[Original Research]

CHEST

Effect of Combined β-Lactam/Macrolide Therapy on Mortality According to the Microbial Etiology and Inflammatory Status of Patients with Community-Acquired Pneumonia

Q25 *Adrian Ceccato, MD; Catia Cilloniz, PhD; Ignacio Martin-Loeches, MD, PhD; Otavio T. Ranzani, MD, PhD; Albert Gabarrus, MSc; Leticia Bueno, RN; Carolina Garcia-Vidal, MD, PhD; Miquel Ferrer, MD, PhD;* Q1 Q2 *Michael S. Niederman, MD; and Antoni Torres, MD, PhD*

BACKGROUND: Antibiotic combinations that include macrolides have shown lower mortality rates than β-lactams in monotherapy or combined with fluoroquinolones in patients with community-acquired pneumonia (CAP). However, this effect has not been studied according to the levels of C-reactive protein in CAP with identified microbial cause. In patients with CAP and known microbial cause we aimed to evaluate 30-day mortality of a β-lactam plus macrolide (BL + M) compared with a fluoroquinolone alone or with a β-lactam (FQ ± BL).

METHODS: We analyzed a prospective observational cohort of patients with CAP admitted to the Hospital Clinic of Barcelona between 1996 and 2016. We included only patients with known microbial cause.

RESULTS: Of 1,715 patients (29%) with known etiology, a total of 932 patients (54%) received BL + M. Despite lower crude mortality in the BL + M group in the overall population (BL + M, 5% vs FQ ± BL, 8%; $P = .015$), after adjustment by a propensity score and baseline characteristics, the combination of BL + M had a protective effect on mortality only in patients with high inflammatory response (C-reactive protein, > 15 mg/dL) and pneumococcal CAP (adjusted OR, 0.28; 95% CI, 0.09-0.93). No benefits on mortality were observed for the population without high inflammatory response and pneumococcal CAP or with other etiologies.

CONCLUSIONS: The combination of a β-lactam with a macrolide was associated with decreased mortality in patients with pneumococcal CAP and in patients with high systemic inflammatory response. When both factors occurred together, BL + M was protective for mortality in the multivariate analysis. CHEST 2019; ■(■):■-■

KEY WORDS: community-acquired pneumonia; inflammatory response; macrolide; sepsis; Q7 *Streptococcus pneumoniae*

ABBREVIATIONS: BL + M = β-lactam plus macrolide; CAP = community-acquired pneumonia; CRP = C-reactive protein; FQ ± BL = fluoroquinolone alone or with a β-lactam; IQR = interquartile range; PSI = Pneumonia Severity Index; RCT = randomized clinical trial; SOFA = Sequential Organ Failure Assessment

AFFILIATIONS: From the Department of Pneumology (Drs Ceccato, Cilloniz, Ranzani, Ferrer, and Torres, Mr Gabarrus, and Ms Bueno), Respiratory Institute (ICR), the Hospital Clinic of Barcelona, the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), the University of Barcelona (UB), SGR 911-CIBER de Enfermedades

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Community-acquired pneumonia (CAP) is a major cause of death worldwide.[1] The mortality attributed to CAP is high, despite adequate and early empiric antimicrobial treatment.[2] Empiric antibiotics must cover the main pathogens that cause pneumonia. Guidelines suggest the use of a β-lactam plus a macrolide (BL + M), or a β-lactam plus a fluoroquinolone or a fluoroquinolone alone (FQ ± BL), as empiric treatment for hospitalized patients, but with fluoroquinolone monotherapy restricted to non-ICU patients.[3-5]

Few randomized clinical trials (RCTs) have compared these antibiotic regimens, and the data available are the result of retrospective observational analyses.[6-17] In many of these studies, combinations of a BL + M showed better results than β-lactam monotherapy, even in patients with higher severity disease or when the responsible pathogen is resistant to macrolides. These benefits have been attributed to the immunomodulatory effect of macrolides in addition to their antimicrobial effect.[18,19] However, fluoroquinolones also have an immunomodulatory effect and a similar antimicrobial spectrum for usual etiologic pathogens of CAP.[20] Pneumococcal pneumonia usually has a higher inflammatory response than pneumonia caused by other organisms, with some exceptions such as *Legionella pneumophila*[21] and toxin-producing *Staphylococcus aureus*. Therefore, we might expect a greater beneficial effect of including a macrolide in pneumococcal CAP compared with other etiologic groups. Indeed, several studies have shown the benefits of including macrolides in the treatment of pneumococcal CAP compared with monotherapy, particularly in the presence of bacteremia.[13,22-24]

The hypothesis of this study was that combining a β-lactam with a macrolide in patients with CAP resulted in decreased 30-day mortality, when compared with a quinolone-based regimen. We also aimed to test whether stratifying patients according to microbial etiology of CAP and the level of systemic inflammation was related to this benefit in mortality.

Methods

Study Design and Patients

We performed an observational study on a prospective cohort of consecutive patients with CAP who were admitted to the Hospital Clinic of Barcelona (January 1996 to December 2016).

Inclusion criteria were as follows: (1) adults ≥ 18 years old at diagnosis; (2) CAP confirmed by chest radiograph and consistent clinical manifestations (eg, fever, cough, sputum production, pleuritic chest pain); (3) patients with known etiology; and (4) patients who received a BL + M or FQ ± BL as empiric treatment.

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) severe immunosuppression, as in transplantation, HIV coinfection, or in patients receiving chemotherapy or other immunosuppressive drugs (> 20 mg of prednisone-equivalent per day for 2 weeks or more); and (4) empiric treatment with combinations other than those described above.

Ethics Statement

The Ethics Committee of the Hospital Clinic of Barcelona approved the study for the purpose of publication (Register: 2009/5451). The need for written informed consent was waived because of the noninterventional design. Patients' identity remained anonymous.

Data Collection

The comorbidities were recorded from the medical records. Clinical, laboratory, and radiographic characteristics were recorded on admission (described in detail in the online article). During hospitalization, the following data were recorded: length of stay, admission to the ICU, need for mechanical ventilation (invasive or noninvasive), and 30-day mortality.

Severe CAP was defined according to American Thoracic Society/Infectious Diseases Society of America guidelines.[3] Pneumonia Severity Index (PSI),[25] Sequential (previously, Sepsis-Related) Organ Failure Assessment (SOFA),[26] and CURB-65[27] scores were used to stratify cases according to severity.

Microbiologic Evaluation

Microbiologic examination is described in detail in the online article.

Definitions

We separated the patients according to initial antimicrobial treatment into two groups: patients who received a BL + M, and patients who received an FQ ± BL.

We also grouped them according to etiology into three groups: patients with pneumococcal etiology, patients with atypical pathogen etiology (*Chlamydophila pneumoniae*, *Chlamydia psittaci*, *Coxiella burnetii*,

Respiratorias (CIBERES), and ICREA Academia, Barcelona, Spain; the Department of Intensive Care (Dr Martin-Loeches), St. James's Hospital, Dublin, Ireland; the Respiratory Intensive Care Unit (Dr Ranzani), Pulmonary Division, Heart Institute, Hospital das Clínicas, University of São Paulo, São Paulo, Brazil; the Infectious Diseases Service (Dr Garcia-Vidal), Hospital Clinic, University of Barcelona, Barcelona, Spain; and the Division of Pulmonary and Critical Care Medicine (Dr Niederman), Weill Cornell Medical College, New York Presbyterian/Weill Cornell Medical Center, New York, NY.

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CORRESPONDENCE TO: Antoni Torres, MD, PhD, Department of Pneumology, Hospital Clinic of Barcelona, Villarroel 170, Barcelona 08036, Spain; e-mail: atorres@clinic.cat

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Mycoplasma pneumoniae, and *Legionella pneumophila*) and patients with other etiology (organisms not included in previous groups, or polymicrobial etiology).

We defined patients with a high inflammatory response as those with a C-reactive protein (CRP) level greater than 15 mg/dL at admission, based on the results of a previous study.[28]

Appropriateness of empiric antimicrobial treatment in patients was defined when the isolated pathogens were susceptible in vitro to one or more of the antimicrobials administered.

Outcomes

The main outcome was 30-day all-cause mortality.

Statistical Analysis

We report the number and percentage of patients for categorical variables, the median and interquartile range (IQR) for continuous variables with a nonnormal distribution, and the mean and standard deviation for those with a normal distribution. Categorical variables were compared using the χ^2 test or the Fisher exact test. Continuous variables were compared using the *t* test or the nonparametric Mann-Whitney test.

Logistic regression analyses[29] were used to examine the associations between 30-day mortality and risk factors. 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 multivariable model. Finally, a backward stepwise selection ($P_{in} < .05$, $P_{out} > .10$) was used to determine factors associated with 30-day mortality. If two independent variables were highly correlated ($r > |\pm 0.30|$), the variable with the largest variance was excluded from the multivariable analyses.[30] The OR and 95% CI were calculated.

A propensity score for patients receiving antimicrobial treatment was developed[31] because the antimicrobial treatment was not randomly administered to these patients, resulting in a potential confounding factor and selection bias. The propensity score was determined, irrespective of the outcome, through a multinomial logistic regression to predict the influence of 18 predetermined variables on the use of antimicrobial treatment. Variables were chosen for inclusion in the propensity score calculation according to the methods of Brookhart et al[32] and included variables associated with antimicrobial use and outcome. The score was finally entered as a continuous variable in the multivariable logistic regression analysis for 30-day mortality, together with the antimicrobial treatment, the microbial etiology, the year of occurrence of pneumonia, and admission to the ICU. As sensitivity analyses, the same analyses were performed on the subset of patients with pneumococcal CAP, and for patients with CRP > 15 mg/dL.

We used the multiple imputation method[33] for missing data in the multivariable analyses. The level of significance was set at .05 (two-tailed). All analyses were performed with SPSS Statistics version 23.0 (IBM, Armonk, NY).

Results

Patient Characteristics

Of the 6,442 patients with CAP admitted during the study period, 1,715 (28%) were included in the present study; the main exclusion criterion was unknown etiology in 3,840 patients (60%) (Fig 1). Nine hundred and thirty-two patients (54%) received empiric antibiotic treatment with a BL + M, and 783 patients (46%) received an FQ ± BL.

The baseline characteristics of the two groups are summarized in Table 1. Patients who received a BL + M had more frequent chronic pulmonary disease and were

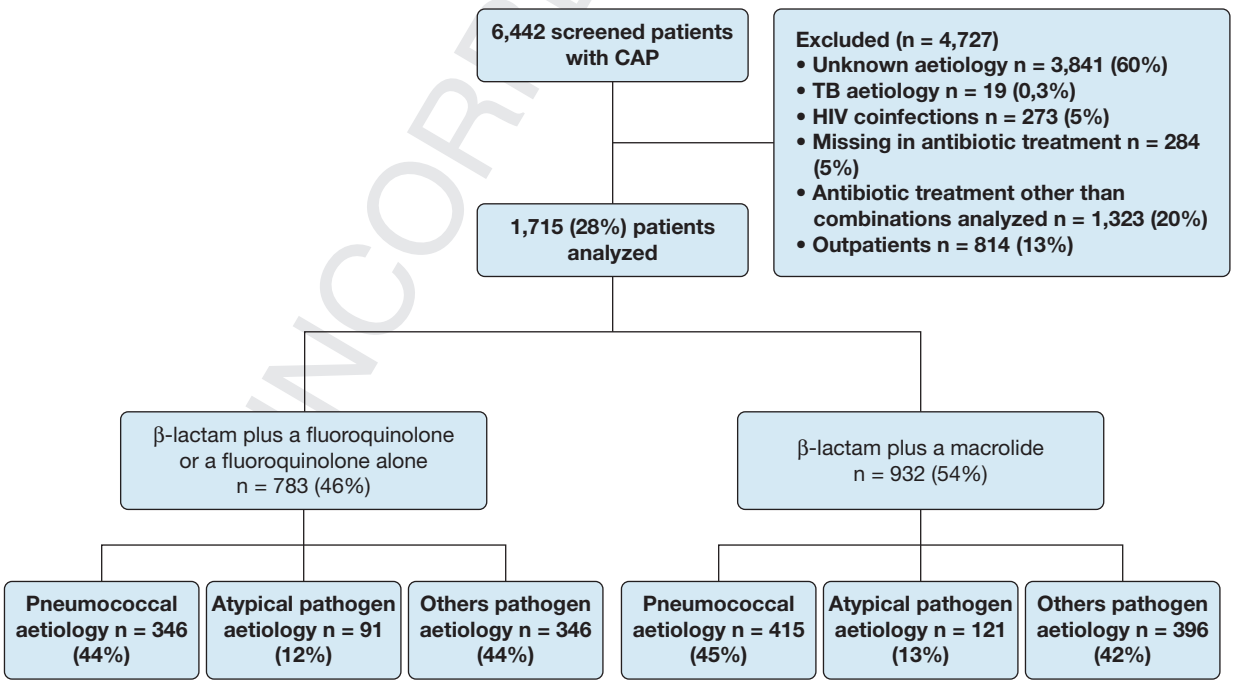

Figure 1 – *Flowchart. CAP = community-acquired pneumonia.*

TABLE 1] Baseline Characteristics of Patients

Variable	β-Lactam Plus Macrolide (n = 932)	β-Lactam Plus Fluoroquinolone or Fluoroquinolone Alone (n = 783)	*P* Value
Age, median (IQR), y	72 (57-80)	71 (55-80)	.512
Elderly (> 65 y old), No. (%)	607 (65)	475 (61)	.057
Male sex, No. (%)	602 (65)	475 (61)	.094
Pneumococcal vaccine, No. (%)	94 (16)	133 (19)	.195
Influenza vaccine, No. (%)	225 (38)	316 (45)	**.016**
Chronic pulmonary disease, No. (%)	469 (51)	322 (42)	**< .001**
Heart failure, No. (%)	122 (13)	107 (14)	.722
Chronic renal failure, No. (%)	65 (7)	48 (6)	.486
Hepatic disease, No. (%)	67 (7)	41 (5)	.102
Diabetes mellitus, No. (%)	178 (19)	164 (21)	.301
Neurologic disease, No. (%)	104 (11)	110 (15)	**.045**
Former or current smoker, No. (%)	591 (63)	458 (58)	**.043**
Alcohol consumption, No. (%)	160 (17)	125 (16)	.474
Nursing home, No. (%)	21 (3)	51 (7)	**< .001**
Previous antibiotic therapy, No. (%)	164 (18)	176 (24)	**.004**
Systemic steroids, No. (%)	27 (4)	48 (6)	.088
Inappropriate treatment, No. (%)	23 (5)	19 (5)	.697
Creatinine, median (IQR), mg/dL	1.1 (0.9-1.5)	1.1 (0.9-1.6)	.285
C-reactive protein, median (IQR), mg/dL	22 (11-29)	22 (12-30)	.169
White blood cell count, median (IQR), × 10^9/L	13.8 (8.9-18.6)	13.1 (9-18.3)	.581
Pao_2/Fio_2, median (IQR), mm Hg	281 (238-314)	271 (229-314)	.072

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

more often former or current smokers; they had less frequent neurologic disease, previous influenza vaccination, nursing home residence, or previous antibiotic therapy.

The main causal organism was *Streptococcus pneumoniae* in both groups (Fig 1). Detailed information on microbial etiology is shown in Table 2. High inflammatory response (CRP > 15 mg/dL) at admission was present in 534 patients (70%) with pneumococcal CAP, 117 patients (55%) with atypical etiology, and 341 patients (46%) with another etiology.

We found no differences in severity scores such as CURB-65, PSI, or SOFA; however, patients who received an FQ ± BL were more frequently admitted to the ICU, and more often required noninvasive ventilation, or presented with severe CAP, particularly septic shock. No differences were observed in the requirement for invasive mechanical ventilation (Table 3).

Antibiotic Treatment

Among 1,715 patients, 1,387 (81%) were treated with a β-lactam; of these, 1,209 (87%) received ceftriaxone.

Patients treated with a BL + M received azithromycin in 758 cases (81%), erythromycin in 111 cases (12%), and clarithromycin in 63 cases (7%).

In patients treated with an FQ ± BL, 455 (58%) received a fluoroquinolone in combination with a β-lactam. In this group 767 patients (98%) received levofloxacin, 12 patients (1.5%) received ciprofloxacin, and 4 patients (0.5%) received moxifloxacin; all patients given ciprofloxacin received that treatment in combination with a β-lactam.

Outcomes

Patients receiving a BL + M had lower crude 30-day mortality compared with patients who received an FQ ± BL (5% vs 8%; $P = .015$) (Table 4). Similar results were observed in patients with a high inflammatory response (BL + M, 3% vs FQ ± BL, 8%; $P < .001$) and for patients with pneumococcal CAP (BL + M, 4% vs FQ ± BL, 9%; $P = .004$). The greatest difference in mortality was observed in patients with both a high inflammatory response and pneumococcal CAP (BL + M, 2% vs FQ ± BL, 10%; $P \leq .001$). No

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TABLE 2] Microbial Etiology of Pneumonia

Pathogen	β-Lactam Plus Macrolide (n = 932) (%)	β-Lactam Plus Fluoroquinolone or Fluoroquinolone Alone (n = 783) (%)
Pneumococcal pneumonia	415 (45)	346 (44)
Invasive pneumococcal pneumonia	185 (20)	145 (19)
Atypical bacteria	121 (13)	91 (12)
Legionella pneumophila	68 (7)	51 (7)
Chlamydophila pneumoniae	21 (2)	12 (2)
Mycoplasma pneumoniae	21 (2)	20 (3)
Other etiologies	396 (43)	316 (44)
Haemophilus influenzae	50 (5)	22 (3)
Klebsiella pneumoniae	3 (0.5)	9 (1)
Escherichia coli	11 (1.5)	6 (1)
Pseudomonas aeruginosa	34 (4)	17 (2)
Staphylococcus aureus	19 (3)	15 (2)
Respiratory virus	102 (11)	152 (19)
Moraxella catarrhalis	0 (0)	5 (1)
Polymicrobial	148 (16)	91 (12)

Percentages calculated on nonmissing data.

differences in 30-day mortality between both groups were observed in patients with atypical or other etiologies. Moreover, we grouped all patients without pneumococcal CAP and without a high inflammatory response and again no significant differences were observed.

TABLE 3] Severity Scores, Site of Care, and Main Complications

Variable	β-Lactam Plus Macrolide (n = 932)	β-Lactam Plus Fluoroquinolone or Fluoroquinolone Alone (n = 783)	*P* Value
CURB-65 risk classes 3-5, No. (%)	174 (20)	157 (22)	.390
PSI score, median (IQR)	98 (76-121)	101 (77-124)	.245
PSI risk classes IV and V, No. (%)	428 (57)	340 (60)	.365
SOFA score, median (IQR)	2 (2-3)	2 (1-3)	.762
Site of care, No. (%)			**< .001**
General ward	759 (82)	561 (72)	
ICU	171 (18)	221 (28)	
Length of hospital stay, median (IQR), d	7 (5-11)	8 (6-13)	**< .001**
Severe CAP, No. (%)	187 (27)	227 (35)	**.001**
Noninvasive mechanical ventilation, No. (%)	17 (2)	47 (7)	**< .001**
Invasive mechanical ventilation,[a] No. (%)	63 (7)	65 (9)	.176
Septic shock, No. (%)	69 (7)	96 (12)	**.001**
Severe CAP non admitted to ICU			
Major criteria, No. (%)	3 (9)	4 (11)	.72
≥ 3 minor criteria, No. (%)	70 (58)	78 (73)	**.021**
Major criteria and ≥ 3 minor criteria, No. (%)	7 (10)	4 (9)	.91

Percentages calculated on nonmissing data. Boldface entries indicate statistical significance. Severe CAP was defined according to American Thoracic Society/Infectious Diseases Society of America criteria.[3] CURB-65 = confusion, blood urea nitrogen, respiratory rate, blood pressure, age > 65 y; PSI = Pneumonia Severity Index; SOFA = Sequential Organ Failure Assessment.

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

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TABLE 4] Crude 30-Day Mortality in Overall Population and Subpopulations

	β-Lactam Plus Macrolide	β-Lactam Plus Fluoroquinolone or Fluoroquinolone Alone	*P* Value
Overall population	n = 932	n = 783	
30-day mortality, No. (%)	45 (5)	60 (8)	**.015**
Pneumococcal pneumonia	n = 415	n = 345	
30-day mortality, No. (%)	17 (4)	32 (9)	**.004**
High inflammatory response (CRP > 15 mg/dL)	n = 398	n = 481	
30-day mortality, No. (%)	11 (3)	40 (8)	**< .001**
Pneumococcal pneumonia and high inflammatory response	n = 178	n= 239	
30-day mortality, No. (%)	3 (2)	25 (10)	**< .001**
Pneumococcal pneumonia without high inflammatory response	n = 94	n = 78	
30-day mortality, No. (%)	7 (7)	6 (8)	.95
Patients without pneumococcal pneumonia and high inflammatory response	n = 220	n = 242	
30-day mortality, No. (%)	8 (4)	15 (6)	.21
Atypical pathogens and without high inflammatory response	n = 25	n = 14	
30-day mortality, No. (%)	0 (0)	0 (0)	…
Atypical pathogens and high inflammatory response	n = 55	n = 63	
30-day mortality, No. (%)	0 (0)	1 (2)	> .999
Other pathogens and without high inflammatory response	n = 97	n = 125	
30-day mortality, No. (%)	6 (6)	9 (7)	.77
Other pathogens and high inflammatory response	n = 165	n = 179	
30-day mortality, No. (%)	8 (5)	14 (8)	.26

High inflammatory response was defined as CRP > 15 mg/dL. Boldface entries indicate statistical significance. CRP = C-reactive protein.

In the overall population and specifically in patients with pneumococcal pneumonia, the propensity-adjusted multivariable analysis did not show any significant association between the antibiotic treatment and 30-day mortality (e-Tables 1, 2; e-Fig 1); however, for the population with a high inflammatory response we observed a significant interaction between antimicrobial treatment and etiology, specifically for patients with pneumococcal CAP, who also received antibiotic treatment with a BL + M (adjusted OR, 0.28; 95% CI, 0.09-0.92; $P = .036$) (Table 5). The multivariable analysis adjusted by propensity score for 30-day mortality also showed that PSI risk classes IV and V, acute respiratory distress syndrome, septic shock, and inappropriate treatment were independent risk factors for death. The area under the receiver-operating characteristic curve was 0.85 (95% CI, 0.80-0.89) (e-Fig 1) for the model of 30-day mortality.

Internal validation of the logistic regression model for patients with high inflammatory response was conducted by bootstrapping with 1,000 samples (e-Table 3). All variables included in the model demonstrated robust results, with low 95% CIs around the original coefficients.

Discussion

In this well-characterized cohort of patients with CAP we compared the effect of two types of empiric antibiotic treatments, BL + M and FQ ± BL, on 30-day mortality. After adjusting for confounders, BL + M did not protect for mortality in the overall population; however, our analyses revealed that the combination of a BL + M compared with an FQ ± BL had an independent association with less 30-day mortality only in patients with pneumococcal CAP and in those with a high inflammatory response (CRP > 15 mg/L), with the greatest benefit in those with both factors present. No differences in mortality were observed between groups of patients with other microbial etiologies and high inflammatory response.

Several observational studies have shown that the combination of a β-lactam with a macrolide is better

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TABLE 5] Significant Univariate and Multivariable Logistic Regression Analyses for 30-Day Mortality: Patients With High Inflammatory Response

Variable	Univariate			Multivariable[a,b]		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Interaction treatment and etiology			.062			.11
β-Lactam plus a macrolide and *Streptococcus pneumoniae*	0.27	0.09-0.80	**.019**	0.28	0.09-0.92	**.036**
β-Lactam plus a macrolide and Atypical bacterial	0.44	0.04-5.53	.52	0.59	0.04-7.83	.69
β-Lactam plus macrolide treatment	0.97	0.46-2.03	.93	1.32	0.58-3.00	.50
Etiology			.11			.27
Streptococcus pneumoniae	1.52	0.77-2.98	.23	1.36	0.64-2.88	.42
Atypical bacterial etiology	0.36	0.08-1.64	.19	0.41	0.09-1.98	.27
Other etiology	1	…	…	1	…	…
Admission after Year 2007	1.47	0.90-2.42	.13	1.06	0.45-2.48	.89
ICU admission	6.65	3.93-11.23	**< .001**	1.93	0.89-4.20	.096
Elderly (> 65 y old)	2.32	1.29-4.18	**.005**	…	…	…
PSI IV and V	5.96	2.82-12.60	**< .001**	3.97	1.81-8.71	**.001**
ARDS	6.80	3.61-12.80	**< .001**	2.63	1.24-5.61	**.012**
Acute renal failure	5.99	3.46-10.35	**< .001**	…	…	…
Septic shock	10.75	6.31-18.30	**< .001**	4.17	2.05-8.45	**< .001**
Adequate antibiotic treatment	0.17	0.07-0.42	**< .001**	0.34	0.12-0.95	**.040**

Boldface entries indicate statistical significance. PSI = Pneumonia Severity Index.
[a]Adjusted by propensity score.
[b]Hosmer-Lemeshow goodness-of-fit test $P = .88$.

than a β-lactam alone. Therefore, clinical guidelines suggest the use of a combination of a β-lactam with a macrolide or a fluoroquinolone, or a fluoroquinolone alone, for patients with CAP (but fluoroquinolone monotherapy only for patients with nonsevere CAP). The beneficial effect of a BL + M over a combination of a β-lactam with a fluoroquinolone or a fluoroquinolone alone is less clear. In this study we compared these combinations in various subgroups and found differences in favor of the macrolide combination in a specific group of patients. Benefits in pneumococcal bacteremic CAP were previously reported for a BL + M combination even though, when compared with fluoroquinolone-based therapies, no benefits were observed[13]; however, this study did not look at the inflammatory status. A recent study has shown better outcomes in patients who received macrolide therapy and presented with bacteremic pneumonia.[34] Moreover, the most common cause of bacteremic pneumonia was pneumococcus in 74% of patients, and although the authors did not look at CRP levels, patients with invasive pneumococcal CAP usually presented greater levels of CRP.[35] A recent meta-analysis that compared the combination of a β-lactam with a macrolide vs a β-lactam with a fluoroquinolone showed no significant differences in short-term mortality (adjusted risk ratio, 1.26; 95% CI, 0.95-1.67; I^2, 43%)[36]; and another meta-analysis showed that ceftriaxone combination therapy was similar in terms of treatment success compared with fluoroquinolone monotherapy in patients with CAP.[37] The study by Postma et al[6] was a cluster-randomized clinical trial that showed that a β-lactam was not inferior to a combination of a β-lactam with a macrolide or a fluoroquinolone alone for patients with nonsevere CAP; however, this study had several methodologic limitations that made the conclusions not generalized. A recent Q12 post-hoc analysis of a multicenter cohort in Japan evaluated the role of CRP in patients treated with a β-lactam compared with a combination β-lactam plus macrolide, showing mortality benefit regardless of whether the CRP level was above or below 15 mg/dL.[38] CRP is an inflammatory marker that can predict poor outcomes and treatment failure in patients with CAP or sepsis for other causes, and could be used for evaluate Q13 response to treatment.[39-41] As in previous studies on adjuvant treatments in CAP,[28,42] we looked at specific populations in whom a BL + M could have a beneficial effect. Furthermore, a recent report by the US National

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Heart, Lung, and Blood Institute[43] recognized severe pneumonia with high inflammatory response as an endotype, and proposed that its presence might be used to guide therapy.

Macrolides and fluoroquinolones have immunomodulatory activity. Both act by reducing the levels of proinflammatory cytokines and increasing the levels of antiinflammatory cytokines in in vitro and in vivo models.[20,44,45] The fluoroquinolones have effects on intracellular cyclic AMP and phosphodiesterases, and on transcription factors such as NF-κB, activator protein 1.[44] Macrolides have effects on structural cells of the respiratory tract such as endothelial and epithelial cells, mainly on the expression of adhesion molecules, reducing the adherence of pneumococci to the respiratory epithelium.[18,19,46,47] A potential explanation of the impact on pneumococcal CAP with a high inflammatory response is the fact that macrolides not only inhibit bacterial protein synthesis but are also potent inhibitors of the production of pneumolysin, even at subinhibitory concentrations.[48,49] The combined impact on bacteria and on the host response may explain our findings.[22-24]

The main limitation of this study is that it was performed at a single center, and so the results should be confirmed in other databases or in prospective RCTs. Another limitation is that we observed that patients who received fluoroquinolones alone or in combinations had more severe disease and were admitted to the ICU more frequently; this may represent a bias in our study, given that physicians, including the ICU team, more often used fluoroquinolones in patients with more severe disease. We tried to address this issue by adjusting all the multivariable analyses by ICU admission. In addition, the etiology of CAP identified in our study showed a high frequency of pneumococcal infection, a finding that is at variance with the data in a large study from the United States.[50] Our results suggest the need for a new RCT in a population with *S. pneumoniae* and high inflammatory response to evaluate the mortality benefit of adding a macrolide to a β-lactam. The strengths of our study are that we analyzed a large database with a well-characterized population with microbiologic data. In addition, we compared combinations of a β-lactam with either a macrolide or a fluoroquinolone; both regimens are active against the most common pathogens causing CAP, and both macrolides and fluoroquinolones have immunomodulatory activity.

In conclusion, the combination of a β-lactam with a macrolide was associated with decreased mortality in patients with pneumococcal CAP and in patients with high systemic inflammatory response. When both factors occurred together, BL + M combinations were protective for mortality in the multivariate analysis.

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Additional information: The e-Appendix, e-Figure, and e-Tables can be found in the Supplemental Materials section of the online article.

References

1. Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. *Lancet*. 2015;386(9998):1097-1108.
2. Shindo Y, Ito R, Kobayashi D, et al. Risk factors for 30-day mortality in patients with pneumonia who receive appropriate initial antibiotics: an observational cohort study. *Lancet Infect Dis*. 2015;15(9):1055-1065.
3. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27-S72.
4. National Institute for Health and Care Excellence. Pneumonia in adults: diagnosis and management. Clinical guideline CD191. Published December 2014. Accessed April 5, 2018, https://www.nice.org.uk/guidance/cg191/chapter/1-Recommendations#community-acquired-pneumonia-2.
5. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections: full version. *Clin Microbiol Infect*. 2011;17(suppl 6):E1-E59.
6. Postma DF, van Werkhoven CH, van Elden LJR, et al. Antibiotic treatment strategies for community-acquired pneumonia in adults. *N Engl J Med*. 2015;372(14):1312-1323.
7. Garin N, Genné D, Carballo S, et al. β-Lactam monotherapy vs β-lactam-macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. *JAMA Intern Med*. 2014;174(12):1894-1901.
8. Asadi L, Sligl WI, Eurich DT, et al. Macrolide-based regimens and mortality in hospitalized patients with community-acquired pneumonia: a systematic review

and meta-analysis. *Clin Infect Dis*. 2012;55(3):371-380.

9. Mortensen EM, Halm EA, Pugh MJ, et al. Association of azithromycin with mortality and cardiovascular events among older patients hospitalized with pneumonia. *JAMA*. 2014;311(21):2199-2208.
10. Martin-Loeches I, Lisboa T, Rodriguez A, et al. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. *Intensive Care Med*. 2010;36(4):612-620.
11. Lee JS, Giesler DL, Gellad WF, Fine MJ. Antibiotic therapy for adults hospitalized with community-acquired pneumonia: a systematic review. *JAMA*. 2016;315(6):593-602.
12. Rodrigo C, Mckeever TM, Woodhead M, Lim WS. British Thoracic Society. Single versus combination antibiotic therapy in adults hospitalised with community acquired pneumonia. *Thorax*. 2013;68(5):493-495.
13. De la Calle C, Ternavasio-de la Vega HG, Morata L, et al. Effectiveness of combination therapy versus monotherapy with a third-generation cephalosporin in bacteraemic pneumococcal pneumonia: a propensity score analysis. *J Infect*. 2018;76(4):342-347.
14. Nie W, Li B, Xiu Q. β-Lactam/macrolide dual therapy versus β-lactam monotherapy for the treatment of community-acquired pneumonia in adults: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2014;69(6):1441-1446.
15. Paul M, Nielsen AD, Gafter-Gvili A, et al. The need for macrolides in hospitalised community-acquired pneumonia: propensity analysis. *Eur Respir J*. 2007;30(3):525-531.
16. Restrepo MI, Mortensen EM, Waterer GW, Wunderink RG, Coalson JJ, Anzueto A. Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia. *Eur Respir J*. 2009;33(1):153-159.
17. Pereira JM, Gonçalves-Pereira J, Ribeiro O, Baptista JP, Froes F, Paiva JA. Impact of antibiotic therapy in severe community-acquired pneumonia: data from the INFAUCI study. *J Crit Care*. 2018;43:183-189.
18. Giamarellos-Bourboulis EJ. Macrolides beyond the conventional antimicrobials: a class of potent immunomodulators. *Int J Antimicrob Agents*. 2008;31(1):12-20.
19. Kovaleva A, Remmelts HHF, Rijkers GT, Hoepelman AIM, Biesma DH, Oosterheert JJ. Immunomodulatory effects of macrolides during community-acquired pneumonia: a literature review. *J Antimicrob Chemother*. 2012;67(3):530-540.
20. Dalhoff A, Shalit I. Immunomodulatory effects of quinolones. *Lancet Infect Dis*. 2003;3(6):359-371.
21. Menéndez R, Sahuquillo-Arce JM, Reyes S, et al. Cytokine activation patterns and biomarkers are influenced by microorganisms in community-acquired pneumonia. *Chest*. 2012;141(6):1537-1545.
22. Baddour LM, Yu VL, Klugman KP, et al. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. *Am J Respir Crit Care Med*. 2004;170(4):440-444.
23. Martínez JA, Horcajada JP, Almela M, et al. Addition of a macrolide to a β-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. *Clin Infect Dis*. 2003;36(4):389-395.
24. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. *Arch Intern Med*. 2001;161(15):1837-1842.
25. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336(4):243-250.
26. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure: on behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707-710.
27. Lim WS, Eerden MM van der, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58(5):377-382.
28. Torres A, Sibila O, Ferrer M, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA*. 2015;313(7):677-686.
29. Hosmer D, Lemeshow S. *Applied Logistic Regression*. New York: Wiley; 1989.
30. Healey JF. *Statistics: A Tool for Social Research*. 9th ed. Belmont, CA: Wadsworth; 2011.
31. Joffe MM, Rosenbaum PR. Invited commentary: propensity scores. *Am J Epidemiol*. 1999;150(4):327-333.
32. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T. Variable selection for propensity score models. *Am J Epidemiol*. 2006;163(12):1149-1156.
33. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393.
34. Arnold FW, Lopardo G, Wiemken TL, et al. Macrolide therapy is associated with lower mortality in community-acquired bacteraemic pneumonia. *Respir Med*. 2018;140:115-121.
35. Ceccato A, Torres A, Cilloniz C, et al. Invasive disease vs urinary antigen-confirmed pneumococcal community-acquired pneumonia. *Chest*. 2017;151(6):1311-1319.
36. Vardakas KZ, Trigkidis KK, Falagas ME. Fluoroquinolones or macrolides in combination with β-lactams in adult patients hospitalized with community acquired pneumonia: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2017;23(4):234-241.
37. Zhang Y-Q, Zou S-L, Zhao H, Zhang M-M, Han C-L. Ceftriaxone combination therapy versus respiratory fluoroquinolone monotherapy for community-acquired pneumonia: a meta-analysis. *Am J Emerg Med*. 2018;36(10):1759-1765.
38. Okumura J, Shindo Y, Takahashi K, et al. Central Japan Lung Study Group. Mortality in patients with community-onset pneumonia at low risk of drug-resistant pathogens: impact of β-lactam plus macrolide combination therapy. *Respirology*. 2018;23(5):526-534.
39. Chalmers JD, Singanayagam A, Hill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. *Am J Med*. 2008;121(3):219-225.
40. Menéndez R, Cavalcanti M, Reyes S, et al. Markers of treatment failure in hospitalised community acquired pneumonia. *Thorax*. 2008;63(5):447-452.
41. Póvoa P, Teixeira-Pinto AM, Carneiro AH. Portuguese Community-Acquired Sepsis Study Group (SACiUCI). C-reactive protein, an early marker of community-acquired sepsis resolution: a multi-center prospective observational study. *Crit Care*. 2011;15(4):R169.
42. Welte T, Dellinger RP, Ebelt H, et al. Efficacy and safety of trimodulin, a novel polyclonal antibody preparation, in patients with severe community-acquired pneumonia: a randomized, placebo-controlled, double-blind, multicenter, phase II trial (CIGMA study). *Intensive Care Med*. 2018;44(4):438-448.
43. Dela Cruz CS, Wunderink RG, Christiani DC, et al. Future research directions in pneumonia: NHLBI Working Group Report. *Am J Respir Crit Care Med*. 2018;15(198):256-263.
44. Dalhoff A. Immunomodulatory activities of fluoroquinolones. *Infection*. 2005;33(suppl 2):55-70.
45. Prina E, Ceccato A, Torres A. New aspects in the management of pneumonia. *Crit Care*. 2016;20(1):267.
46. Pasquale TR, Tan JS. Nonantimicrobial effects of antibacterial agents. *Clin Infect Dis*. 2005;40(1):127-135.
47. Lagrou K, Peetermans WE, Jorissen M, Verhaegen J, Van Damme J, Van Eldere J.

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Subinhibitory concentrations of erythromycin reduce pneumococcal adherence to respiratory epithelial cells in vitro. *J Antimicrob Chemother*. 2000;46(5):717-723.

48. Anderson R, Feldman C. Pneumolysin as a potential therapeutic target in severe pneumococcal disease. *J Infect*. 2017;74(6): 527-544.

49. Anderson R, Steel HC, Cockeran R, et al. Clarithromycin alone and in combination with ceftriaxone inhibits the production of pneumolysin by both macrolide-susceptible and macrolide-resistant strains of *Streptococcus pneumoniae*. *J Antimicrob Chemother*. 2007;59(2):224-229.

50. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med*. 2015;373(5):415-427.

FLA 5.5.0 DTD ■ CHEST2049_proof ■ 26 December 2018 ■ 8:15 pm ■ EO: CHEST-18-2078