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## Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia

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**Abstract Objective:** To assess the effect on survival of macrolides or fluoroquinolones in intubated patients admitted to the intensive care unit (ICU) with severe community-acquired pneumonia (severe CAP). **Methods:** Prospective, observational cohort, multicenter study conducted in 27 ICUs of 9 European countries. Two hundred eighteen consecutive patients requiring invasive mechanical ventilation for an admission diagnosis of CAP were recruited. **Results:** Severe sepsis and septic shock were present in 165 (75.7%) patients. Microbiological documentation was obtained in 102 (46.8%) patients. ICU mortality was 37.6% ( $n = 82$ ). Non-survivors were older ( $58.6 \pm 16.1$  vs.  $63.4 \pm 16.7$  years,  $P < 0.05$ ) and presented a higher score on the simplified Acute Physiology Score II at admission ( $45.6 \pm 15.4$  vs.  $50.8 \pm 17.5$ ,  $P < 0.05$ ).

Monotherapy was given in 43 (19.7%) and combination therapy in 175 (80.3%) patients. Empirical antibiotic therapy was in accordance with the 2007 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines in 100 (45.9%) patients (macrolides in 46 patients and fluoroquinolones in 54). In this cohort, a Cox regression analysis adjusted by severity identified that macrolide use was associated with lower ICU mortality (hazard ratio, HR 0.48, confidence intervals, 95% CI 0.23–0.97,  $P = 0.04$ ) when compared to the use of fluoroquinolones. When more severe patients presenting severe sepsis and septic shock were analyzed ( $n = 92$ ), similar results were obtained (HR 0.44, 95% CI 0.20–0.95,  $P = 0.03$ ). **Conclusions:** Patients with severe community-acquired pneumonia had a low adherence with the 2007 IDSA/ATS guidelines. Combination therapy with macrolides should be preferred in intubated patients with severe CAP.

### Keywords

Severe community-acquired pneumonia · Macrolides · Critical care · Mortality

## Introduction

Community-acquired pneumonia (CAP) is the leading cause of infectious death and severe sepsis and is the seventh leading cause of overall death [1]. Severe CAP is defined as having the need for aggressive intensive care unit (ICU) management due to shock, organ dysfunction or need for mechanical ventilation. Strict adherence to the 2005 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines improves outcomes [2, 3], but survival has shown little improvement in the past 3 decades.

Combination antibiotic therapy improves ICU survival in patients with severe CAP [4], and adding a macrolide or fluoroquinolone to a  $\beta$ -lactam is recommended by the 2007 IDSA/ATS guidelines [5]. The addition of macrolides may have potential benefits for severely ill patients other than just antibiotic susceptibility. Recent studies suggested that macrolides may have beneficial effects in severe CAP [6] because of their immunomodulatory effects rather than due to their antimicrobial properties [7].

Studies in bacteremic pneumococcal pneumonia, CAP, severe sepsis and septic shock due to CAP have suggested a benefit with appropriate therapy in which a macrolide is combined with a  $\beta$ -lactam. However, in patients with severe CAP, according to the guidelines, there are limited data to support the use [4, 8–10]. In addition, it is not clear if the benefit is the combination therapy or the association with a macrolide and not the fluoroquinolones.

Therefore, our objective was to assess the effect on survival of using macrolides or fluoroquinolones in combination therapy in a cohort of patients hospitalized with severe CAP in 27 European ICUs. Our hypothesis was that in patients with severe CAP treated according to the 2007 IDSA/American Thoracic Society ATS guidelines, the addition of a macrolide was associated with lower ICU mortality. A secondary objective was to assess the degree of agreement with the 2007 IDSA/ATS guidelines for CAP.

## Materials and methods

### Study design

A total of 2,436 consecutive patients with mechanical ventilation for more than 48 h admitted to ICUs in 27 hospitals in Europe were eligible. One investigator at each hospital prospectively recorded variables in a previously designed database. The participating centers either received ethical approval from their institutions or ethical approval was waived.

Details on the setup of this observational study can be found elsewhere [11]. Immunocompromised patients were excluded for analysis. Cases presumed to be caused by coagulase-negative *Staphylococci* or *Enterococci* spp. were considered contaminated and classified as unknown. Cases with nonbacterial pneumonia (virus, tuberculosis) were excluded. The study cohort was divided in two groups according to the antibiotic administered (macrolides vs. quinolones) in IDSA/ATS-compliant regimens. The primary outcome was mortality in the ICU and within 30 days. A sub-analysis was performed considering only patients with severe sepsis and septic shock.

### Variables

Relationships with mortality were evaluated for the following variables: age, gender, lifestyle risk factors and pre-existing comorbidities [alcoholism, chronic obstructive pulmonary disease (COPD), cardiovascular disease and diabetes mellitus]. Disease severity was assessed by the simplified Acute Physiology Score (SAPS II) based on the first 24 h of ICU observation, the development of severe sepsis and ICU mortality.

### Definitions

Community-acquired pneumonia was defined as an acute lower respiratory tract infection characterized by: (1) an acute pulmonary infiltrate evident on chest radiographs and compatible with pneumonia, (2) confirmatory findings of clinical examination and (3) acquisition of the infection outside a hospital. Community-acquired pneumonia was considered severe when it required ICU admission [12]. Patients were admitted to the ICU either because they were potential candidates for mechanical ventilation and/or because they were judged to be in an unstable condition requiring intensive medical or nursing care [13, 14].

Patients with human immunodeficiency virus (HIV) infection, neoplasia, those taking cytotoxic drugs or long-term oral steroid therapy, such as a daily dose of 20 mg of prednisolone or the equivalent for >2 weeks, were considered immunocompromised and were excluded.

Sepsis, severe sepsis and septic shock were defined following the criteria of the American College of Chest Physicians and the Society of Critical Care Medicine [15, 16].

Patients with and without severe sepsis were compared. Antimicrobial therapy was considered guideline-concordant if it agreed with either the 2007 IDSA or ATS guidelines. Macrolides administered were either azithromycin or clarithromycin. Dosing was considered in agreement with 2007 IDSA/ATS guidelines to define the

appropriateness of empirical treatment. No patients were switched from macrolides to fluoroquinolones—and vice versa—during the course of the disease. Treatment decisions for all study participants, including type of resuscitation, determination of the need for intubation, other coadjuvant therapy and type of antibiotic therapy administered (class of combination therapy), were not standardized and were made by the attending physician.

#### Statistical analysis

Discrete variables were expressed as counts (%) and continuous variables as mean and standard deviation (SD), unless stated otherwise; all statistical tests were two-sided. Differences in categorical variables were calculated using two-sided likelihood ratio  $\chi$ -square test or Fisher's exact test, and the Mann-Whitney  $U$  test or Kruskal-Wallis test was used for continuous variables, when appropriate. Cox proportional-hazards regression analysis was used to assess the impact of independent variables on ICU mortality across the time. Variables significantly associated with mortality in the univariate analysis were entered in the model. In order to avoid spurious associations, variables entered in the regression models were those with a relationship in univariate analysis ( $P \leq 0.05$ ) or a plausible relationship with the dependent variable. Results are presented as HR and 95% CI. Results are presented as odds ratio (OR) and 95% CI. Potential explanatory variables were checked for collinearity prior to inclusion in the regression models using a tolerance and variance inflation factor. Data analysis was

performed using SPSS for Windows 13.0.0 (SPSS, Chicago, IL).

## Results

### Study population

A total of 257 intubated patients with severe CAP were enrolled. Immunocompromised patients ( $n = 39$ ) were excluded. A total of 218 patients were included in the final analysis. One hundred forty-nine (68.3%) patients were male, the mean age was 60.4 (16.4) years, and the mean SAPS II score at ICU admission was 47.6 (16.4). Severe sepsis and septic shock were present in 165 (75.7%). Patients with severe sepsis/septic shock presented longer ICU stay among survivors. Differences in baseline characteristics between patients with and without severe sepsis/septic shock are summarized in Table 1.

### Documentation of etiology

Microbiological documentation was obtained in 102 (46.8%) patients. Blood cultures provided a definitive diagnosis in only 20 cases (9.2%). *Streptococcus pneumoniae* ( $n = 33$ ; 32.4%) was identified as the most prevalent pathogen, followed by 23 cases of *Staphylococcus aureus* (22.5%) and 11 *Haemophilus influenzae* (10.8%). Table 2 details the prevalence of microorganisms isolated in patients with and without severe sepsis and septic shock. No significant differences in etiology

**Table 1** Comparison of demographic and clinical characteristics among patients with CAP with or without severe sepsis

	Overall ( $n = 218$ )	Sepsis ( $n = 53$ )	Severe sepsis/septic shock ( $n = 165$ )	$P$ value
Age mean years (SD)	60.9 (16.07)	63.1 (16.61)	59.6 (16.42)	0.17
Male gender, $n$ (%)	149 (68.3%)	20 (60.6%)	129 (69.7%)	0.31
Mean SAPS II score (SD)	46.5 (16.1)	42.61 (14.51)	48.51 (16.65)	0.05
Mean SOFA score (SD)	7.5 (3.5)	6.35 (3.6)	8.1 (3.7)	0.01
Length of stay ICU, days (SD)	18.7 (15.9)	16.5 (15.8)	21.4 (15.3)	0.08
Length of stay hospital, days (SD)*	33.5 (25.1)	29.6 (23.9)	38.8 (26.0)	0.05
Preexisting comorbid conditions				
COPD, $n$ (%)	40 (18.3%)	8 (15.1%)	32 (19.4%)	0.54
Diabetes, $n$ (%)	33 (15.1%)	5 (14.7%)	28 (15.2%)	0.99
Cardiomyopathy, $n$ (%)	53 (24.3%)	16 (30.2%)	37 (22.4%)	0.27
Cirrhosis, $n$ (%)	11 (5.0%)	3 (5.7%)	8 (4.8%)	0.73
Chronic renal failure, $n$ (%)	18 (8.3%)	3 (5.7%)	15 (9.1%)	0.57
Alcohol, $n$ (%)	32 (14.7%)	7 (13.2%)	25 (15.2%)	0.82
ICU mortality, $n$ (%)	82 (37.6%)	7 (21.2%)	75 (40.5%)	0.02
Bacteremia, $n$ (%)	20 (9.2%)	2 (9.1%)	18 (13.3%)	0.74

SAPS Simplified Acute Physiology Score, SOFA Sequential Organ Failure Assessment, ICU intensive care unit, COPD chronic obstructive pulmonary disease

\* In survivors

**Table 2** Prevalence of microorganisms isolated in patients with and without severe sepsis

	Overall (n = 102)	Patients with sepsis (n = 17)	Patient with shock/severe sepsis (n = 85)	P value
<i>S. pneumoniae</i>	33 (32.3%)	2 (5.9%)	31 (16.8%)	0.12
<i>S. aureus</i>	24 (23.5%) <sup>a</sup>	5 (11.8%) <sup>a</sup>	19 (10.3%)	0.76
<i>H. influenzae/M. catarrhalis</i>	12 (11.7%)	5 (11.8%)	7 (3.8%)	0.73
<i>P. aeruginosa</i>	11 (10.8%)	2 (5.9%)	9 (4.9%)	0.68
Enterobacteriaceae	13 (12.7%)	2 (5.9%)	11 (6.0%)	0.99
<i>L. pneumophila</i>	3 (2.9%)	–	3 (1.6%)	1
Miscellaneous <sup>b</sup>	6 (5.8%)	1 (7.7%)	5 (5.1%)	0.33
Overall	102	17 (16.7%)	85 (83.3%)	0.71

<sup>a</sup> Including one episodes of oxacillin-resistant *S. aureus*

<sup>b</sup> Miscellaneous: includes four episodes of *Chlamydomydia pneumoniae*, one episode of *Mycoplasma pneumonia* and one episode of *Nocardia asteroides*

**Table 3** Comparison of demographic and clinical characteristics among patients with CAP that received initial macrolide versus quinolones therapy in accordance with 2007 IDSA/ATS guidelines. Survivors vs. non-survivors

	Survivors (n = 137)	Non-survivors (n = 81)	P value
Age mean years (SD)	58.6 (16.1)	63.4 (16.7)	0.03
Male gender, n (%)	97 (71.3%)	52 (63.4%)	0.22
Mean SAPS II score (SD)	45.6 (15.5)	50.8 (17.5)	0.02
Mean SOFA score (SD)	7.4 (3.7)	8.3 (3.6)	0.16
Preexisting comorbid conditions			
COPD, n (%)	28 (20.6%)	12 (14.6%)	0.36
Diabetes, n (%)	17 (12.5%)	16 (19.5%)	0.17
Cardiomyopathy, n (%)	29 (21.3%)	24 (29.3%)	0.19
Cirrhosis, n (%)	5 (3.6%)	6 (7.4%)	0.33
Chronic renal failure, n (%)	8 (5.9%)	10 (12.2%)	0.08
Alcohol, n (%)	22 (16.2%)	10 (12.2%)	0.55
Bacteremia, n (%)	12 (12.4%)	8 (13.3%)	0.99
IDSA/ATS compliant, n (%)	63 (46.3%)	37 (45.1%)	0.88
Macrolides, n (%)	34 (54.0%)	12 (32.4%)	0.05
Quinolones, n (%)	29 (46.0%)	25 (67.6%)	0.04

SAPS Simplified Acute Physiology Score, SOFA Sequential Organ Failure Assessment, ICU intensive care unit, COPD chronic obstructive pulmonary disease, IDSA Infectious Disease Society of America, ATS American Thoracic Society

were documented. Inadequate empirical therapy was documented in only 5% of the episodes.

#### ICU characteristics

Overall ICU mortality was 37.6% (n = 82). Early mortality (within the first 3 days) was observed in only ten (12.3%) patients. Non-survivors were older (58.4 SD 16.3 vs. 63.9 SD 16.2 years,  $P < 0.01$ ) and presented a significantly higher SAPS II score at admission (45.4 SD 15.5 vs. 51.3 SD 17.2,  $P < 0.01$ ) when compared to survivors. Differences in baseline characteristics between survivors and non-survivors are summarized in Table 3.

#### Empirical antimicrobial therapy

Monotherapy was given in 43 (19.7%) and combination therapy in 175 (80.3%) patients. Empirical antibiotic

treatment was in accordance with the 2007 IDSA/ATS guidelines in 100 (45.9%) patients. Combination was prescribed with macrolides in 46 patients and fluoroquinolones in 54 patients. Concerning distribution, in the macrolide group, the vast majority 41 (89.1%) of the patients received a third generation cephalosporin, 2 (4.3%) a fourth generation cephalosporin and 3 (6.5%) piperacilin/tazobactam. Meanwhile, 22 (40.7%) patients in the quinolone group received a third generation cephalosporin, 6 (11.1%) a fourth generation cephalosporin, 12 (22.2%) carbapenem and 14 (25.9%) piperacilin/tazobactam. The quinolones used are detailed in Table 4. The characteristics of patients treated with a macrolide or a quinolone are shown in Table 5.

Mortality in the ICU was significantly lower for subjects who received macrolides compared to patients who received quinolones (26.1% vs. 46.3%,  $P < 0.05$ ) (Fig. 1). When excluding ciprofloxacin, no significant differences were documented. Similar results were obtained with 30-day mortality. In 100 patients receiving

**Table 4** Quinolone-based regimens in accordance with the 2007 IDSA/ATS guidelines

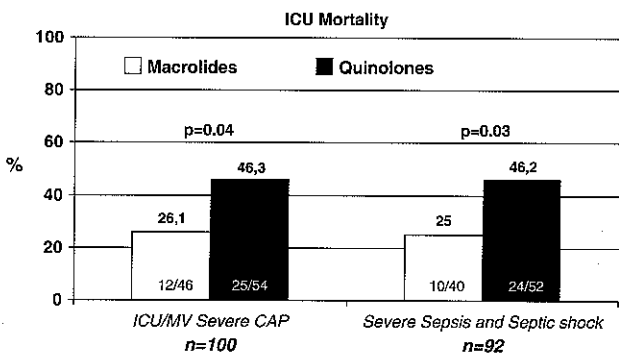
	Levofloxacin* (n = 28)	Ciprofloxacin (n = 18)	Moxifloxacin (n = 8)
No antipseudomonal $\beta$ -lactam	16 (29.6%)		1 (1.8%)
Antipseudomonal $\beta$ -lactam	12 (22.2%)	18 (33.3%)	7 (12.9%)

\* Fifteen (53.5%) patients received a dosage of levofloxacin >500 mg/day

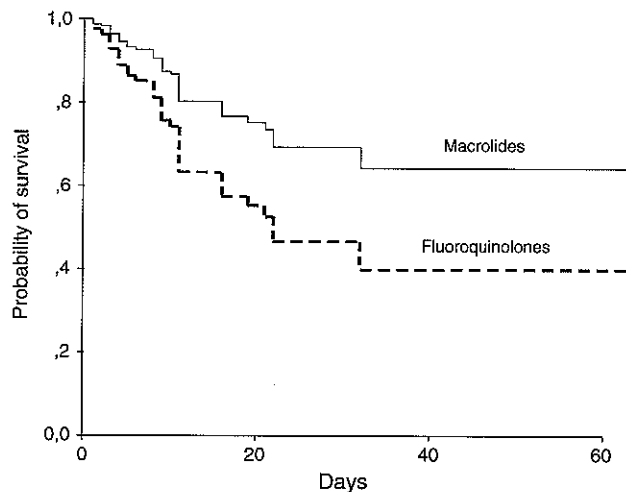
**Table 5** Comparison of demographic and clinical characteristics among 100 patients with CAP that received initial macrolide versus quinolones therapy in accordance with the 2007 IDSA/ATS guidelines

	Overall				Severe sepsis and septic shock			
	IDSA/ATS concordant (n = 100)	Macrolides (n = 46)	Quinolones (n = 54)	P value	IDSA/ATS concordant (n = 92)	Macrolides (n = 40)	Quinolones (n = 52)	P value
Age mean years (SD)	57.6 (16.2)	58.2 (16.4)	57.1 (16.2)	0.73	57.8 (16.1)	58.9 (16.3)	57.04 (16.1)	0.58
Male gender, n (%)	61 (61.0%)	25 (54.3%)	36 (66.7%)	0.22	58 (63.0%)	22 (55.0%)	36 (69.2%)	0.19
Mean SAPS II score (SD)	46.9 (15.6)	44.3 (15.5)	49.2 (15.5)	0.11	46.6 (15.6)	44.1 (16.1)	48.6 (15.2)	0.18
Mean SOFA score (SD)	7.68 (3.9)	7.18 (3.9)	8.14 (3.9)	0.26	7.85 (3.9)	7.33 (4.0)	8.29 (3.8)	0.29
Preexisting comorbid conditions								
COPD, n (%)	14 (14.0%)	7 (15.2%)	7 (13.0%)	0.77	14 (15.2%)	7 (17.5%)	7 (13.5%)	0.77
Diabetes, n (%)	18 (18.0%)	7 (15.2%)	11 (20.4%)	0.61	16 (17.4%)	6 (15.0%)	10 (19.2%)	0.78
Cardiomyopathy, n (%)	23 (23.0%)	10 (21.7%)	13 (24.1%)	0.81	22 (23.9%)	9 (22.5%)	13 (25.0%)	0.81
Chronic renal failure, n (%)	11 (11.0%)	3 (6.5%)	8 (14.8%)	0.21	11 (12.0%)	3 (7.5%)	8 (15.4%)	0.33
Alcohol, n (%)	14 (14.0%)	4 (8.7%)	10 (18.5%)	0.24	13 (14.1%)	4 (10.0%)	9 (17.3%)	0.37
Bacteremia, n (%)	10 (10.0%)	6 (13.0%)	4 (7.4%)	0.73	9 (12.7%)	5 (14.7%)	4 (10.8%)	0.73

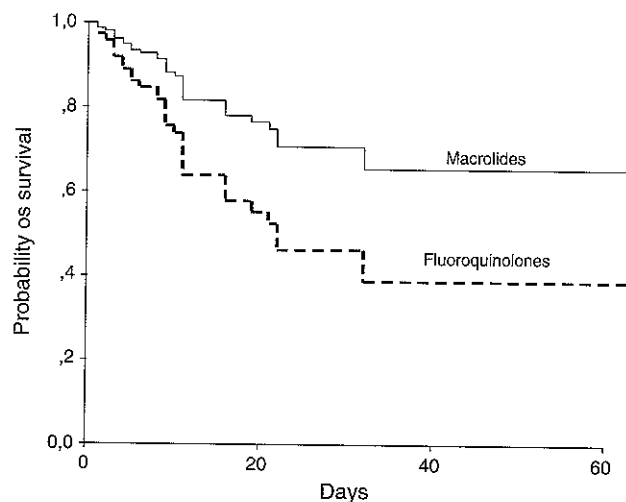
SAPS Simplified Acute Physiology Score, SOFA Sequential Organ Failure Assessment, ICU intensive care unit, COPD chronic obstructive pulmonary disease, IDSA Infectious Disease Society of America, ATS American Thoracic Society

**Fig. 1** Intensive care unit mortality among IDSA/ATS guideline-adherent patients according to the treatment in combination with a macrolide or a quinolone

combination therapy in accordance with 2007 IDSA/ATS guidelines, a Cox regression analysis adjusted by etiology and severity identified that using a macrolide was associated with lower ICU mortality (HR 0.48, 95% CI 0.23–0.97,  $P = 0.04$ ) when compared to quinolone use (Fig. 2). When the model was adjusted for etiology, the use of macrolides remained associated with lower mortality. Moreover, when patients presenting severe sepsis/septic shock due to CAP were analyzed ( $n = 92$ ), a similar protective survival effect was observed in the

**Fig. 2** Survival graph for patients treated in accordance with IDSA/ATS guideline in combination with a macrolide or a quinolone (censored at 60 days)

macrolide combination therapy group (HR 0.44, 95% CI 0.20–0.95,  $P = 0.03$ ) (Fig. 3). The numbers were too small to allow for analysis of the administration of macrolides in patients with sepsis.



**Fig. 3** Survival graph for severe sepsis/septic shock patients treated in accordance with IDSA/ATS guideline in combination with a macrolide or a quinolone (censored at 60 days)

## Discussion

This analysis of a large cohort, prospective, multicenter research study of critically ill patients requiring mechanical ventilation for severe CAP confirms that treatment with macrolide in combination therapy according to the 2007 IDSA/ATS guidelines improves survival when compared to fluoroquinolones. Moreover, the protective effect of macrolide therapy was more pronounced when the more severe end of the spectrum of CAP patients was selected. Another important finding was the low adherence to the 2007 IDSA/ATS guidelines in severely ill patients with CAP in the ICU setting. Moreover no differences in mortality rates were found; however, this was in accordance with other studies [17].

For the majority of patients with CAP who are hospitalized and not severely ill, fluoroquinolone monotherapy remains an approved, tested and reliable option [18, 19]. The 2007 IDSA/ATS guidelines showed that, in patients admitted to the ICU, fluoroquinolones represented a better option with a strong recommendation [5], even though recently a potential benefit associated with the use of macrolides in combination has been suggested. Despite the benefit showed by macrolides when administered in combination [4, 20–22], this is the first study that evaluates the survival when considering either macrolides or quinolones in accordance with the 2007 IDSA/ATS guidelines. In the subset of more severely ill patients, it has been published that macrolide represents a better choice. Restrepo et al. [6] reported that the use of macrolides in combination therapy improved outcomes in patients with severe sepsis due to CAP. Moreover, in a large cohort of patients affected with CAP, Tessmer et al. [23] showed a superior effect of  $\beta$ -lactam therapy plus a macrolide in patients in the risk classes

with high confusion, respiratory rate, blood pressure and age over 65 years (CRB-65).

Combining antibiotics that act by different mechanisms may achieve synergistic killing, and expand the antimicrobial spectrum, but macrolides when given in combination achieve an antiinflammatory effect in patients with CAP that exceeds just their antibacterial effect [24]. On the other hand, combination therapies may increase costs and toxicities, although macrolides have been used since their discovery in the 1950s with very rare complications and low cost, with the potential benefit supported by many studies in terms of survival.

In addition to their antiinfective properties, macrolides possess immunomodulatory effects by inhibiting neutrophil oxidation bursts, decreasing elastase activity, suppressing granulocyte macrophage-colony stimulating factor, and reducing or blocking the production of many proinflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8 and tumor necrosis factor- $\alpha$  [25], perhaps by suppressing the transcription factor nuclear factor- $\kappa$ B or activator protein-1. Moreover, favorable pharmacokinetics and pharmacodynamics, high concentrations at sites of infections and additional properties of macrolides may enhance their efficacy [26].

Interestingly, new strategies for reducing mortality have been developed over the last years with controversial results, including the use of glucocorticoid or other anti-inflammatory agents [27]. However, the benefits for the more aggressive forms of CAP are consistent, and higher when a macrolide is given with another atypical agent than if the other atypical agent is given alone, suggesting a non-antibacterial benefit that is cheaper and has fewer secondary effects.

This study has several strengths. Data were generated from a multi-institutional study and represent an interesting sampling from different European ICUs. Our study enrolled patients prospectively and represents a homogeneous population from critical care and mechanically ventilated patients. In addition, our study differs significantly from others because it emphasized the low adherence to IDSA/ATS guidelines in European ICUs. The original approach to our study was to confirm the best regimen in patients who were under guideline-adherent treatment, showing the superiority of one regimen (macrolides) over the other (quinolones). A table has been added to emphasize differences among studies (Table 6) [4, 6, 18–21, 28–31].

The present study has several potential limitations that should be addressed. First, this is an observational, non-interventional study. Prescription of antibiotics was chosen in accordance with the protocol agreed by the institution; however, the administration of either macrolides or quinolones was comparable (46% vs. 54%). Also the use of adjuvant therapies was left to the discretion of the attending physician and was not standardized. Secondly, the pneumonia severity index

**Table 6** Published studies assessing combination therapy and macrolide administration in combination in adult patients hospitalized with CAP

First author	Cohort	Site	Outcome	Country	Study design
Gleason [29]	Elderly patients ( $\geq 65$ years) with CAP	Ward	Lower 30-day mortality with $\beta$ -lactam plus macrolide	USA	Multicentre retrospective
Waterer [22]	Pneumococcal bacteremia	Ward	Lower hospital mortality with combination	USA	Multicentre retrospective
Brown [28]	CAP	Ward	Lower 30-day mortality with $\beta$ -lactam plus macrolide	USA	Multicentre retrospective
Martinez [21]	Pneumococcal bacteremia	Ward	Lower in-hospital mortality with $\beta$ -lactam plus macrolide	Spain	Monocentre retrospective
Baddour [20]	Pneumococcal bacteremia	Ward and ICU	Lower 14-day mortality with combination	International	Multicentre prospective
Rodriguez [4]	CAP	ICU	Lower 28-day mortality with combination	Spain	Multicentre prospective
Mortensen [31]	CAP	Ward and ICU	Lower 30-day mortality with $\beta$ -lactam plus other than FQ	USA	Multicentre retrospective
Metersky [30]	Pneumococcal bacteremia	Ward	Lower 30-day mortality with $\beta$ -lactam plus macrolide	USA	Multicentre retrospective
Restrepo [6]	Severe sepsis pneumonia	Ward and ICU	Lower 30- and 90-day mortality with combination plus macrolide	USA	Multicentre retrospective
Tessmer [23]	CAP	Ward	Lower 14- and 30-day mortality with $\beta$ -lactam plus macrolide	Germany	Multicentre prospective
Martín-Loeches	Intubated CAP	ICU	Lower ICU mortality IDSA/ATS combination with macrolide	Europe	Multicentre prospective

(PSI) and/or confusion, urea, respiratory rate, blood pressure and age over 65 years (CURB-65)/CRB-65 scores were not used in determining severity since these tools have limitations in identifying all patients with severe CAP who require ICU admission [32]. The PSI fairly correlates with a person's subsequent risk for either severe sepsis or septic shock from CAP [33]. The 2007 ATS/IDSA CAP guidelines recognize the deficiencies of PSI and other previously published criteria for severe CAP, and suggest an alternative risk stratification tool, although this too needs prospective validation [34]. Clinicians must understand the limitations of the PSI and recognize that other factors are at play when deciding who requires ICU admission for CAP. Thirdly, although the sample size was relatively small, mortality differences were very important, and the study power was around 95%. Finally, dosing was considered in agreement with the 2007 IDSA/ATS guidelines to define the appropriateness of empirical treatment. It is crucial to note that underdosing is a common problem in patients with severe sepsis, mechanical ventilation with a high volume of distribution and low albuminemia, and represents an important challenge in managing critically ill patients [35–37].

In conclusion, this study suggests that macrolides used in accordance with the 2007 IDSA/ATS guidelines may improve survival when compared with fluoroquinolones. Whereas a randomized controlled trial (RCT) would be preferable, only a minority of patients with a PSI above 90 are enrolled in RCTs [38], making it unlikely to have this study available in the future.

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**Conflict of interest statement** The authors declare no conflict of interest regarding this manuscript.

## Appendix

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