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Published in:
Clinical Microbiology and Infection

DOI:
10.1016/j.cmi.2017.03.010

Publication date:
2017

Clinical Microbiology and Infection 23 (2017) 774.e1–774.e7

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Predictors for individual patient antibiotic treatment effect in hospitalized community-acquired pneumonia patients

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ARTICLE INFO

Article history:
Received 4 January 2017
Received in revised form
13 March 2017
Accepted 14 March 2017
Available online 20 March 2017

Editor: Dr C. Pulcini

Keywords:
Antibiotic treatment
Clinical predictors
Community-acquired pneumonia
Outcomes
Treatment effect

ABSTRACT

Objective: Our objective was to identify clinical predictors of antibiotic treatment effects in hospitalized patients with community-acquired pneumonia (CAP) who were not in the intensive care unit (ICU).
Methods: Post-hoc analysis of three prospective cohorts (from the Netherlands and Spain) of adult patients with CAP admitted to a non-ICU ward having received either β-lactam monotherapy, β-lactam + macrolide, or a fluoroquinolone-based therapy as empirical antibiotic treatment. We evaluated candidate clinical predictors of treatment effects in multiple mixed-effects models by including interactions of the predictors with empirical antibiotic choice and using 30-day mortality, ICU admission and length of hospital stay as outcomes.
Results: Among 8562 patients, empirical treatment was β-lactam in 4399 (51.4%), fluoroquinolone in 3373 (39.4%), and β-lactam + macrolide in 790 (9.2%). Older age (interaction OR 1.67, 95% CI 1.23–2.29, p 0.034) and current smoking (interaction OR 2.36, 95% CI 1.34–4.17, p 0.046) were associated with lower effectiveness of fluoroquinolone on 30-day mortality. Older age was also associated with lower effectiveness of β-lactam + macrolide on length of hospital stay (interaction effect ratio 1.14, 95% CI 1.06–1.22, p 0.008).
Conclusions: Older age and smoking could influence the response to specific antibiotic regimens. The effect modification of age and smoking should be considered hypothesis generating to be evaluated in future trials. **A.F. Simonetti, Clin Microbiol Infect 2017;23:774.e1–774.e7**

Introduction

Community-acquired pneumonia (CAP) is a leading cause of hospitalization and death worldwide [1–3]. Although recent studies described a downward trend in 30-day mortality in hospitalized patients with CAP over the last 20 years [4,5], the reported hospital mortality in these patients remains high, ranging from 4% to 15% [4–7].

For patients with CAP admitted to a non-intensive-care-unit (non-ICU), international guidelines recommend either β-lactam monotherapy, β-lactam + macrolide combination therapy or respiratory fluoroquinolone monotherapy as empirical treatment [8–10]. However, the necessity for atypical coverage in non-severe CAP patients is uncertain because beneficial effects on mortality were only found in observational studies, not in randomized controlled trials [11,12]. Moreover, the use of macrolides and fluoroquinolones has been related to increased risks of antimicrobial resistance and adverse drug effects [13–17]. A limitation of the studies performed so far is that they compared interventions within the whole domain of hospitalized CAP (e.g. at the population level), lacking power for proper subgroup analyses.

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http://dx.doi.org/10.1016/j.cmi.2017.03.010
1198-743X/

Despite important advancements in diagnostic testing, a causative pathogen is not detected in the majority of patients with CAP; and if detected there is often a delay of up to 48 hours [2]. Initial antibiotic treatment is therefore almost always empirical. However, CAP is a heterogeneous disease due to heterogeneity in both host and pathogen factors. Therefore, an individualized antibiotic treatment approach might prove beneficial.

The concept of individualized medicine, initially referred to the use of genomics in clinical care, has extended to recognizing the heterogeneity of each individual patient, particularly their risk factors for developing disease or having poor outcomes, and using this to inform treatment decisions. Biomarkers and clinical predictors have been widely studied in CAP in an attempt to predict the microbial aetiology [18,19] or clinical outcomes, such as early treatment failure or all-cause mortality [20–25]. Yet, predictors of pathogens are weak at best, and predictors of all-cause mortality do not inform the treating physician about the necessity to adjust empirical therapy. To pave the way for individualized medicine for CAP, it is necessary to take a further step and assess differences in treatment response based on multiple patient factors.

The objective of this study was to find candidate predictors at an individual patient level for effect modification of empirical antibiotic regimens (β-lactam, β-lactam + macrolide and fluoroquinolone) in patients with CAP hospitalized to non-ICU wards.

Patients and methods

Setting, study population and research design

This is a post-hoc analysis of three cohorts of hospitalized patients with CAP, two from the Netherlands and one from Spain [4,12,26]. The Dutch cohorts were from two large randomized clinical trials conducted in the Netherlands. All patients hospitalized for CAP from The Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA), and all patients included in the Community-Acquired Pneumonia—Study on the Initial Treatment with Antibiotics of Lower Respiratory Tract Infections (CAP-START) were included.

The Spanish (Bellvitge) cohort includes all patients with X-ray-confirmed CAP admitted via the emergency department of Bellvitge University Hospital. The Supplementary material (Table S1) shows the main characteristics of the three cohorts. For the purpose of this study, we only analysed patients who received β-lactam, β-lactam + macrolide or fluoroquinolone as empirical antibiotic treatment.

Data collection

Empirical antibiotic treatment was defined as the antibiotic treatment administered in the first calendar day of hospitalization (Dutch cohorts) or prospectively collected as a specific item in the data collection form (Bellvitge cohort), as the first antibiotic regimen administered to the patient after admission.

Data on clinical presentation, laboratory results, microbiological test results, antibiotic use and clinical outcome were retrieved from medical records. In the absence of notes in clinical records, the following variables were assumed to be absent/negative: pneumococcal or influenza vaccination, clinical symptoms (cough, purulent sputum, pleuritic chest pain, headache, gastrointestinal symptoms, chills), confusion, hypotension, tachycardia, positive urinary antigen for *Streptococcus pneumoniae*. Definitions of predictors and empirical antibiotic treatment are explained in the Supplementary material (Appendix S1).

All studies were approved by the Institutional Review Board in the participating hospitals and the informed consent covered the current analysis. To protect personal privacy, data were anonymized.

Outcomes

The primary outcome was all-cause mortality within 30 days after admission. The 30-day mortality was either assessed at a long-term follow-up visit (Bellvitge), from general practitioner medical records (Bellvitge, CAPiTA), or from the municipal records database (CAP-START). The secondary outcomes were ICU admission after the first day of hospitalization and length of hospital stay (LOS). All outcomes were measured and analysed at the individual patient level.

Predictors

Through an extensive search in PubMed we selected a list of candidate clinical predictors of treatment effects on CAP. These clinical predictors should be present and known at admission and associated either to specific CAP aetiology or to clinical outcome.

A complete list of the predictors chosen for the analysis and the correspondent bibliography are shown in the Supplementary material (Appendix S1).

In addition, the year of admission was included as a confounding variable, categorized in four periods of 5 years each, as follows: 1995–1999, 2000–2004, 2005–2009, 2010–2014.

Statistical analysis

Data are presented as percentages and numbers, means with SDs, medians with interquartile ranges (IQRs), or proportions with 95% CIs, as appropriate.

For binary outcomes we used mixed-effects logistic regression models—see the Supplementary material (Appendix S1) for details. To identify candidate predictors of treatment effects we applied a two-step approach. First, we estimated for each candidate predictor the interaction effect with antibiotic treatment in separate models, including the fixed effects, random effects, and the single interaction effect. Interaction variables with a two-sided $p < 0.10$ using the Wald test were included in the second step of our analysis. There we constructed a mixed-effects model including all selected interactions from the first step and all previously mentioned fixed and random effects. The p values of the second-step model were corrected for multiple testing using the Benjamini–Hochberg (BH) method [28]. Two-sided BH adjusted values of $p < 0.05$ were considered statistically significant. Associations are given as ORs with 95% CIs. Effect modifiers for the LOS were tested similarly with mixed-effects linear regression models, after log-transforming length of stay. The exponent of the regression coefficients was interpreted as the effect ratio, e.g. an effect ratio of 2 for factor *x* implies that a patient with *x* has an LOS twice that of a patient without *x*.

We performed sensitivity analyses including only patients with radiologically confirmed CAP and we performed analyses stratified per cohort. Assumptions of the models were tested visually by plotting residuals. Missing data on smoking habits (6.6% of missing data), pre-hospital antibiotic use (2.5%), living in a residential care home for the elderly (12.4%), serum sodium concentration (12.4%), leucocyte count (0.2%) and Pneumonia Severity Index (PSI) (0.1%) were imputed by multiple imputations (ten imputation data sets), assuming data missing at random. Descriptive statistics and multiple imputations were performed using the Statistical Package for the Social Sciences for Windows (Version SPSS 21.0.0.0). Mixed-effects models were performed with R (R Core Team, 2015), and the R-package lme4 (Bates, Maechler, Bolker, Walker 2015).

Results

A total of 8562 patients were included: 2184 (25.5%) from the CAPiTA cohort, 2154 (25.2%) from the CAP-START cohort and 4224

(49.3%) from the Bellvitge cohort (see Supplementary material, Fig. S1). Patient characteristics are described in Table 1. A probable or definite microbiological diagnosis was made in 46.3% of patients. The diagnostic work-up by cohorts is described in the Supplementary material (Table S2). The causative pathogens identified per age group are summarized in the Supplementary material (Table S3). The majority of patients received β-lactam as empirical treatment (4399; 51.4%), followed by fluoroquinolone (3373; 39.4%) and β-lactam + macrolide (790; 9.2%). The different empirical antibiotics administered in each cohort, either in monotherapy or in combination, are listed in the Supplementary material (Table S4).

Clinical predictors for treatment effect: 30-day mortality

In the first-step models, five interactions between a clinical predictor and antibiotic empirical treatment were significant at a p-value of <0.10 for 30-day mortality: age, current smoking, tachycardia at admission (heart rate >125 bpm), confusion at admission, and pleuritic chest pain. In the second step we tested the combination of these five interactions (Table 2). After correction for multiple testing, the following predictors of treatment effect for 30-day mortality were statistically significant: increasing age with the use of fluoroquinolone versus β-lactam (interaction OR 1.67, per unit increase of standardized age, 95% CI 1.23–2.29, BH adjusted p 0.034) and active smoking with the use of fluoroquinolone versus β-lactam (interaction OR 2.36, 95% CI 1.34–4.17, BH adjusted p 0.046).

Clinical predictors for treatment effect: ICU admission

In the first-step models, three interactions between clinical predictors and antibiotic empirical treatment were statistically significant at p <0.10 for ICU admission: admission during influenza season, having a positive urinary antigen test for *S. pneumoniae*, and leucopenia (leucocyte count <4000 cells/μL) or extreme leucocytosis (leucocyte count >20 000 cells/μL) at admission. In the second step we tested the combination of these three interactions (Table 3). After

Table 1
Principal clinical characteristics and outcomes in each cohort

	CAPiTA [26] $n = 2184$ (25.5%)	CAP-START [12] $n = 2154$ (25.2%)	BELLVITGE [4] $n = 4224$ (49.3%)	All $n = 8562$
Age, years (IQR)	76.0 (72–82)	70.0 (59–79)	70.5 (58–79)	73.0 (63–80)
Male sex, *n* (%)	1545 (70.7)	1250 (58.0)	2860 (67.7)	5655 (66.0)
Elderly home, *n* (%)	81 (4.1)	102 (4.8)	234 (6.9)	417 (5.6)
Current smoker, *n* (%)	323 (19.0)	441 (21.1)	1037 (24.7)	1801 (22.5)
Influenza season, *n* (%)	1565 (71.7)	1553 (72.1)	3230 (76.5)	6348 (74.1)
Streptococcus pneumoniae vaccination, *n* (%)	1066 (48.8)	44 (2.0)	710 (16.8)	1820 (21.3)
Influenza virus vaccination, *n* (%)	1916 (87.7)	1396 (64.8)	2001 (47.4)	5313 (62.1)
Outpatient antibiotic, *n* (%)	656 (31.0)	639 (30.4)	882 (21.4)	2177 (26.1)
β-lactams, *n* (%)	373 (17.8)	366 (17.7)	538 (13.2)	1277 (15.5)
Atypical coverage, *n* (%)	296 (14.1)	251 (12.1)	327 (8.0)	874 (10.6)
Comorbidities				
Cerebrovascular disease, *n* (%)	278 (12.7)	221 (10.3)	343 (8.1)	842 (9.8)
COPD, *n* (%)	1351 (61.9)	973 (45.2)	1230 (29.1)	3554 (41.5)
Malignancy, *n* (%)	301 (13.8)	364 (16.9)	414 (9.8)	1079 (12.6)
Cardiovascular, *n* (%)	909 (41.6)	454 (21.1)	1042 (24.7)	2405 (28.1)
Immunosuppression, *n* (%)	235 (10.8)	210 (9.7)	337 (8.0)	782 (9.1)
Symptoms (days), days (IQR)	3 (1–6)	3 (1–7)	3 (2–6)	3 (1–7)
Cough, *n* (%)	1509 (69.1)	1776 (82.5)	3585 (84.9)	6870 (80.2)
Purulent sputum, *n* (%)	924 (42.3)	1247 (57.9)	2022 (47.9)	4193 (49.0)
Gastrointestinal symptoms, *n* (%)	167 (7.6)	291 (13.5)	635 (15.0)	1093 (12.8)
Pleuritic chest pain, *n* (%)	225 (10.3)	294 (13.6)	1767 (41.8)	2286 (26.7)
Headache, *n* (%)	78 (3.6)	99 (4.6)	618 (14.6)	795 (9.3)
Chills, *n* (%)	320 (14.7)	426 (19.8)	1927 (45.6)	2673 (31.2)
Confusion, *n* (%)	291 (13.3)	193 (9.0)	586 (13.9)	1070 (12.5)
Fever, *n* (%)	786 (36.7)	1206 (57.1)	2013 (48.1)	4005 (47.5)
Hypotension, *n* (%)	343 (15.7)	293 (13.6)	635 (15.0)	1271 (14.8)
Heart rate >125 bpm, *n* (%)	202 (9.2)	269 (12.5)	352 (8.3)	823 (9.6)
Respiratory failure, *n* (%)	528 (24.2)	837 (38.9)	2435 (57.6)	3800 (44.4)
Bilateral infiltrate on chest X-ray, *n* (%)	185 (8.5)	190 (8.8)	627 (14.8)	1002 (11.7)
Pleural fluid on chest X-ray, *n* (%)	206 (9.4)	146 (6.8)	708 (16.8)	1060 (12.4)
Positive urinary antigen for *S. pneumoniae*, *n* (%)	166 (7.6)	197 (9.1)	939 (22.2)	1302 (15.2)
PSI score, points (IQR)	107 (91–125)	86 (66–107)	99 (77–124)	98 (79–120)
PSI class I, *n* (%)	0	0	184 (4.4)	184 (2.2)
PSI class II, *n* (%)	34 (1.6)	644 (29,9)	672 (16.0)	1350 (15.8)
PSI class III, *n* (%)	506 (23.2)	556 (25.8)	859 (20.4)	1921 (22.5)
PSI class IV, *n* (%)	1228 (56.2)	770 (35.7)	1641 (39,0)	3639 (42.6)
PSI class V, *n* (%)	416 (19.0)	184 (8.5)	857 (20.3)	1457 (17.0)
Antibiotic empirical treatment				
β-lactam monotherapy, *n* (%)	1493 (68.4)	730 (33.9)	2176 (51.5)	4399 (51.4)
β-lactam + macrolide, *n* (%)	64 (2.9)	536 (24.9)	190 (4.5)	790 (9.2)
Fluoroquinolone-based,[a] *n* (%)	627 (28.7)	888 (41.2)	1858 (44.0)	3373 (39.4)
Outcomes				
30-day mortality, *n* (%)	195 (9.2)	114 (5.3)	261 (6.2)	570 (6.7)
Early mortality,[b] *n* (%)	55 (2.5)	12 (0.6)	89 (2.1)	156 (1.8)
ICU admission, *n* (%)	112 (5.1)	41 (1.9)	207 (4.9)	360 (4.2)
Length of hospital stay, days (IQR)	7 (5–11)	6 (4–9)	8 (5–11)	7 (5–10)

Abbreviations: COPD, chronic obstructive pulmonary disease; ICU, Intensive Care Unit; IQR, interquartilic range; PSI, Pneumonia Severity Index.
[a] Fluoroquinolone-based treatment was defined as any regimen including a fluoroquinolone (fluoroquinolone in monotherapy or in combination therapy).
[b] Early mortality: mortality for any cause in the first 48 hours from admission.

Table 2
Thirty-day mortality: difference in response to antibiotic empirical strategy by clinical predictors in the second-step mixed-effects logistic regression model

	Adjusted interaction OR (95% CI)	BH p-value for interaction
Age*BLM	1.67 (1.03–2.72)	0.282
Age*FQL	1.67 (1.23–2.29)	0.034
Smoker*BLM	1.10 (0.40–2.99)	>0.999
Smoker*FQL	2.36 (1.34–4.17)	0.046
Heart rate >125 bpm*BLM	0.36 (0.11–1.20)	0.487
Heart rate >125 bpm*FQL	1.32 (0.73–2.41)	>0.999
Confusion*BLM	0.73 (0.33–1.60)	>0.999
Confusion*FQL	0.53 (0.32–0.87)	0.123
Pleuritic chest pain*BLM	2.47 (1.01–6.02)	0.282
Pleuritic chest pain*FQL	0.99 (0.53–1.83)	>0.999

Abbreviations: BH, Benjamini–Hochberg method; BLM, β-lactam plus macrolide; FQL, fluoroquinolone-based.

Table 3
Intensive care unit admission: difference in response to antibiotic empirical strategy by clinical predictors in the second-step mixed-effects logistic regression model

	Adjusted interaction OR (95% CI)	BH p-value for interaction
Influenza season*BLM	0.76 (0.29–1.90)	>0.999
Influenza season*FQL	0.66 (0.37–1.16)	>0.999
Streptococcus pneumoniae + Ag*BLM	0.45 (0.09–2.19)	>0.999
S. pneumoniae + Ag*FQL	0.46 (0.25–0.84)	0.117
Leucocyte count <4000 cells/μL*BLM	3.27 (0.60–17.83)	>0.999
Leucocyte count <20000 cells/μL*BLM	4.42 (1.83–10.66)	0.029
Leucocyte count <4000 cells/μL*FQL	3.71 (1.34–10.28)	0.117
Leucocyte count <20000 cells/μL*FQL	1.30 (0.69–2.46)	>0.999

Abbreviations: Ag, urinary antigen; BH, Benjamini–Hochberg method; BLM, β-lactam plus macrolide; FQL, fluoroquinolone-based.

correction for multiple testing, the only statistically significant predictor of treatment effect for ICU admission was extreme leucocytosis for the use of β-lactam + macrolide versus β-lactam (interaction OR 4.42, 95% CI 1.83–10.66, BH adjusted p 0.029).

Clinical predictors for treatment effect: length of hospital stay

In the first-step models, 12 interactions between clinical predictors and antibiotic empirical treatment were statistically significant at p <0.10 for LOS: increasing age, previous outpatient antibiotic treatment with atypical coverage, history of cardiovascular disease, new or worsened coughing, presentation with gastrointestinal symptoms, headache, duration of symptoms (in days), having a positive urinary antigen test for *S. pneumoniae*, serum sodium concentration, presentation with bilateral infiltrates or pleural fluid on chest X-ray and PSI score. In the second step we tested the combination of these 12 interactions (Table 4). After correction for multiple testing, the only statistically significant predictor of treatment effect for LOS was increasing age with the use of β-lactam + macrolide versus β-lactam (interaction effect

Table 4
Length of hospital stay: difference in response to antibiotic empirical strategy by clinical predictors in the second-step mixed-effects linear regression model

	Adjusted interaction effect ratio (95% CI)	BH p-value for interaction
Age*BLM	1.14 (1.06–1.22)	0.008
Age*FQL	1.02 (0.98–1.06)	>0.999
Outpatient atypical coverage*BLM	0.81 (0.69–0.96)	0.213
Outpatient atypical coverage*FQL	0.93 (0.84–1.02)	0.591
History of cardiovascular disease*BLM	1.04 (0.92–1.18)	>0.999
History of cardiovascular disease*FQL	1.02 (0.95–1.09)	>0.999
New or worsened coughing*BLM	0.94 (0.83–1.07)	>0,999
New or worsened coughing*FQL	1.02 (0.95–1.10)	>0.999
Gastrointestinal symptoms*BLM	0.87 (0.75–1.00)	0.394
Gastrointestinal symptoms*FQL	0.94 (0.86–1.02)	0.591
Headache*BLM	0.96 (0.77–1.18)	>0.999
Headache*FQL	0.95 (0.86–1.06)	>0.999
Streptococcus pneumoniae + Ag*BLM	1.19 (1.01–1.40)	0.375
S.pneumoniae + Ag*FQL	1.11 (1.02–1.20)	0.167
PSI-score*BLM	1.00 (1.00–1.00)	>0.999
PSI-score*FQL	1.00 (1.00–1.00)	>0.999
Sodium^2*BLM	0.98 (0.93–1.04)	>0.999
Sodium^2*FQL	1.03 (1.00–1.06)	0.519
Number of symptom days*BLM	1.00 (0.99–1.00)	>0.999
Number of symptom days*FQL	1.00 (0.99–1.00)	0.519
Pleural fluid on chest X-ray*BLM	1.02 (0.85–1.22)	>0.999
Pleural fluid on chest X-ray* FQL	1.06 (0.97–1.16)	0.765
Bilateral infiltrate on chest X-ray*BLM	1.01 (0.85–1.19)	>0.999
Bilateral infiltrate on chest X-ray*FQL	1.13 (1.03–1.24)	0.167

Abbreviations: Ag, antigen; BH, Benjamini–Hochberg method; BLM, β-lactam plus macrolide; FQL, fluoroquinolone-based.

ratio 1.14 per unit increase of standardized age, 95% CI 1.06–1.22, BH adjusted p 0.008).

Sensitivity analyses

Sensitivity analyses of the three final models in patients with radiologically confirmed CAP did not reveal substantial changes in the estimates of interactions (see Supplementary material, Table S4). Subsequently, we performed the analyses in each of the three cohorts separately (see Supplementary material, Table S4). In the 30-day mortality model, the ORs for the interaction between increasing age and fluoroquinolone use were consistent in the three cohorts, ranging from 1.62 to 1.75, whereas the OR for the interaction between being an active smoker and fluoroquinolone use showed greater variation (1.45 to 3.97) albeit all in the same direction. In the LOS model, the effect size for the interaction between increasing age and β-lactam + macrolide treatment ranged from 0.93 to 1.78. In the ICU admission model, the ORs for the interaction of leucocytosis with β-lactam + macrolide use showed substantial inter-cohort differences (from 1.58 to 48.91).

Finally, since the analyses yielded similar interaction effect estimates in models without inclusion of confounders, confounding by indication appeared to be limited for the interaction effect (see Supplementary material, Table S4).

Individual predicted treatment effect on 30-day mortality

Focusing on our primary outcome, we refitted the step 2 model, restricted to the significant interaction variables (increasing age and to be a current smoker), to construct a predictive model of 30-day mortality based on the provided antibiotic treatment (Fig. 1). According to this model, in older currently smoking patients empirical treatment with fluoroquinolone is associated with higher 30-day mortality than empirical treatment with β-lactam. Yet, in young non-smoking patients, fluoroquinolone empirical treatment was predicted to be associated with lower 30-day mortality. There were no clear effects for β-lactam + macrolide versus β-lactam.

Discussion

In this post-hoc analysis of three prospective cohorts from the Netherlands and Spain we identified age and smoking as candidate clinical predictors for the response to empirical antibiotic treatment, from an individualized patient perspective. In a previous clinical trial comparing β-lactam with β-lactam + macrolide [11] authors indicate an interaction effect of high PSI classes classification and monotherapy, with a reduced hazard ratio for clinical stability. Conversely, in a recent register-based cohort study comparing narrow-spectrum with broad-spectrum β-lactam therapy in patients with CAP, the authors did not find significant interaction effects of clinical variable with antibiotic effectiveness [29].

Our findings suggest that older age and smoking are associated with increased 30-day mortality in patients receiving fluoroquinolone as empirical treatment, either alone or combined with β-lactams. In older patients the beneficial effects of atypical coverage could be less than in younger patients, partly due to a lower incidence of CAP caused by atypical pathogens, as reported in different series [19,30,31] and also observed in our data (see Supplementary material, Table S3). Moreover, adverse effects and toxicity of fluoroquinolone (among them the QT interval prolongation [32]) could be more pronounced in older patients, possibly due to a decline in renal function and changes in pharmacokinetics [33]. Older age was also related with decreased effectiveness of β-lactam + macrolide, with an interaction OR of 1.67. However, presumably due to the lower number of patients with this regimen, the association was not statistically significant.

Yet, the direction of the effect of smoking was unexpected, especially in the light of studies reporting a higher proportion of smokers in *Legionella pneumophila*-infected patients, which should, in contrast to our findings, favour fluoroquinolone-based treatment in smokers [34,35]. This finding raises new questions about a possible interaction between smoking and antibiotic effectiveness. To the best of our knowledge, currently there is no mechanism that could explain such an interaction. We can only hypothesize that smoking patients might have malignancies, chronic obstructive pulmonary disease, or other unexplored characteristics, which were not yet recognized and/or reported in the medical chart, which could interact with fluoroquinolone use in a detrimental way. Still, due to the large variability of the ORs between cohorts, this finding should be interpreted with caution.

Older age was related to an increase in LOS in patients who received β-lactam + macrolide as empirical treatment, with an addition of 1 day on the median LOS of 7 days. As mentioned above, the lower incidence of atypical pathogens in older patients could lead to less beneficial effects of β-lactam + macrolide in these patients. Furthermore, this finding could refer to the well-described association between macrolide use and cardiac events [15,16], which more frequently occur in older patients. Unfortunately, our data did not allow testing of this hypothesis. Moreover, we observed that the effect size of the interaction between age and β-lactam + macrolide use was highly variable between the three cohorts, raising uncertainty on the generalizability of this finding.

Similarly, the large confidence interval of the OR and the wide range of ORs between the three cohorts for the association between ICU admission and leucocyte count >20 000 cells/μL in patients who received β-lactam + macrolide prohibit firm conclusions.

Of note, the interaction between PSI score and empirical antibiotic treatment showed no effect on clinical outcome. In current clinical practice, the choice of empirical antibiotic treatment is mainly based on clinical severity criteria, supported by disease severity scores such as the PSI score [8,10]. Our findings suggest that the PSI score does not predict whether a patient will respond better to one empirical antibiotic treatment over another, suggesting that we need to re-evaluate how we select empirical antibiotics to treat patients with CAP.

The key strengths of this study are the large number of patients from different cohorts allowing us to assess treatment effects in subgroup analyses, the high-quality prospective data collection, and the inclusion of all possible relevant clinical predictors in the analysis. This study could serve as a prototype for future research in CAP, being the first study in using the novel approach of identifying predictors for the effect of empirical treatment strategies, instead of looking at predictors for clinical outcome or causative pathogen. One source of weakness in this study is the presence of some important differences between cohorts. In the Bellvitge cohort all patients included have confirmed CAP on chest X-ray, unlike the Dutch cohorts. Whereas patients with radiologically confirmed CAP represent a more well-defined disease entity, the Dutch cohorts included all patients that were treated for a clinical diagnosis of CAP, improving generalizability of the results to daily clinical practice. However, a sensitivity analysis that included only X-ray-confirmed CAP showed similar results. Furthermore, there is a large variability in the presence of some clinical signs and symptoms between the three cohorts (Table 1), which is probably due to a lack of uniformity in the collection of clinical data. The possibility of misreporting clinical characteristics could underestimate their modifying effect on treatment and hence influence results. To correct for clustering within the cohorts, we used mixed-effects regression models. In addition, we performed a sensitivity analysis stratified by cohorts to assess the robustness of our findings in each of the cohorts.

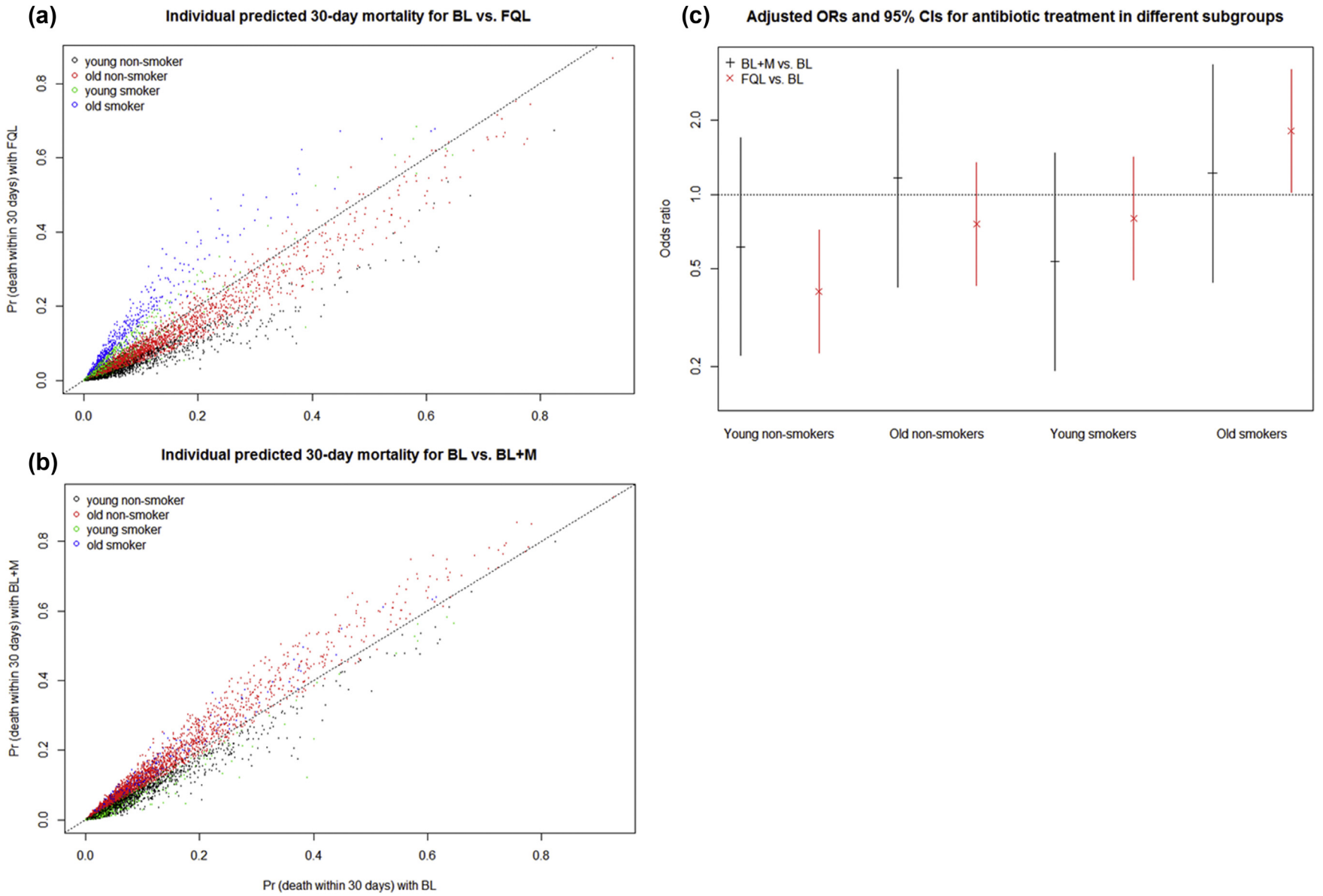

Fig. 1. Predicted 30-day mortality at individual patient level. (a) Individual predicted 30-day mortality in a logistic regression model restricted to the significant interaction variables (age and smoking habit), comparing patients who receive β-lactam with patients who receive fluoroquinolone as empirical treatment. (b) Individual predicted 30-day mortality in a logistic regression model restricted to the significant interaction variables (age and smoking habit), comparing patients who receive β-lactam with patients who receive β-lactam + macrolide as empirical treatment. (c) Adjusted (Benjamini–Hochberg method) OR with 95% CI for 30-day mortality in different subgroups of patients, divided for their group age and smoking habit.

Importantly, these are all observational data, and we could not rule out confounding by indication of the different empirical antibiotic treatments used, although we adjusted for multiple confounders in the multivariate models. Yet, as we focus on the interaction effect of clinical factors with empirical antibiotic treatment, we can postulate that the same bias is present in all the different strata, so not largely biasing the direction and size of the interaction effect.

Moreover, as we cannot rule out bias on the direct effects of antibiotics, the same interaction effect could either mean benefit for one group, or harm for the other group. For example, we cannot claim that fluoroquinolone-based treatment is harmful in older smoking patients, as our results could also be interpreted the other way round, meaning that they are beneficial in younger and non-smoking patients. Considering this limitation, our results should be considered hypothesis generating and need to be confirmed in a randomized controlled trial designed to estimate these interaction effects.

In conclusion, it is plausible that older age influences the response to specific antibiotic treatment, as we found a relationship with both the use of fluoroquinolone and increased 30-day mortality and β-lactam + macrolide use and LOS in older patients. Current smoking was also associated with a decreased response to fluoroquinolone. Future trials evaluating antibiotic strategies for CAP could assess the treatment effects in patients of different age categories and smoking status. In addition, further research illuminating the causal mechanism underlying the identified associations needs to be performed.

Funding

This study was supported by research grants from the Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III [FIS 10/01318] and Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III. Dr Simonetti was the recipient of a mobility research grant from Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC).

Transparency declaration

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2017.03.010.

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