

1 Article

2 Impact of Cefotaxime Non-susceptibility on the 3 Clinical Outcomes of Bacteremic Pneumococcal 4 Pneumonia

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

32 **Keywords:** cefotaxime; pneumonia; bacteremia; outcomes

33

34 1. Introduction

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

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

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

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

52 2. Methods

53 2.1. Ethics statement

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

57 2.2. Study design and patients

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

63 2.3. Data collection and evaluation

64 The following data were obtained from all patients: age, gender, comorbidities, McCabe score
65 [10], Pneumonia Severity Score (PSI)[11] was calculated in 312 cases, recent antimicrobial or steroid
66 treatment (within the last month), recent hospitalization (within the last month), surgery and other
67 invasive procedures, shock at presentation, etiology (microorganisms), empirical antimicrobial
68 treatment, appropriateness of empirical therapy, and 30-day mortality. Patients were then
69 prospectively followed up by a senior infectious disease specialist who assessed the medical history,
70 physical examination, microbiological tests, and complementary imaging to determine the source of
71 infection.

72 2.4. Definitions

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

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

85 2.5. Microbiological evaluation and diagnostic criteria

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

88 standard techniques. The minimum inhibitory concentrations (MIC) of *S. pneumoniae* isolates were
 89 determined using the E-test method and broth microdilution (Sensititre, Trek Diagnostic Systems,
 90 West Sussex, UK), for penicillin, cefotaxime, ceftriaxone, cefepime, imipenem, meropenem,
 91 erythromycin, clindamycin, levofloxacin, and vancomycin. Ceftriaxone susceptibility results were
 92 categorized as susceptible (MIC ≤ 0.5 $\mu\text{g}/\text{mL}$) and non-susceptible (intermediate, MIC >0.5 to ≤ 2 μg
 93 $/\text{mL}$ and resistant, MIC >2 $\mu\text{g}/\text{mL}$).

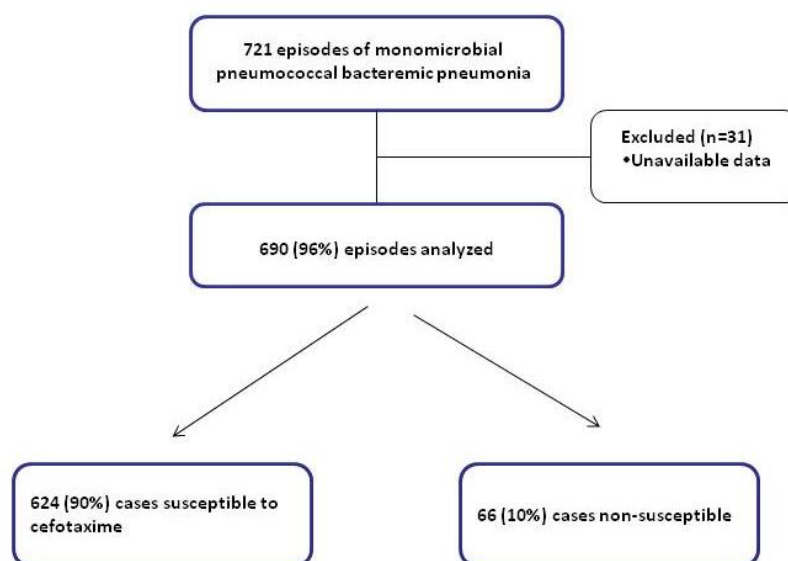
94 2.6. Statistical analysis

95 We report the number and percentage of patients for categorical variables and the mean and
 96 standard deviation (SD) for continuous variables. Categorical variables were compared using the χ^2
 97 test or the Fisher exact test, whereas continuous variables were compared using the *t*-test. Logistic
 98 regression analyses [13,14] were then used to examine the associations between 30-day mortality and
 99 risk factors. First, each risk factor was tested individually. Second, all risk factors that showed an
 100 association in the univariate model ($p < 0.10$) were added to the multivariate model. Finally, a
 101 backward stepwise selection ($p_{\text{in}} < 0.05$, $p_{\text{out}} > 0.10$) was used to determine the factors associated with
 102 30-day mortality. Multicollinearity was assessed using the variance inflation factor. Odds ratios (ORs)
 103 and 95% confidence intervals (CIs) were calculated. The Hosmer–Lemeshow goodness-of-fit test was
 104 performed to assess the overall fit of the multivariable model. We also calculated the area under the
 105 receiver operating characteristic curve (AUC) of the final model. To evaluate possible overfitting and
 106 instability of the selection variables, we performed internal validation using ordinary nonparametric
 107 bootstrapping with 1,000 samples and bias-corrected, accelerated 95% CIs [15]. All analyses were
 108 performed with IBM SPSS, Version 23.0 (IBM Corp., Armonk, NY, USA), and the significance level
 109 was set at 0.05 (two-tailed).

110 3. Results

111 3.1. Patients' characteristics

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



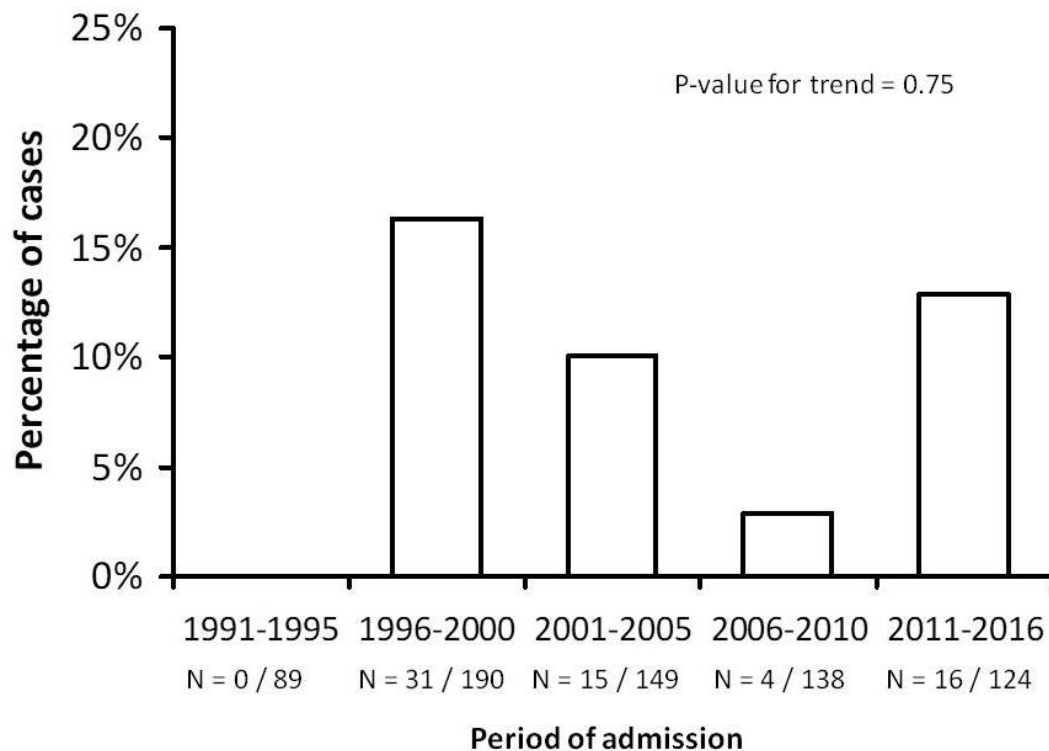
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Figure 1. Flow diagram of population selection.

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

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



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

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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

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

137 3.2. Microbiology

138 Data regarding serotypes were available in 134 cases; serotypes covered by the PCV7 vaccine (4, 6B,
 139 9V, 14, 18C, 19F, and 23F) and PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) represented
 140 13% and 68% of all serotypes, respectively. The most frequent serotypes in the susceptible group were:
 141 serotype 1 (25 cases, 20%), 19A (15 cases, 12%), 3 (15 cases, 12%) and 7F (11 cases, 9%), whereas, three
 142 serotypes (8 cases, 6%) were reported in the non-susceptible group: 11A (2 cases), 14 (5 cases), and 19F (1
 143 case). The empiric antimicrobial therapy given was comparable between the susceptible and non-susceptible
 144 groups.

145 3.3. Clinical outcomes

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

148 3.4. Factors associated with 30-day mortality

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

153 **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

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

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

168 4. Discussion

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

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

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

198 independently associated with mortality, neither erythromycin resistance nor penicillin resistance
199 significantly affected clinical outcomes. One of the few studies that investigate ceftriaxone non-
200 susceptible was the study by Choi et al. [22] that investigated the impact of penicillin non-
201 susceptibility on the clinical outcomes of patients with non-meningeal pneumococcal
202 bacteremia and reported that the 30-day mortality was similar between patients with resistant and
203 susceptible strains. In the multivariate analysis of this study, ceftriaxone non-susceptibility (OR
204 4.88; 95% CI 1.07–22.27; $p = 0.041$) was an independent risk factor for 30-day mortality but not all
205 patients were treated with a 3GC.

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

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

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

230 5. Conclusion

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

234 **Acknowledgments:** The results of this study have not been published elsewhere. We are indebted to all medical
235 and nursing colleagues for their assistance and cooperation in this study. Dr Cillóniz is the recipient of a
236 Postdoctoral Grant (Strategic plan for research and innovation in health-PERIS 2016-2020).

237 **Author Contributions:** Conception and design: CC, CdC, AT and As; Acquisition, analysis or interpretation of
238 data: CC, CD, CGV, CD, AG; Drafting the manuscript for important intellectual content: CC, CD, CdC, CGV,
239 AT, FM, CC, AS; Statistical analysis: AG; Administrative, technical or material support: CC, CD, CdC, CGV, AG;
240 All authors reviewed, revised, and approved the manuscript for submission; Study supervision: CC, AT and AS.

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

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