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EDITORIAL

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Are macrolides now obligatory in severe community-acquired pneumonia?

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In this issue of Intensive Care Medicine, Martin-Loeches and colleagues [1] present an analysis of a cohort of 218 patients with community-acquired pneumonia requiring mechanical ventilation enrolled into a larger, observational, multi-center European study. The major finding of the study in this issue was that the 42 patients who received a macrolide antibiotic had half the mortality rate of other patients after adjusting for severity of illness at presentation.

That macrolide antibiotics appear to confer a significant survival advantage in patients with severe community-acquired pneumonia is not a new concept, with multiple observational and retrospective studies demonstrating substantial mortality benefits [2–7]. However, as has been pointed out in many editorials and reviews, none of these studies are prospective, randomized controlled trials. In the absence of scientifically irrefutable evidence, at what point does the weight of data in favor of using macrolides become so overwhelming that their use is obligatory?

If we look at the potential downsides of making macrolides obligatory, then there is an obvious economic cost if they are not needed. However, relative to most costs in health care, the economic burden is trivial. Unnecessary macrolide use could perceivably contribute to increased antibiotic resistance to this class of antibiotics in the community, but the reality is that patients hospitalized with community-acquired pneumonia account for a minute portion of total antibiotic use, and this is not a sustainable argument given the already widespread use of this class of agents in the outpatient setting for upper and lower respiratory tract infections. Overuse of macrolides, like any antibiotic, could theoretically lead to selection for multi-resistant pathogens. However, the risk of this seems to be smaller than for broad-spectrum beta-lactams, third-generation cephalosporins and fluroquinolones, which all have well-documented track records of this adverse side effect. As with all antibiotics, drug reactions can occur, but macrolides are generally a very safe class of antibiotics. An increased incidence of arrhythmias has been reported with macrolides because of prolongation of the Q-T interval, but overall the risk is no greater than that associated with fluroquinolones [8].

If there is no major downside to adding a macrolide, the next question is whether these are the best agents or whether other antibiotics or antibiotic combinations have an equivalent or greater beneficial effect. One of the proposed (and I think the least likely) potential explanations for the benefit of macrolides is covering unrecognized 'atypical' pathogens (such as *Legionella spp.* or *Mycoplasma*). If this were the mechanism, then there should be equivalent benefit from fluroquinolones and tetracyclines. However, just as previous observational studies have shown [9, 10], the current study by Martin-Loeches and colleagues [1] also clearly demonstrates that fluroquinolones do not give the same apparent protective effect as macrolides. Although much more limited, there are also some data suggesting that tetracyclines are also not as efficacious as macrolides [10].

That the benefit of macrolides is almost certainly not driven by undiagnosed atypical pathogens invalidates the

argument that physicians do not need to use them if they have a low prevalence of atypical pathogens in their region. There is substantive evidence for macrolides having an immunomodulating effect on the host immune response [11], and this may be a key factor in their apparent clinical benefit. However, the recent demonstration that most patients with community-acquired pneumonia and sepsis-related organ dysfunction have high systemic pneumococcal bacterial loads [12] suggests to me that the now well-recognized anti-toxin effects of macrolides, even in macrolide-resistant organisms [13], also play a key role. Importantly, neither fluroquinolones nor tetracyclines were observed to have anti-pneumolysin effects in pneumococci [13].

Clearly not all patients admitted to hospital with community-acquired pneumonia will die with or without a macrolide, so can we select those who will benefit? The research group reporting in this journal had previously suggested that the most benefit may be for patients with shock [6]; however, their current analysis clearly extends the indication to patients requiring mechanical ventilation [1]. Unfortunately, while it is straight forward if patients require inotropic support or mechanical ventilation at the time of presentation, our ability to predict patients who will deteriorate over the first 24 h after admission remains more limited. As the proposed mechanisms by which macrolides improve outcome may clearly be more effective prior to significant organ failure being established, it would seem prudent to give a macrolide to any patient with significant physiological compromise. Better predictive tools, such as quantitative systemic bacterial load [12], may help improve the selection of at-risk patients in the future.

Given the overwhelming weight of data, I believe that macrolides should be obligatory in all cases of severe community-acquired pneumonia. With odds ratios for death ranging from two to six times greater in non-macrolide-treated patients [1, 3, 4, 7], and given the low risk and cost of such treatment, refusal to do so out of scepticism of the data is unjustifiable. We would all like the definitive prospective trial, but that is unlikely to occur for financial, logistic and even ethical reasons. Hopefully, the growing animal [14, 15] and human data [16] suggesting macrolides are of benefit in sepsis due to many causes other than community-acquired pneumonia will be extended into prospective randomized, controlled trials, and then the issue of not having this data in community-acquired pneumonia will become moot.

References

1. Martin-Loeches I, Lisboa T, Rodriguez A, Putensen C, Annane D, Restrepo MI, Garnacho-Montero J, Rello J (2009) Combination antibiotic therapy with macrolides improves survival in patients with severe community-acquired pneumonia. Intensive Care Med. doi: 10.1007/s00134-009-1730-y
2. Mufson MA, Stanek RJ (1999) Bacteremic pneumococcal pneumonia in one American city: a 20-year longitudinal study, 1978–1997. Am J Med 107:34S–43S
3. Waterer GW, Somes GW, Wunderink RG (2001) Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 161:1837–1842
4. Baddour LM, Yu VL, Klugman KP, Feldman C, Ortqvist A, Rello J, Morris AJ, Luna CM, Snydman DR, Ko WC, Chedid MB, Hui DS, Andremont A, Chiou CC (2004) Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am J Respir Crit Care Med 170:440–444
5. Martinez JA, Horcajada JP, Almela M, Marco F, Soriano A, Garcia E, Marco MA, Torres A, Mensa J (2003) Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 36:389–395
6. Rodriguez A, Mendia A, Sirvent JM, Barcenilla F, de la Torre-Prados MV, Sole-Violan J, Rello J (2007) Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. Crit Care Med 35:1493–1498
7. Restrepo MI, Mortensen EM, Waterer GW, Wunderink RG, Coalson JJ, Anzueto A (2009) Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia. Eur Respir J 33:153–159
8. Zambon A, Polo Friz H, Contiero P, Corrao G (2009) Effect of macrolide and fluoroquinolone antibacterials on the risk of ventricular arrhythmia and cardiac arrest: an observational study in Italy using case-control, case-crossover and case-time-control designs. Drug Saf 32:159–167
9. Mortensen EM RM, Anzueto A, Pugh J (2006) The impact of empiric antimicrobial therapy with a beta-lactam and fluroquinolone on mortality for patients with severe pneumonia. Crit Care
10. Metersky ML, Ma A, Houck PM, Bratzler DW (2007) Antibiotics for bacteremic pneumonia: improved outcomes with macrolides but not fluoroquinolones. Chest 131:466–473
11. Parnham MJ (2005) Immunomodulatory effects of antimicrobials in the therapy of respiratory tract infections. Curr Opin Infect Dis 18:125–131
12. Rello J, Lisboa T, Lujan M, Gallego M, Kee C, Pryce TM, Waterer GW (2009) Adverse clinical outcomes from pneumococcal pneumonia are predicted by quantitative bacterial load in blood at presentation to the emergency department. Chest in press
13. Anderson R, Steel HC, Cockeran R, von Gottberg A, de Gouveia L, Klugman KP, Mitchell TJ, Feldman C (2007) Comparison of the effects of macrolides, amoxicillin, ceftriaxone, doxycycline, tobramycin and fluoroquinolones, on the production of pneumolysin by Streptococcus pneumoniae in vitro. J Antimicrob Chemother 60:1155–1158

14. Giamarellos-Bourboulis EJ, Baziaka F, Antonopoulou A, Koutoukas P, Kousoulas V, Sabracos L, Panagou C, Perrea D, Giamarellou H (2005) Clarithromycin co-administered with amikacin attenuates systemic inflammation in experimental sepsis with Escherichia coli. Int J Antimicrob Agents 25:168–172

15. Cirioni O, Ghiselli R, Silvestri C, Kamysz W, Orlando F, Riva A, Kamysz E, Castelletti S, Rocchi M, Saba V, Scalise G, Giacometti A (2008) Efficacy of the combination of tachyplesin III and clarithromycin in rat models of *Escherichia coli* sepsis. Antimicrob Agents Chemother 52:4351–4355

16. Giamarellos-Bourboulis EJ, Pechere JC, Routsi C, Plachouras D, Kollias S, Raftogiannis M, Zervakis D, Baziaka F, Koronaios A, Antonopoulou A, Markaki V, Koutoukas P, Papadomichelakis E, Tsaganos T, Armaganidis A, Koussoulas V, Kotanidou A, Roussos C, Giamarellou H (2008) Effect of clarithromycin in patients with sepsis and ventilator-associated pneumonia. Clin Infect Dis 46:1157–1164

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ORIGINAL

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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 ± 16.1 vs. 63.4 ± 16.7 years, $P < 0.05$) and presented a higher score on the simplified Acute Physiology Score II at admission (45.6 ± 15.4 vs. 50.8 ± 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 β-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 β-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 asses 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 administrated (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 azithromicin or clarithromicin. 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 χ-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
S. pneumoniae	33 (32.3%)	2 (5.9%)	31 (16.8%)	0.12
S. aureus	24 (23.5%)[a]	5 (11.8%)[a]	19 (10.3%)	0.76
H. influenza/M. catarrhalis	12 (11.7%)	5 (11.8%)	7 (3.8%)	0.73
P. aeruginosa	11 (10.8%)	2 (5.9%)	9 (4.9%)	0.68
Enterobacteriacea	13 (12.7%)	2 (5.9%)	11 (6.0%)	0.99
L. pneumophila	3 (2.9%)	–	3 (1.6%)	1
Miscellaneous[b]	6 (5.8%)	1 (7.7%)	5 (5.1%)	0.33
Overall	102	17 (16.7%)	85 (83.3%)	0.71

[a] Including one episodes of oxacillin-resistant *S. aureus*

[b] Miscellaneous: includes four episodes of *Chlamydophila 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.%)	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 β-lactam	16 (29.6%)		1 (1.8%)
Antipseudomonal β-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

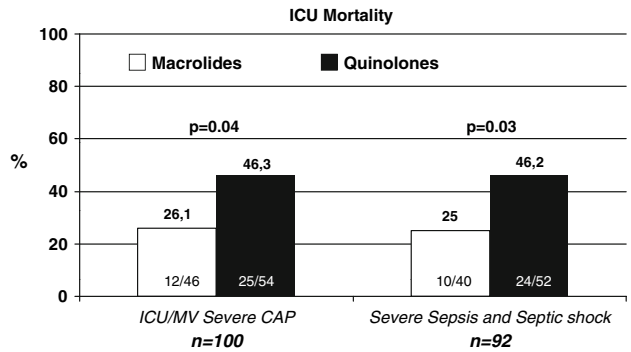

Fig. 1 Intensive care unit mortality among IDSA/ATS guideline-adherent patients according to the treatment in combination with a macrolide or a quinolone

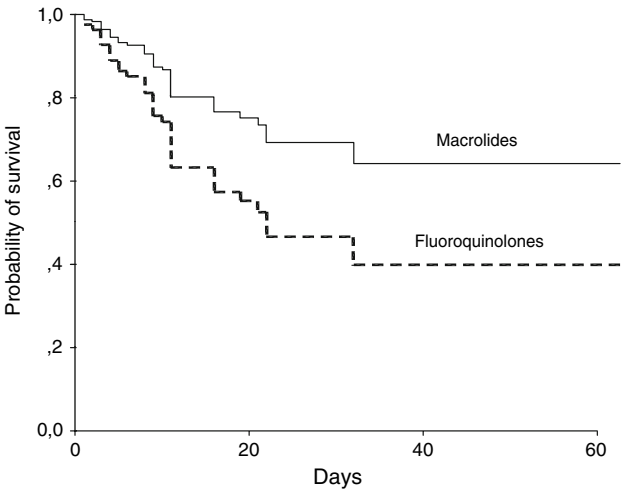

Fig. 2 Survival graph for patients treated in accordance with IDSA/ATS guideline in combination with a macrolide or a quinolone (censored at 60 days)

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 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.

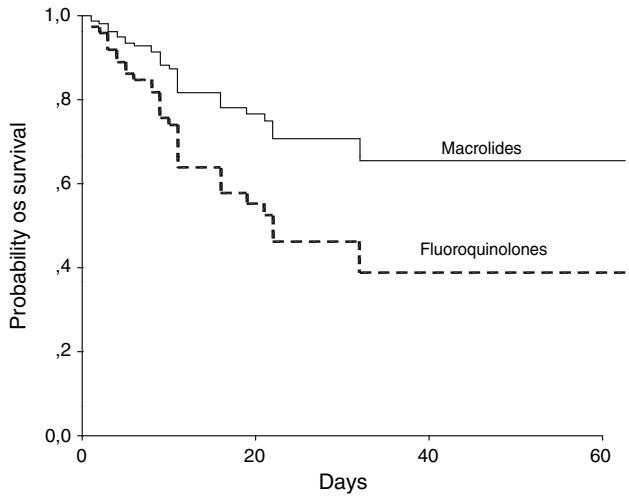

Fig. 3 Survival graph for severe sepsis/septic shock patients treated in accordance with IDSA/ATS guideline in combination with a macrolide or a quinolone (censored at 60 days)

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 β-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 simulating 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 (TNF-α) [25], perhaps by suppressing the transcription factor nuclear factor-κB 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 (≥65 years) with CAP	Ward	Lower 30-day mortality with β-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 β-lactam plus macrolide	USA	Multicentre retrospective
Martinez [21]	Pneumococcal bacteremia	Ward	Lower in-hospital mortality with β-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 β-lactam plus other than FQ	USA	Multicentre retrospective
Metersky [30]	Pneumococcal bacteremia	Ward	Lower 30-day mortality with β-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 β-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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References

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 29:1303–1310
2. Bodi M, Rodriguez A, Sole-Violan J, Gilavert MC, Garnacho J, Blanquer J, Jimenez J, de la Torre MV, Sirvent JM, Almirall J, Doblas A, Badia JR, Garcia F, Mendia A, Jorda R, Bobillo F, Valles J, Broch MJ, Carrasco N, Herranz MA, Rello J (2005) Antibiotic prescription for community-acquired pneumonia in the intensive care unit: impact of adherence to Infectious Diseases Society of America guidelines on survival. Clin Infect Dis 41:1709–1716
3. Shorr AF, Bodi M, Rodriguez A, Sole-Violan J, Garnacho-Montero J, Rello J, for the CAPUCI Study Investigators (2006) Impact of antibiotic guideline compliance on duration of mechanical ventilation in critically ill patients with community-acquired pneumonia. Chest 130:93–100
4. Rodríguez A, Mendia A, Sirvent JM, Barcenilla F, de la Torre-Prados MV, Solé-Violán J, Rello J, CAPUCI Study Group (2007) Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. Crit Care Med 35:1493–1498
5. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, Torres A, Whitney CG (2007) Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/ American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 44(Suppl 2):S27–S72
6. Restrepo MI, Mortensen EM, Waterer GW, Wunderink RG, Coalson JJ, Anzueto A (2009) Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia. Eur Respir J 33:153–159
7. Giamarellos-Bourboulis EJ, Adamis T, Laoutaris G, Sabracos L, Koussoulas V, Mouktaroudi M, Perrea D, Karayannacos PE, Giamarellou H (2004) Immunomodulatory clarithromycin treatment of experimental sepsis and acute pyelonephritis caused by multidrug-resistant *pseudomonas aeruginosa*. Antimicrob Agents Chemother 48:93–99
8. Garcia Vazquez E, Mensa J, Martinez JA, Marcos MA, Puig J, Ortega M, Torres A (2005) Lower mortality among patients with community-acquired pneumonia treated with a macrolide plus a beta-lactam agent versus a beta-lactam agent alone. Eur J Clin Microbiol Infect Dis 24:190–195
9. Houck PM, MacLehose RF, Niederman MS, Lowery JK (2001) Empiric antibiotic therapy and mortality among medicare pneumonia inpatients in ten western states: 1993, 1995, and 1997. Chest 119:1420–1426
10. Mortensen EM, Restrepo M, Anzueto A, Pugh J (2004) Effects of guideline-concordant antimicrobial therapy on mortality among patients with community-acquired pneumonia. Am J Med 117:726–731
11. Koulenti D, Lisboa T, Brun-Buisson C, Krueger W, Macor A, Sole-Violan J, Diaz E, Topeli A, DeWaele J, Carneiro A, Martin-Loeches I, Armaganidis A, Rello J (2009) The spectrum of practice in the diagnosis of nosocomial pneumonia in patients requiring mechanical ventilation in European ICUs. Crit Care Med 37:2360–2368
12. de Castro FR, Torres A (2003) Optimizing treatment outcomes in severe community-acquired pneumonia. Am J Respir Med 2:39–54
13. Rello J, Bodi M, Mariscal D, Navarro M, Diaz E, Gallego M, Valles J (2003) Microbiological testing and outcome of patients with severe community-acquired pneumonia. Chest 123:174–180
14. Bartlett JG, Dowell SF, Mandell LA, File TM Jr, Musher DM, Fine MJ (2000) Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Diseases Society of America. Clin Infect Dis 31:347–382
15. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G (2003) 2001 SCCM/ESICM/ACCP/ ATS/SIS.CCM/ESICM/ACCP/ATS/ SIS International Sepsis Definitions Conference. Crit Care Med 31:1250-1256
16. Bone RC (1996) Why sepsis trials fail. JAMA 276:565–566
17. Dambrava PG, Torres A, Vallès X, Mensa J, Marcos MA, Peñarroja G, Camps M, Estruch R, Sánchez M, Menéndez R, Niederman MS (2008) Adherence to guidelines' empirical antibiotic recommendations and community-acquired pneumonia outcome. Eur Respir J 32:892–901
18. Weiss K, Low DE, Cortes L, Beaupre A, Gauthier R, Gregoire P, Legare M, Nepveu F, Thibert D, Tremblay C, Tremblay J (2004) Clinical characteristics at initial presentation and impact of dual therapy on the outcome of bacteremic *Streptococcus pneumoniae* pneumonia in adults. Can Respir J 11:589–593

19. Sollet JP (2006) Respiratory tract infections: at-risk patients, who are they? Implications for their management with levofloxacin. Int J Antimicrob Agents 28 Suppl 2:S113–S114
20. Baddour LM, Yu VL, Klugman KP, Feldman C, Ortkvist A, Rello J, Morris AJ, Luna CM, Snydman DR, Ko WC, Chedid BF, Hui DS, Andremont A, Chiou CCC, the International Pneumococcal Study Group (2004) Combination antibiotic therapy may lower mortality in severely ill patients with *Streptococcus pneumoniae* bacteremia. Am J Respir Crit Care Med 170:400–404
21. Martinez JA, Horcajada JP, Almela M, Marco F, Soriano A, Garcia E, Marco MA, Torres A, Mensa J (2003) Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 36:389–395
22. Waterer GW, Somes GW, Wunderink RG (2001) Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 161:1837–1842
23. Tessmer A, Welte T, Martus P, Schnoor M, Marre R, Suttorp N (2009) Impact of intravenous β-lactam/macrolide versus β-lactam monotherapy on mortality in hospitalized patients with community-acquired pneumonia. J Antimicrob Chemother 63:1025–1033
24. Tamaoki J, Kadota J, Takizawa H (2004) Clinical implications of the immunomodulatory effects of macrolides. Am J Med 117(Suppl 9A):5S–11S
25. Healy DP (2007) Macrolide immunomodulation of chronic respiratory diseases. Curr Infect Dis Rep 9:7–13
26. Vanaudenaerde BM, Wuyts WA, Geudens N, Dupont LJ, Schoofs K, Smeets S, Van Raemdonck DE, Verleden GM (2007) Macrolides inhibit IL17-induced IL8 and 8-isoprostane release from human airway smooth muscle cells. Am J Transplant 7:76–82
27. Wunderink RG (2009) Adjunctive therapy in community-acquired pneumonia. Semin Respir Crit Care Med 30:146–153
28. Brown RB, Iannini P, Gross P, Kunkel M (2003) Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: análisis of a hospital claims-made database. Chest 123:1503–1511
29. Gleason PP, Meehan TP, Fine JM, Galusha DH, Fine MJ (1999) Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. Arch Intern Med 159:2562–2572
30. Metersky ML, Ma A, Houck PM, Bratzler DW (2007) Antibiotics for bacteremic pneumonia: improved outcomes with macrolides but not fluoroquinolones. Chest 131:466–473
31. Mortensen EM, Restrepo MI, Anzueto A, Pugh J (2006) The impact of empiric antimicrobial therapy with a β-lactam and fluoroquinolone on mortality for patients hospitalized with severe pneumonia. Crit Care 10:R8
32. Capelastegui A, Espana PP, Quintana JM, Areitio I, Gorordo I, Egurrola M, Bilbao A (2006) Validation of a predictive rule for the management of community-acquired pneumonia. Eur Respir J 27:151–157
33. Dremsizov T, Clermont G, Kellum JA, Kalassian KG, Fine MJ, Angus DC (2006) Severe sepsis in community-acquired pneumonia: when does it happen, and do systemic inflammatory response syndrome criteria help predict course? Chest 129:968–978
34. Shorr AF, Wunderink R (2008) There is no "CAP" on the importance of community acquired pneumonia in the ICU. Chest 133:590–592
35. Roberts JA, Lipman J (2006) Antibacterial dosing in intensive care: pharmacokinetics, degree of disease, and pharmacodynamics of sepsis. Clin Pharmacokinet 45:755–773
36. Pea F, Viale P (2009) Bench-to-bedside review: appropriate antibiotic therapy in severe sepsis and septic shock—does the dose matter? Crit Care 13:214
37. Roberts JA, Lipman J, Blot S, Rello J (2008) Better outcomes through continuous infusion of time-dependent antibiotics to critically ill patients? Curr Opin Crit Care 14:390–396
38. Murphy TF (2008) Placebo-controlled trials of treatments for community acquired pneumonia: review of the literature and discussion of feasibility and potential value. Clin Infect Dis 47:S145–S149