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Article

Impact of Cefotaxime Non-susceptibility on the Clinical Outcomes of Bacteremic Pneumococcal Pneumonia

Catia Cillóniz[1], Cristina de la Calle[2], Cristina Dominedò[3], Carolina García-Vidal[2], Celia Cardozo[2], Albert Gabarrús[1], Francesc Marco[4], Antoni Torres[1] and Alex Soriano[2]

[1] Department of Pneumology, Institut Clinic del Tórax, Hospital Clinic of Barcelona - Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona (UB) - SGR 911- Ciber de Enfermedades Respiratorias (Ciberes) Barcelona, Spain.
[2] Department of Infectious Disease, Hospital Clinic of Barcelona, Spain.
[3] Department of Anesthesiology and Intensive Care Medicine, Fondazione Policlinico Universitario A. Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy.
[4] Department of Microbiology, Hospital Clinic of Barcelona, Spain
Correspondence: Professor Alex Soriano; Department of Infectious Disease, Hospital Clinic of Barcelona; C/ Villarroel 170, 08036 Barcelona, Spain; Phone: (+34) 93-227-5779; Email: asoriano@clinic.cat

Abstract: Background: We aimed to analyze the impact of cefotaxime non-susceptibility on the 30-day mortality rate in patients receiving a third-generation cephalosporin for pneumococcal bacteremic pneumonia. **Methods:** We conducted a retrospective observational study of prospectively collected data from the Hospital Clinic of Barcelona. All adult patients with monomicrobial bacteremic pneumonia due to *Streptococcus pneumoniae* and treated with a third-generation cephalosporin from January 1991 to December 2016 were included. Risk factors associated with 30-day mortality were evaluated by univariate and multivariate analyses. **Results:** During the study period, 721 eligible episodes were identified, and data on the susceptibility to cefotaxime was obtainable for 690 episodes. Sixty six (10%) cases were due to a cefotaxime non-susceptible strain with a 30-day mortality rate of 8%. Variables associated with 30-day mortality were age, chronic liver disease, septic shock, and the McCabe score. Infection by a cefotaxime non-susceptible *S. pneumoniae* did not increase the mortality rate. **Conclusion**: Despite the prevalence of cefotaxime non-susceptible *S. pneumoniae* has increased in recent years. We found no evidence to suggest that patients hospitalized with bacteremic pneumonia due to these strains had worse clinical outcomes than patients with susceptible strains.

Keywords: cefotaxime; pneumonia; bacteremia; outcomes

1. Introduction

Antimicrobial resistance has emerged as an important public health problem globally [1,2]. The most common community pathogen, *Streptococcus pneumoniae* is associated with pneumonia, bacteremia, and meningitis[3]. This pathogen has also been associated with higher morbidity and mortality rates, especially in vulnerable populations, such as children and adults aged >65 years [4,5]. Indeed, the case fatality rates of invasive pneumococcal disease are 10%–30% in adults and <3% in children [6].

S. pneumoniae has also become increasingly resistant to many antimicrobials [7], with resistance patterns varying considerably by geographic area and over time [1,8]. This is important because antimicrobial-resistant patterns modify the clinical presentation of pneumococcal disease, making its

diagnosis and treatment more complex, and affecting clinical outcomes [7]. Despite the increase in antimicrobial resistance, cefotaxime and ceftriaxone remain the most active cephalosporins [9]. To date, however, the clinical impact of third-generation cephalosporins (3GC) non-susceptibility on clinical outcomes has not been comprehensively evaluated in cases of pneumococcal bacteremic pneumonia.

In the present study, we aimed to analyze the effect of 3GC non-susceptibility on the outcomes of patients with bacteremic pneumococcal pneumonia treated empirically with a third-generation cephalosporin.

2. Methods

2.1. Ethics statement

The study was approved by the Ethics Committee of our institution (*Comité Ètic d'Investigació Clínica*, register: 2009/5451). The need for written informed consent was waived because of the non-interventional study design.

2.2. Study design and patients

This was a retrospective observational study of data that were prospectively collected at the Hospital Clinic of Barcelona. All adult patients with monomicrobial bacteremic pneumonia due to *S. pneumoniae* admitted to the hospital between January 1991 and December 2016 were included. We excluded cases of bacteremic pneumonia not caused by *S. pneumoniae* and cases with incomplete clinical data. The patients were then divided into two groups based on their susceptibility to 3GC.

2.3. Data collection and evaluation

The following data were obtained from all patients: age, gender, comorbidities, McCabe score [10], Pneumonia Severity Score (PSI)[11] was calculated in 312 cases, recent antimicrobial or steroid treatment (within the last month), recent hospitalization (within the last month), surgery and other invasive procedures, shock at presentation, etiology (microorganisms), empirical antimicrobial treatment, appropriateness of empirical therapy, and 30-day mortality. Patients were then prospectively followed up by a senior infectious disease specialist who assessed the medical history, physical examination, microbiological tests, and complementary imaging to determine the source of infection.

2.4. Definitions

Pneumonia was defined as the presence of a new pulmonary infiltrate on chest x-ray at hospital admission with symptoms and signs of lower respiratory tract infection. Pneumococcal bacteremia was diagnosed when a pneumococcal isolate was recovered from a blood culture of patients with pneumonia. Underlying diseases were classified according to the modified McCabe and Jackson criteria into rapidly fatal, finally fatal, or non-fatal [10].

Prior antimicrobial therapy was defined as the use of any antimicrobial agent for at least 3 days during the month before the onset of bacteremia. Prior steroid therapy was defined as the use of at least 10 mg of prednisone (or equivalent dose of another steroid) during the month before admission. Septic shock was defined as a systolic blood pressure <90 mmHg, peripheral hypoperfusion, and use of vasopressors for >4 h after initial fluid replacement [12]. The most widely used third-generation cephalosporin in our institution (>90%) is ceftriaxone and the standard dose is 1g q24h for non-critically ill patients and 2 g q24h for critically ill patients.

2.5. Microbiological evaluation and diagnostic criteria

During the study period, blood cultures were processed using a BACTEC 9240 system (Becton eDickinson Microbiology Systems), with an incubation period of 5 days. Isolates were identified by

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standard techniques. The minimum inhibitory concentrations (MIC) of *S. pneumoniae* isolates were determined using the E-test method and broth microdilution (Sensititre, Trek Diagnostic Systems, West Sussex, UK), for penicillin, cefotaxime, ceftriaxone, cefepime, imipenem, meropenem, erythromycin, clindamycin, levofloxacin, and vancomycin. Ceftriaxone susceptibility results were categorized as susceptible (MIC ≤0.5 μg /mL) and non-susceptible (intermediate, MIC >0.5 to ≤2 μg /mL and resistant, MIC >2 μg/mL).

2.6. Statistical analysis

We report the number and percentage of patients for categorical variables and the mean and standard deviation (SD) for continuous variables. Categorical variables were compared using the χ^2 test or the Fisher exact test, whereas continuous variables were compared using the *t*-test. Logistic regression analyses [13,14] were then used to examine the associations between 30-day mortality and risk factors. First, each risk factor was tested individually. Second, all risk factors that showed an association in the univariate model ($p < 0.10$) were added to the multivariate model. Finally, a backward stepwise selection ($p_{in} < 0.05$, $p_{out}>0.10$) was used to determine the factors associated with 30-day mortality. Multicollinearity was assessed using the variance inflation factor. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the multivariable model. We also calculated the area under the receiver operating characteristic curve (AUC) of the final model. To evaluate possible overfitting and instability of the selection variables, we performed internal validation using ordinary nonparametric bootstrapping with 1,000 samples and bias-corrected, accelerated 95% CIs [15]. All analyses were performed with IBM SPSS, Version 23.0 (IBM Corp., Armonk, NY, USA), and the significance level was set at 0.05 (two-tailed).

3. Results

3.1. Patients' characteristics

During the study period, we identified 721 episodes of monomicrobial bacteremic pneumococcal pneumonia; of these, 31 were excluded because they were missing important data. Finally, in 690 episodes of pneumococcal bacteremia were included. The prevalence of 3GC non-susceptible *S. pneumoniae* strains during the study is shown in Figure 1.

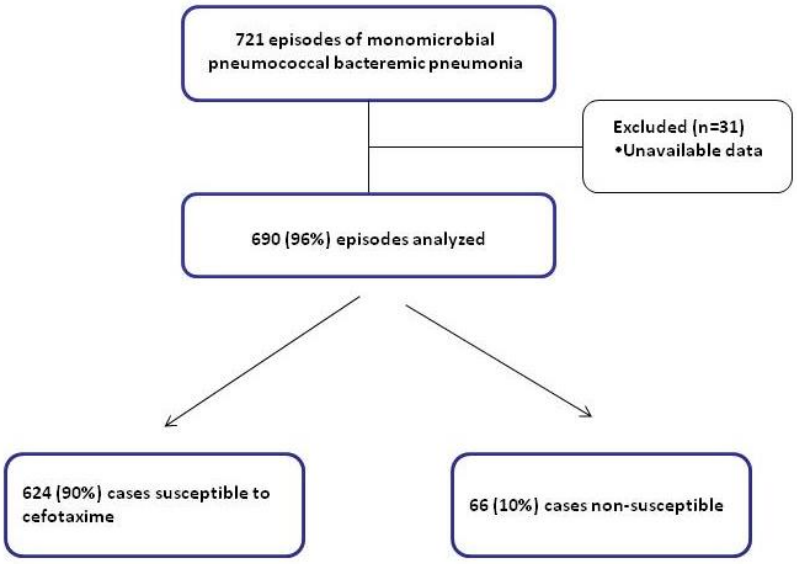

Figure 1. Flow diagram of population selection.

Our cohort comprised 439 males (64%) and 251 females (36%), with a mean (SD) age of 66.5 (19.9) years; notably, 309 (45%) were aged >65 years. The main comorbidities were chronic obstructive pulmonary disease (21%), human immunodeficiency virus infection (20%), diabetes mellitus (16%), and chronic liver disease (9%). Overall, 94 cases (14%) presented with septic shock, and the 30-day mortality was 47(7.0%). All included patients received a third-generation cephalosporin empirically either as monotherapy (n = 183, 27%) or in combination with a macrolide (n = 350; 51%) or a fluoroquinolone (n = 157; 23%).

We identified that 66 cases (10%) were due to a 3GC non-susceptible *S. pneumoniae*. Notably, the prevalence of these strains did not change significantly over time (p = 0.75) (Figure 2). The characteristics of patients according to 3GC susceptibility are shown in Table 1. Patients with 3GC non-susceptibility were almost 10 years older than those with a susceptible strain (p = 0.003). Most cases had a pneumonia severity index of IV–V (68%) and a McCabe score of 1 (66%).

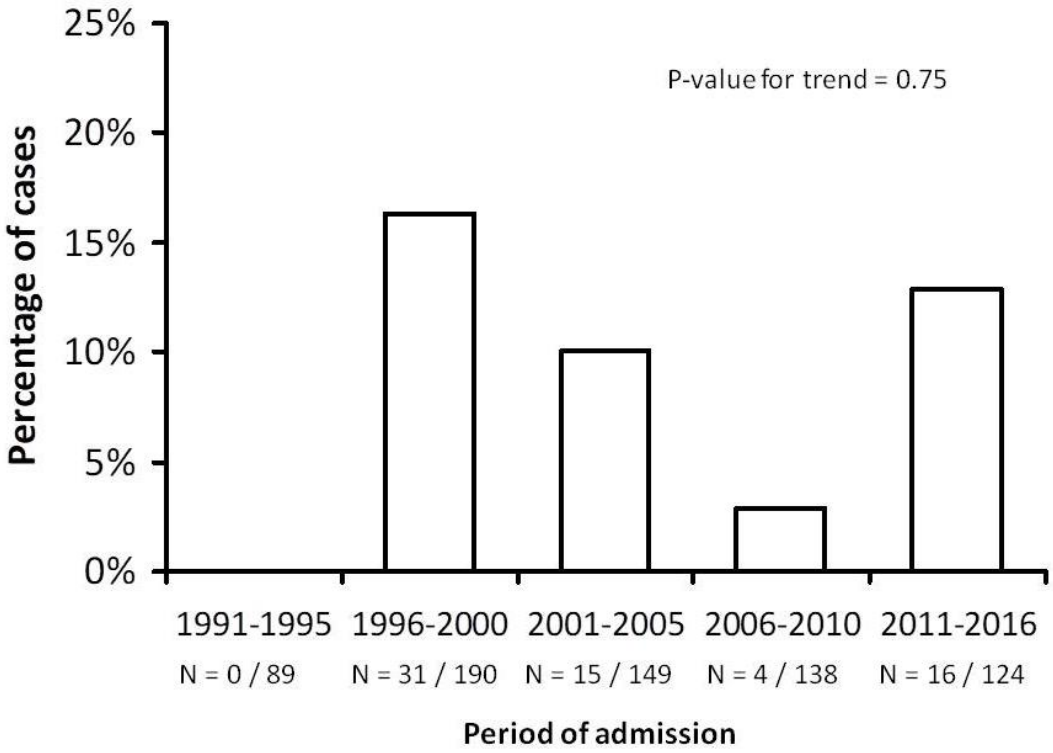

Figure 2. Temporal distribution of non-susceptible cefotaxime during the study.

Table 1. Patient demographics and clinical characteristics at admission.

	Non-susceptible to 3GC (N = 66)	Susceptible to 3GC (N = 624)	P-value
Age, years, mean (SD)	67 (20)	59 (19)	**0.001**
Age >65 years, n (%)	42 (64)	267 (43)	**0.001**
Male, gender, n (%)	38 (58)	401 (64)	0.28
Current alcohol user, n (%)	4 (6)	34 (5)	0.78
Previous antimicrobials, n (%)	4 (6)	19 (3)	0.26
Shock, n (%)	8 (12)	85 (14)	0.73
Previous systemic steroids, n (%)	4 (6)	50 (8)	0.54
Mechanical ventilation, n (%)	0	4 (1)	>0.99
Fever, n (%)	63 (95)	605 (97)	0.42
Comorbidities, n (%)			

	Non-susceptible to 3GC (N = 66)	Susceptible to 3GC (N = 624)	P-value
COPD	17 (26)	128 (21)	0.32
HIV	14 (21)	122 (20)	0.75
Neoplasm	14 (21)	98 (16)	0.25
Chronic cardiovascular disease	9 (14)	59 (9)	0.28
Diabetes mellitus	15 (23)	96 (15)	0.12
Chronic renal disease	3 (5)	30 (5)	>0.99
Chronic liver disease	10 (15)	74 (12)	0.44
Empiric therapy			
Cephalosporin monotherapy	19 (29)	164 (26)	
Cephalosporin + quinolone	10 (15)	147 (24)	0.16
Cephalosporin + macrolide	37 (56)	313 (50)	0.12
McCabe score			0.73
1	43 (66)	438 (71)	
2	21 (32)	174 (28)	
3	1 (2)	7 (1)	
PSI score			0.11
PSI I–III	8 (32)	140 (49)	
PSI IV–V	17 (68)	147 (51)	
30-day mortality, n (%)	5 (8)	42 (7)	0.80

Data are number of patients (%) or mean (standard deviation). Percentages were calculated on non-missing data. Abbreviations: COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; PSI, pneumonia severity index.

3.2. Microbiology

Data regarding serotypes were available in 134 cases; serotypes covered by the PCV7 vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F) and PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) represented 13% and 68% of all serotypes, respectively. The most frequent serotypes in the susceptible group were: serotype 1 (25 cases, 20%), 19A (15 cases, 12%), 3 (15 cases, 12%) and 7F (11 cases, 9%), whereas, three serotypes (8 cases, 6%) were reported in the non-susceptible group: 11A (2 cases), 14 (5 cases), and 19F (1 case). The empiric antimicrobial therapy given was comparable between the susceptible and non-susceptible groups.

3.3. Clinical outcomes

We found no evidence that patients with 3GC non-susceptible *S. pneumoniae* bacteremic pneumonia presented with more severe disease or had worse clinical outcomes (Table 1).

3.4. Factors associated with 30-day mortality

The univariate logistic regression analysis revealed several variables significantly associated with 30-day mortality (Table 2). Among these, age, presence of septic shock at admission, chronic liver disease, and McCabe score remained independently associated with 30-day mortality in the multivariate analysis.

Table 2. Univariate and multivariate logistic regression analyses of predictors of 30-day mortality.

Variable	Univariate[a]			Multivariable[bc]		
	OR	95% CI	P-value	OR	95% CI	P-value
Non-susceptible to 3GC	1.13	0.43–2.96	0.81	0.83	0.28–2.50	0.74
Age (+1 year)	1.03	1.01–1.05	0.001	1.04	1.02–1.06	<0.001
Septic shock	13.01	6.89–24.59	<0.001	17.54	8.72–35.27	<0.001
Chronic renal disease	3.89	1.05–14.46	0.042	-	-	-
Chronic liver disease	2.37	1.16–4.86	0.019	2.33	0.94–5.75	0.068
McCabe score[d]			0.009			0.061

Variable	Univariate[a]			Multivariable[bc]		
	OR	95% CI	P-value	OR	95% CI	P-value
1	1.00	-	-	1.00	-	-
2	1.45	0.76–2.74	0.26	1.32	0.60–2.89	0.49
3	9.66	2.20–42.51	0.003	8.72	1.43–53.00	0.019

Abbreviations: CI, confidence interval; OR, odds ratio. Data are shown as estimated ORs (95% CIs) of the explanatory variables in the 30-day mortality group. The OR is defined as the probability of membership of the group 30-day mortality divided by the probability of membership of the non-30-day mortality group. The p-value is based on the null hypothesis that all ORs relating to an explanatory variable equal unity (no effect). [a] The variables analyzed in the univariate analysis were: age, gender, McCabe score, cefotaxime, cephalosporin_macrolide_empiric therapy, cephalosporin_quinolone_empiric therapy,cephalosporin_empiric, quinolone_empiric,empiric,macrolide_empiric,communitary origen, fiebre, shock, corticosteroid therapy, diabetes, respiratory disease, hepatic diseases, alcohol, COPD, HIV, chronic renal disease, previous antibiotic therapy, agute renal failure. [b] Adjusted for the antimicrobial susceptibility of pneumococcal bacteremia to 3GC. [c] Hosmer-Lemeshow goodness-of-fit test, p=0.28. [d] The p-value corresponds to differences between the three groups (1, 2, or 3).

The AUC was 0.85 (95% CI, 0.78–0.92) for the 30-day mortality in this model. Internal validation of the logistic regression model (bootstrapping with 1,000 samples) demonstrated robust results for all variables included in the model, with small 95% CIs around the original coefficients.

4. Discussion

The main findings of our study are as follows. First, although we observed an increase in the prevalence of 3GC non-susceptible strains of *S. pneumoniae* in recent years, this prevalence did not change significantly over time. Second, we found no evidence of more severe presentations or worse clinical outcomes in patients admitted to the hospital with 3GC non-susceptible *S. pneumoniae* bacteremic pneumonia. Third, the 30-day mortality was shown to be independently associated with age, septic shock at admission, chronic liver disease, and the McCabe score.

S. pneumoniae remains the leading cause of bacteremia, meningitis, community-acquired pneumonia, and otitis media worldwide. International guidelines for the management of pneumococcal pneumonia recommend the use of β-lactams, such as a 3GC (cefotaxime and ceftriaxone). Although resistance to 3GC remains low worldwide, an increase in the rate of resistance has been reported in many countries due to the spread of pneumococcal resistant clones. Although we reported that the prevalence of 3GC non-susceptibility in pneumococcal bacteremic pneumonia did not change significantly over time during the study period, we observed an increase in the prevalence from 0% in the first period (1991–1995) to 13% in the last period (2011–2016). This observation is consistent with several reports about the global emergence of in vitro antimicrobial resistance in *S. pneumoniae* [16–19]. *Interestingly, a great proportion of all cases were caused by pneumococcal serotypes included in PCV13 vaccine (68%) and in less proportion caused by serotypes covered by PCV7 vaccine (13%). However, in the non-susceptible group the majority of the cases were caused by serotypes covered by PCV7 (63%) and PCV13 (75%) vaccines. Unfortunately, we do not have data about vaccination status in our study population that allows us to made more conclusion about these results.*

There is few information about the impact of 3GC non-susceptible *S. pneumoniae* strains on the outcomes of patients with bacteremic pneumonia. In 2001, Moroney et al. [20] performed a case-control study and found that drug resistance (cefotaxime-non-susceptible) did not demonstrably affect mortality or intensive care unit (ICU) admissions among patients hospitalized with bacteremic or other forms of invasive pneumococcal pneumonia. In 2012, Song et al. [21] published an 11-year study evaluating the risk factors for mortality, and reported the impact of antimicrobial resistance (erythromycin and penicillin resistance) on the clinical outcomes of patients with pneumococcal bacteremia. Whereas an elevated APACHE II score and the presence of solid organ tumors were

independently associated with mortality, neither erythromycin resistance nor penicillin resistance significantly affected clinical outcomes. One of the few studies that investigate ceftriaxone non-susceptible was the study by Choi et al. [22] that investigated the impact of penicillin non-susceptibility on the clinical outcomes of patients with non-meningeal pneumococcal bacteremia and reported that the 30-day mortality was similar between patients with resistant and susceptible strains. In the multivariate analysis of this study, ceftriaxone non-susceptibility (OR 4.88; 95% CI 1.07–22.27; p = 0.041) was an independent risk factor for 30-day mortality but not all patients were treated with a 3GC.

For the present study, we applied the 3GC breakpoints set out in the 2008 Clinical and Laboratory Standards Institute guidance and all the patients included in the study received a 3GC as empirical treatment. The independent risk factors for 30-day mortality in patients with pneumococcal bacteremic pneumonia in the present study were age, septic shock at admission, chronic liver disease, and McCabe score but not the MIC of ceftriaxone. The PKPD parameter that predicts the outcome of ceftriaxone is the time that serum concentration of ceftriaxone is above the MIC (T>MIC). According to prior data, at least 40% of the interval between 2 consecutive doses is the needed exposure to obtain a bacteriostatic effect[23]. Giving 1 or 2g q24h, the probability of attaining this target when the MIC of ceftriaxone is 1-2 μg/mL (intermediate susceptibility) is high and this explain our results. However, the number of strains resistant to ceftriaxone (MIC>2 μg/mL) are few and we cannot predict the response with our cohort.

Previous studies have also emphasized the importance of host factors when predicting severity and outcomes. To date, older age, alcohol abuse, nursing-home residence [24], ICU admission, platelet count <100,000/μL [25], and liver disease [26] have each been significantly associated with mortality. These data support the idea that host factors, mainly chronic comorbidities, are more significantly related to disease severity and clinical outcomes than the inherent resistance of the pathogen in patients with pneumococcal bacteremic pneumonia.

The main limitation of our study is that the number of patients with non-susceptible strains was low and the majority of the patients received combination treatment with a macrolide or a fluoroquinolone and the influence of ceftriaxone alone could not be evaluated. However, the current guidelines[27] recommend combination therapy with a macrolide and so our study shows that non-susceptibility to ceftriaxone do not affect the efficacy of the recommended regimen. The second limitation is the length of the recruitment period (27 years). However, we have followed recommendation of international guidelines each year.

5. Conclusion

In conclusion, we found no evidence to suggest that patients hospitalized for 3GC non-susceptible *S. pneumoniae* bacteremic pneumonia had worse clinical outcomes than patients admitted with antimicrobial-susceptible pathogens.

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Conflicts of interest: The authors declare that they have no conflicts of interest.

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