Infectious Diseases Society of America; CAP = community-acquired pneumonia; IPP = invasive pneumococcal pneumonia; NIPP = noninvasive pneumococcal pneumonia; UAT = urinary antigen test

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Community-acquired pneumonia (CAP) remains a leading cause of death worldwide.[1,2] *Streptococcus pneumoniae* is the most frequent pathogen in CAP and is involved in all settings (outpatients, patients requiring hospitalization, and patients needing intensive care treatment), in all age groups, and regardless of comorbidities present.[3]

A definitive microbiologic diagnosis of pneumococcal pneumonia is difficult to establish, and the proportion of cases attributed to pneumococcus is potentially higher than that of cases with a definitive diagnosis.[4] Among the available techniques for pneumococcus diagnosis, sputum is unreliable because of misclassifications, contributing to uncertainty in epidemiologic studies because etiologic diagnosis can be considered only as probable, or presumptive.[5,6] In contrast, a positive culture result from normally sterile body fluids is considered the "gold standard" in determining invasive pneumococcal disease. In lower respiratory tract infections, blood cultures are employed as the main source to establish the presence of pneumococcal disease. However, blood cultures require laboratory settings and are subject to low sensitivity.[7]

Several studies in adults have demonstrated the effectiveness of the urinary antigen test (UAT) for the rapid diagnosis of pneumococcal pneumonia.[8,9] In contrast to previous methods, UATs have high sensitivity and specificity and can be done as a point-of-care test. Despite having these characteristics favorable for monitoring and surveillance, UATs have not been incorporated in the estimation of pneumococcal disease burden. One of the reasons for this fact could be that pneumococcal pneumonia diagnosed by a positive UAT result is not considered an "invasive disease."

An accurate and feasible method of measuring pneumococcal disease is needed, and a number of adult pneumococcal pneumonias are diagnosed and treated on the basis of UAT results. We hypothesized that pneumococcal pneumonias diagnosed by UAT have different clinical characteristics compared with a classic "invasive disease," but still contribute to the burden of pneumococcal disease.

For these reasons, we aimed to compare the clinical characteristics and outcomes of pneumococcal pneumonias diagnosed as a classic "invasive disease" with pneumococcal pneumonias defined by UAT.

Methods

Study Design and Patients

We performed a prospective, observational study of consecutive patients with CAP who visited the ED at the Hospital Clinic of Barcelona (January 2000 to December 2014).

Inclusion criteria included the following: (1) adults ≥ 18 years old at diagnosis; (2) CAP diagnosis confirmed by chest radiograph and consistent clinical manifestations (eg, fever, cough, sputum production, pleuritic chest pain); and (3) pneumococcal etiology confirmed by UAT or blood or pleural fluid. Patients with health-care associated pneumonia criteria were not included, except nursing home residents since a previous study[10] from our group demonstrated a microbiological pattern similar to CAP.

Exclusion criteria were as follows: (1) previous hospital admission for ≥ 48 hours in the preceding 14 days; (2) absence of complete clinical follow-up for 4 to 6 weeks; (3) unavailable blood culture; (4) severe immunosuppression, such as in transplantation, AIDS,[11] or receiving chemotherapy or other immunosuppressive drugs (> 20 mg prednisone-equivalent per day for 2 weeks or more).

Ethics Statement

The study was approved by the Ethics Committee of the Hospital Clinic of Barcelona (Register: 2009/5451). Written informed consent was waived because of the noninterventional design. Patients' identification remained anonymous.

Definitions

Patients included in the study were stratified into two exclusive groups according to microbial etiology: invasive pneumococcal pneumonia (IPP) defined as pneumonia with *Streptococcus pneumoniae* isolated from blood or pleural fluid (independent of positivity for urinary antigen) and noninvasive pneumococcal pneumonia (NIPP) defined as pneumonia positive for urinary antigen and with negative blood culture results.

Patients with *S pneumoniae* determined by Gram stain or by isolation only in a respiratory sample were not included in the analysis.

Severe pneumonia was defined according to American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines.[2] Pneumonia Severity Index[12] and CURB-65[13] scores were used to stratify cases on the basis of severity. The Pitt score[14] was calculated for patients with bacteremia.

Appropriateness of empiric antibiotic treatment in all patients was defined according to the guidelines of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).[15] We defined pulmonary complications of CAP elsewhere.[16] Extrapulmonary

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complications of CAP were also considered: septic shock and acute renal failure.

Blood or pleural culture results were considered positive when *S pneumoniae* was isolated from blood or pleural samples, respectively. A UAT result for pneumococcus was considered positive in accordance with the manufacturer's instructions (Alere BinaxNOW *Streptococcus pneumoniae* antigen card; Alere Inc.).

Data Collection

Clinical, laboratory, and radiographic characteristics were recorded on admission (for details see e-Appendix 1).

Comorbidities were registered according to medical records (for the full list of comorbidities see e-Appendix 1).

During hospitalization, the following data were recorded: length of stay, admission to the ICU, need for mechanical ventilation support (invasive or noninvasive), time to clinical stability,[2] and mortality.

All patients discharged alive were reexamined or at least contacted by telephone within 30 to 40 days of hospital discharge.

Microbiologic Evaluation

Regular sampling was done in the first 24 hours after ED admission and included respiratory specimens (sputum, tracheobronchial aspirate, bronchoalveolar lavage, and/or pleural fluid when available), two blood cultures, urine samples for detection of *S pneumoniae* and *Legionella pneumophila* serogroup 1, and nasopharyngeal swabs for respiratory virus detection. The UAT for *S pneumoniae* was not performed if the blood culture result had previously confirmed *S pneumoniae*. Blood and respiratory samples were tested by Gram and Ziehl-Neelsen stains and bacterial cultures (see e-Appendix 1).

Statistical Analysis

Data are shown as number of patients (%) for categorical variables and as median (1st quartile-3rd quartile) for continuous variables with nonnormal distribution or as mean (SD) for those with normal distribution. Categorical variables were compared by χ^2 test or Fisher exact test. Continuous variables were compared by *t* test or nonparametric Mann-Whitney test. Logistic regression analyses were used to obtain ORs adjusted for potential confounding factors for the associations between the exposure type of pneumococcal pneumonia and 30-day mortality (for the full list of variables, see e-Appendix 1). In the first step, each risk factor was tested individually. In the second step, all risk factors that showed an association in the univariate model ($P < .10$) were added into the multivariate model. A backward stepwise selection ($P_{in} < .05$, $P_{out} < .10$) was used to determine factors associated with 30-day mortality. The OR and 95% CI were calculated. The Hosmer-Lemeshow goodness-of-fit test was performed to assess the overall fit of the model.[17] Internal validation of the prediction model was conducted by ordinary nonparametric bootstrapping with 1,000 bootstrap samples and bias-corrected, accelerated 95% CIs.[18] Receiver operating characteristic curves were constructed for the ability to predict 30-day mortality of significant variables derived from the multivariate logistic regression model. Furthermore, we calculated sensitivity and specificity, predictive values, and likelihood ratios for the model predictive of 30-day mortality. In the sensitivity analysis we analyzed the clinical outcomes, separating the patients with invasive disease into those with positive or negative UAT results, and also the baseline characteristics and outcomes, excluding cases with previous pneumococcal vaccination and pneumonia in the last year in the NIPP group. The level of significance was set at .05 (two-tailed). All analyses were performed with SPSS Statistics version 22.0 (IBM).

Results

Patient Characteristics

Of the 5,132 patients with CAP admitted during the study period, 779 (15%) had definitive pneumococcal infections and were included in the present study; we did not include 54 patients (1%) with probable pneumococcal pneumonia (Fig 1). Pneumococcal pneumonia was diagnosed by blood culture results (345 patients [44%]) or pleural fluid culture results (16 patients [2%]) in a total of 361 patients (46%) in the IPP group, and 418 (54%) were classified in the NIPP group on the basis of a positive UAT result. All patients in the NIPP group underwent blood culturing and all produced negative results, 78 of them (18%) produced *Streptococcus pneumoniae* in respiratory samples, and 66 (16%) produced polymicrobial isolates, the most common being respiratory virus in 31 patients (8%) and *Haemophilus influenzae* in nine patients (2%). On the other hand, 48 patients with IPP (13%) produced respiratory samples from which *S pneumoniae* was isolated and 42 (12%) produced polymicrobial isolates.

Baseline characteristics of both groups are summarized in Table 1. Compared with the patients with IPP, patients with NIPP had higher rates of influenza vaccination; presented more frequently with chronic pulmonary disease, in particular COPD (44 patients [12%] in the IPP group vs. 81 patients [19%] in the NIPP group; $P = .006$); and more frequently received prior antibiotics compared with the IPP group.

Patients with IPP presented more severe CAP according to ATS/IDSA criteria (major and minor), although there were no significant differences regarding severity scores (Pneumonia Severity Index or CURB-65) (Table 2). Twenty-two patients with bacteremia (8%) presented a Pitt bacteremia score higher than 4 points. Patients with IPP had higher levels of creatinine and C-reactive protein and worse oxygenation at admission. Patients with IPP presented more frequently with pulmonary and extrapulmonary complications.

Antibiotic Treatment

Data on antibiotic treatment were available for 775 patients (99%). The initial empirical treatment was adequate in 99% of patients and not different between groups ($P = .24$) (e-Appendix 1).

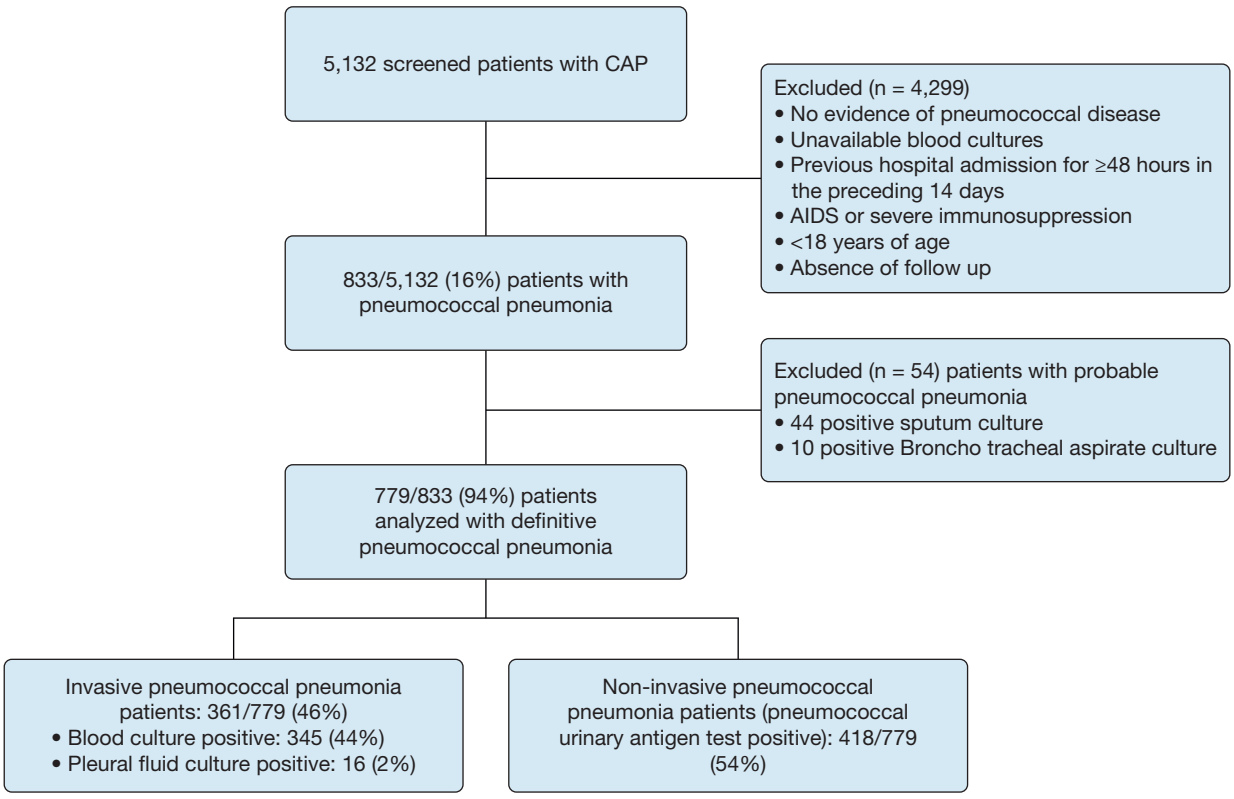

Figure 1 – *Flow diagram of the selected population. CAP = community-acquired pneumonia.*

Outcomes

Patients with IPP required more time to achieve clinical stability, had a greater length of hospital stay, and a higher rate of ICU admission (Table 2). Seven- and 30-day mortality did not differ between groups. Furthermore, the need for noninvasive or invasive mechanical ventilation was similar between groups.

Predictors of 30-Day Mortality

In the multivariate logistic regression analysis, the following risk factors were independently associated with 30-day mortality: age > 74 years, chronic liver disease, mechanical ventilation requirement, and acute renal failure (Table 3). Neither IPP nor NIPP was an independent factor in the multivariate analysis. The area under the receiver operating characteristic curve was 0.93 (95% CI, 0.88-0.97) (e-Fig 1) for the model predictive of 30-day mortality (sensitivity, 88%; specificity, 89%; positive predictive value, 27%; negative predictive value, 99%; positive likelihood ratio, 8.14; and negative likelihood ratio, 0.12). Internal validation of the logistic regression model was conducted by bootstrapping with 1,000 samples (e-Table 1). All the variables included in the model demonstrated robust results, with small 95% CIs around the original coefficients.

Sensitivity Analyses

We analyzed the clinical outcomes, separating the patients with invasive disease into those with positive or negative UAT results. The UAT was performed on 199 patients with IPP, and 156 of them (78%) produced positive UAT results. Only length of stay was higher in patients with positive UAT results, without significant differences in the other variables (e-Table 2).

Also, we analyzed the baseline characteristics and outcomes while excluding NIPP group patients with previous pneumococcal vaccination and pneumonia in the previous year (e-Tables 3 and 4). We observed that patients with NIPP received prior antibiotics more frequently. Patients with IPP presented more severe CAP, and had higher serum levels of C-reactive protein and worse oxygenation at admission. Patients with IPP presented more frequently with pulmonary complications and greater length of stay. However, no difference in mortality was observed.

Discussion

In our study we found that in 418 of 779 patients (54%), definite pneumococcal pneumonia was diagnosed by urinary antigen detection. When we compared patients

TABLE 1] Baseline Characteristics

Characteristic	Invasive Pneumococcal Pneumonia (n = 361)	Noninvasive Pneumococcal Pneumonia (n = 418)	*P* Value
Age, median (IQR), y	63 (48-78)	69 (49-79)	.21
Age, No, (%), y			.11
18-49	99 (27)	107 (26)	
50-64	88 (24)	78 (19)	
65-74	55 (15)	83 (20)	
> 74	119 (33)	150 (36)	
Male sex, No. (%)	213 (59)	244 (58)	.86
Systemic steroids, No. (%)	16 (5)	27 (7)	.21
Pneumococcal vaccine, No. (%)			.21
No	251 (89)	303 (84)	
< 6 mo	13 (5)	24 (7)	
> 6 mo	18 (6)	33 (9)	
Influenza vaccine, No. (%)			**.015**
No	197 (69)	212 (59)	
< 6 mo	63 (22)	103 (28)	
> 6 mo	24 (8)	47 (13)	
Chronic pulmonary disease, No. (%)	128 (36)	186 (45)	**.016**
Heart failure, No. (%)	36 (10)	61 (15)	.061
Chronic renal failure, No. (%)	22 (6)	27 (6)	.88
Hepatic disease, No. (%)	27 (8)	33 (8)	.87
Diabetes mellitus, No. (%)	66 (19)	61 (15)	.13
HIV infection, No. (%)	29 (8)	28 (7)	.47
Neurologic disease, No. (%)	47 (14)	64 (16)	.45
Previous neoplasia, No. (%)	26 (7)	34 (8)	.68
Tobacco, No. (%)			.41
Nonsmoker	158 (45)	168 (41)	
Former smoker	89 (25)	119 (29)	
Current smoker	106 (30)	127 (31)	
Alcohol consumption, No. (%)			.43
No alcohol	276 (78)	319 (77)	
Ex-alcohol addiction	18 (5)	23 (6)	
Active alcohol consumption (< 80 g/d)	52 (15)	68 (16)	
Active alcohol consumption (> 80 g/d)	7 (2)	3 (1)	
Previous pneumonia, No. (%)	45 (13)	63 (15)	.42
Nursing home, No. (%)	11 (3)	23 (6)	.10
Previous antibiotic therapy (last 2 mo), No. (%)	39 (11)	71 (17)	**.022**
Previous antibiotic therapy (last 48 h), No. (%)	10 (3)	27 (7)	**.019**
Creatinine, median (IQR), mg/dL	1.2 (0.9-1.6)	1.1 (0.9-1.5)	**.005**
C-reactive protein, median (IQR), mg/dL	26.6 (17.1-32.1)	21 (10.7-28.9)	**< .001**
White blood cell count, median (IQR), $\times 10^9$/L	14.7 (9.3-20.7)	14.2 (9.5-19.4)	.36
Pa_{O_2}/F_{IO_2}, median (IQR), mm Hg	271 (229-302)	290 (243-333)	**< .001**

Percentages calculated with nonmissing data. Boldface entries indicate statistical significance. IQR = interquartile range.

TABLE 2] Clinical Characteristics and Outcomes

Clinical Characteristic	Invasive Pneumococcal Pneumonia (n = 361)	Noninvasive Pneumococcal Pneumonia (n = 418)	*P* Value
CURB-65 risk classes 3-5, No. (%)	70 (21)	74 (19)	.49
PSI score, median (IQR)	99 (73-124)	94 (70-115)	.17
PSI risk classes IV and V, No. (%)	150 (56)	166 (52)	.34
Site of care, No. (%)			.062
Outpatient	21 (6)	30 (7)	NS
Ward	243 (67)	305 (73)	NS
ICU admission	97 (27)	83 (20)	**.021**
Severe CAP, No. (%)	103 (38)	93 (29)	**.019**
Pulmonary complications, No. (%)	170 (48)	135 (32)	**< .001**
ARDS	13 (4)	14 (3)	.75
Multilobar involvement	113 (31)	95 (23)	**.007**
Pleural effusion	83 (23)	58 (14)	**.001**
Extrapulmonary complications, No. (%)	137 (39)	127 (31)	**.025**
Septic shock	38 (11)	27 (7)	**.040**
Acute renal failure	125 (35)	114 (28)	**.020**
Mechanical ventilation, No. (%)[a]			.16
None	283 (87)	335 (89)	
Noninvasive	19 (6)	11 (3)	
Invasive	23 (7)	29 (8)	
Time to clinical stability, median (IQR), d	6 (3-9)	5 (3-7)	**.026**
Length of hospital stay, median (IQR), d	9 (5-14)	7 (5-10)	**< .001**
7-d mortality, No. (%)	9 (3)	5 (1)	.17
30-d mortality, No. (%)	25 (7)	16 (4)	.052

Percentages calculated with nonmissing data. Boldface entries indicate statistical significance. CAP = community-acquired pneumonia; CURB-65 = confusion, blood urea nitrogen, respiratory rate, blood pressure, age > 65 y; NS = not significant; PSI = Pneumonia Severity Index. See Table 1 legend for expansion of other abbreviation.

[a]Patients who initially received noninvasive ventilation but subsequently needed intubation were included in the invasive mechanical ventilation group.

with invasive pneumococcal disease with patients diagnosed only by UAT, we found clinical and evolutionary differences including higher severity of disease in the IPP group. However, IPP was not a factor independently associated with 30-day mortality compared with pneumococcal disease defined by a positive UAT result with negative blood and pleural fluid culture results.

We believe the burden of pneumococcal disease in adults should be measured by considering the pneumococcal pneumonias defined by both methods: invasive pneumococcal pneumonia and positive for urinary antigen. Indeed, a multicenter study in the United States coincides with our results, showing that 48% of pneumococcal pneumonias could be diagnosed by systematically using UAT.[19] The urinary *Streptococcus pneumoniae* test detects capsular polysaccharide C by means of inmmunochromatography. In the case of pneumonia these soluble microbial antigens are excreted in urine, and this mechanism is independent of the presence of bacteremia. Urinary detection is easy to perform, and it is an inexpensive test that allows the diagnosis of pneumococcal pneumonia with high sensitivity and specificity. In a multicenter study in Spain this technique resulted in high specificity (100%), indicating that in adults this test can be used confidently to diagnose pneumococcal pneumonia.[8]

S pneumoniae continues to be the most prevalent microorganism in CAP. In addition, it is one of the causes of pneumonia that is preventable by pneumococcal vaccination.[20] For this reason it is important to adequately measure the burden of the disease in order to conduct adequate health planning

TABLE 3] Significant Univariate and Multivariate Logistic Regression Analyses for the Prediction of 30-Day Mortality

	Univariate[a]			Multivariate[b]		
Variable	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age, y[c]	…	…	< .001	…	…	**.003**
18-49	1	…	…	1	…	…
50-64	0.12	0.04-0.41	.001	1.09	0.09-14.04	.94
65-74	0.15	0.05-0.51	.002	3.79	0.35-40.88	.27
> 74	0.38	0.15-0.93	.034	13.33	1.59-111.99	**.003**
Chronic renal failure	2.73	1.09-6.84	.032	…	…	…
Chronic liver disease	2.62	1.11-6.20	.028	4.55	1.29-16.04	**.018**
Neurologic disease	2.73	1.34-5.57	.006	…	…	…
Previous neoplasia	2.66	1.12-6.29	.026	…	…	…
Mechanical ventilation[d]	…	…	< .001	…	…	**< .001**
None	1	…	…	1	…	…
Noninvasive	14.14	5.16-38.78	< .001	15.46	3.85-62.09	**< .001**
Invasive	15.49	6.73-35.67	< .001	17.71	5.49-57.10	**< .001**
ARDS	8.83	3.59-21.69	< .001	…	…	…
Acute renal failure	7.13	3.41-14.88	< .001	9.13	2.90-28.71	**< .001**
Septic shock	7.40	3.63-15.11	< .001	…	…	…
Antibiotic treatment[e]	…	…	.002	…	…	…
Quinolone	0.24	0.04-1.35	.11	…	…	…
β-Lactam plus quinolone	1.72	0.57-5.22	.34	…	…	…
β-Lactam plus macrolide	0.46	0.14-1.55	.21	…	…	…
Other	1	…	…	…	…	…
Invasive pneumococcal pneumonia	1.88	0.99-3.57	.056	1.71	0.64-4.56	.28
Year of admission	1.04	0.96-1.12	.34	1.02	0.90-1.15	.76

Boldface entries indicate statistical significance.
[a]The variables analyzed in the univariate analysis included age, sex, influenza and pneumococcal vaccination, chronic pulmonary disease, chronic heart failure, chronic renal disease, chronic liver disease, diabetes mellitus, HIV infection, neurologic disease, previous neoplasia, tobacco, alcohol consumption, C-reactive protein, ARDS, pleural effusion, acute renal failure, septic shock, mechanical ventilation, antibiotic treatment, appropriate empiric treatment, invasive pneumococcal pneumonia, and year of admission.
[b]Hosmer-Lemeshow goodness-of-fit test, $P = .70$.
[c]The *P* value corresponds to differences between the four groups (18-49, 50-64, 65-74, or > 74 y of age).
[d]The *P* value corresponds to differences between the three groups (nonmechanical ventilation, noninvasive mechanical ventilation, or invasive ventilation).
[e]The *P* value corresponds to differences between the four groups (quinolone, β-lactam plus quinolone, β-lactam plus macrolide, or other antibiotic treatment).

and to evaluate vaccination effects. The newer UAT with additional technology can also provide information on the pneumococcal serotype causing pneumonia, as recently used in the CAPITA (Community-Acquired Pneumonia Immunization Trial in Adults) study (at least for the 13 serotypes included in the 13-valent pneumococcal conjugate vaccine). When applied to clinical practice, the knowledge of serotypes from invasive strains plus those detected in urine will provide important epidemiologic information to measure the effectiveness of pneumococcal vaccination and surveillance, and to guide health policy.

We found some clinical differences when comparing the two pneumococcal disease populations. For example, in the IPP group we found less chronic respiratory disease, a lower rate of influenza vaccination, higher levels of creatinine and particularly C-reactive protein, and more severe respiratory failure. Interestingly, the use of prior antibiotics in the previous 2 months was more frequent in the UAT group. Despite the pneumonia severity scores being similar, we found a higher clinical severity of pneumonia in the IPP group. This was confirmed by a higher rate of pulmonary complications, longer length of stay, and longer time to clinical stability. To our

knowledge this is the first report in the literature comparing two large pneumococcal disease populations, defined as those with invasive disease and those only with positive UAT results. Zalacain et al[21] have compared bacteremic pneumococcal pneumonias with and without positive UAT results. They found worse outcomes including treatment failure in those who were bacteremic and had a positive UAT result. We performed a sensitivity analysis, and only length of stay was different when comparing IPP with or without positive UAT results.

An interesting point that should be highlighted is the difference in influenza vaccination: we observed a lower rate of influenza vaccination in the population with invasive disease. Further studies should be conducted to evaluate this finding.

When we analyzed mortality, we found a strong trend to higher crude rates in the invasive group. However, this effect disappeared in the multivariate analysis when adjusting for potential confounders, in which invasive disease was not associated with higher mortality. In the overall population we found that being older (>75 years old), having chronic liver disease at baseline, requiring mechanical ventilation, and having acute renal failure were the factors independently associated with higher mortality. Regarding 30-day mortality, there are controversial data when comparing bacteremic pneumococcal pneumonia with UAT-confirmed pneumococcal pneumonia. van Mens et al[22] found a nonsignificant association with mortality for bacteremia (OR, 2.21; 95% CI, 0.94-5.21; $P = .07$). However, the study by Capelastegui et al[23] found a significant association of bacteremia with mortality (OR, 2.7; 95% CI, 1.5-5; $P = .002$). Both studies included only patients with positive blood culture results and did not include patients with positive pleural fluid culture results.

Given the possibility of false positive results in patients with previous pneumonia or prior pneumococcal vaccination, we conducted a sensitivity analysis excluding these patients in the NIPP group. We observed differences only in the rate of chronic respiratory disease (possibly due to bias selection) and mortality. The UAT may give false positive results in patients with previous pneumococcal infection, especially in patients with COPD for up to 1 year after pneumococcal infections.[24-26] Also, patients with previous vaccination may have false positive results in the early days after vaccination.[27,28]

In our study we excluded patients receiving a diagnosis on the basis of a respiratory sample alone. This decision was based on the fact that respiratory samples cannot offer high sensitivity and specificity.[7,29,30] In addition, these types of samples cannot be obtained from everybody with CAP. For example, only 30% of sputum samples are of good quality and are difficult to obtain from the elderly, or from patients with dehydration or impaired consciousness.[31] Because of these drawbacks we chose to study a homogeneous population of patients from whom blood and urine were easy to obtain. In the near future we are sure that the measured burden of the disease will increase because, in addition to using blood cultures and urinary antigens, we will see implementation of polymerase chain reaction (PCR) techniques such as quantitative *lytA* real-time PCR in nasopharyngeal swab or sputum samples,[32] which are more sensitive techniques than blood cultures or UAT.

The main limitation of this study is that it was performed at a single center and the results must be confirmed by others. The strength of our study is the inclusion of a relatively high number of patients with definite pneumococcal pneumonia.

Conclusion

We believe that the burden of hospitalized patients with pneumococcal pneumonia can be appreciated by combining those diagnosed on the basis of invasive samples with those who produced negative blood culture results but positive UAT results. Since these populations seem to be different, the burden of disease should be reported separately for both.

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