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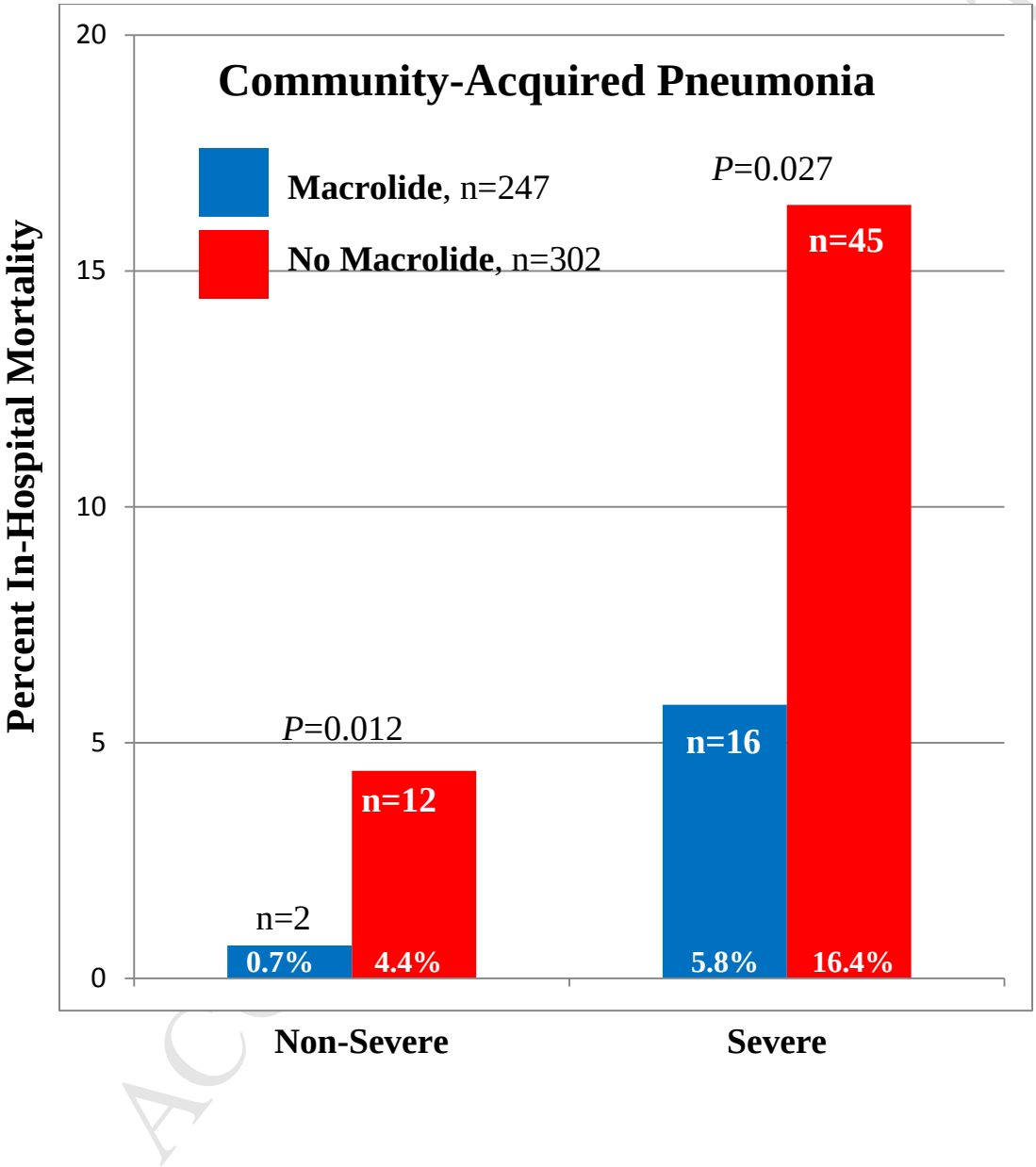
Graphical Abstract

Comparison of mortality difference among patients who had community-acquired pneumonia and bacteremia with and without a macrolide



Macrolide Therapy is Associated with Lower Mortality in Community-Acquired Bacteraemic Pneumonia

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Key Words

Community-acquired pneumonia, mortality, bacteremia, antimicrobial treatment

Take home message:

In patients with bacteremic CAP, an antimicrobial regimen including a macrolide was associated with lower mortality.

Abbreviation List

CAP – community-acquired pneumonia

CAPO – Community-Acquired Pneumonia Organization

CI – confidence interval

HIV – human immunodeficiency virus

IQR – interquartile ratio

OR – odds ratio

PSI – pneumonia severity index

RCT – randomized control trial

RR – relative risk

SD – standard deviation

Abstract

Background: Community-acquired pneumonia (CAP) has a potential complication of bacteremia. The objective of this study was to define the clinical outcomes of patients with CAP and bacteremia treated with and without a macrolide.

Materials and Methods: Secondary analysis of the Community-Acquired Pneumonia Organization database of hospitalized patients with CAP. Patients with a positive blood culture were categorized based on the presence or absence of a macrolide in their initial antimicrobial regimen, and severity of their CAP. Outcomes included in-hospital all-cause mortality, 30-day mortality, length of stay, and time to clinical stability.

Results: Among 549 patients with CAP and bacteremia, 247 (45%) were treated with a macrolide and 302 (55%) were not. The primary pathogen was *Streptococcus pneumoniae* (74%). Poisson regression with robust error variance models were used to compare the adjusted effects of each study group on the outcomes. The unadjusted 30-day mortality was 18.4% in the macrolide group, and 29.6% in the non-macrolide group (adjusted relative risk (aRR)0.81; 95% confidence interval (CI)0.50-1.33; *P*=0.41). Unadjusted in-hospital all-cause mortality was 7.3% in the macrolide group, and 18.9% in the non-macrolide group (aRR 0.54, 95% CI 0.30-0.98; *P*=0.043). Length of stay and time to clinical stability were not significantly different.

Conclusions: In-hosptial mortality, but not 30-day mortality, was significantly better in the macrolide group. Our data support the use of a macrolide in hospitalized patients with CAP and bacteraemia.

Introduction

Despite the introduction of antimicrobials and subsequent investment into the treatment of pneumonia, it is still the 8th leading cause of death in the world; and the number one cause of death due to an infectious disease.[1] Macrolides, combined with a β-lactam such as ceftriaxone, are recommended by the Infectious Diseases Society of America/American Thoracic Society guidelines for community-acquired pneumonia (CAP) for any patient admitted to a general medical ward with CAP. An equally recommended regimen is a respiratory fluoroquinolone alone. In ICU patients, a β-lactam may be combined with a macrolide or a fluoroquinolone. Both the macrolide and non-macrolide options cover typical (*e.g., Streptococcus pneumoniae)* and atypical (*e.g., Chlamydia pneumoniae, Legionella pneumophila,* and *Mycoplasma pneumoniae*) pathogens. Macrolides are known to have antibacterial as well as immunomodulatory properties. [2-4] This immunomodulation activity cannot be studied without the confounder of antibacterial properties because everyone with CAP receives an antimicrobial, but the combined immunomodulatory and antibacterial activity may still be studied by comparing those who received a macrolide to those who did not. The benefit of immunomodulation may be better recognized in patients with CAP complicated by bacteremia because the difference in outcomes is easier to appreciate among patients with more severe disease. The objective of this study was to define the clinical outcomes of patients with CAP and bacteremia treated with and without a macrolide.

Materials and Methods

Population and Study Design

This was a secondary analysis of the community-acquired pneumonia organization (CAPO) database from June 1, 2001 to November 29, 2013. The CAPO database includes hospitalized patients with CAP, and for this study represents data from 83 hospitals in 18 countries. Countries were categorized into world regions. The US and Canada were designated as region 1, Europe as region 2, and Central and South America as region 3. The procedure for collecting and validating data was previously described.[5] Each local internal review board approved the study, and patient consent was waived due to the retrospective and observational study design. Medical records were randomly selected among all patients diagnosed with CAP at each participating hospital. All patients with bacteremia were reviewed, but those with positive blood cultures with coagulase-negative *Staphylococcus*, *Enterococcus* spp. *Candida* spp, Salmonella and non-tuberculous mycobacteria were excluded. Patients with CAP due to *S. aureus* with unknown oxacillin sensitivity information were categorized as having Methicillin-sensitive *S. aureus*. Demographic information and antimicrobial treatment were collected.

Definitions

CAP was defined using data that were radiological (the presence of a new pulmonary infiltrate found on chest radiograph), plus clinical (new or increased cough, abnormal temperature (<35.6°C or >37.8°C), or abnormal and leukocyte count (leukocytosis, left shift, or leucopenia as defined by local laboratory values); as described previously.[5] Severity of disease was defined using the pneumonia severity index. Patients were included into the macrolide group if they received a macrolide antibiotic within the first 24 hours of their hospitalization. Patients considered to have non-severe disease had a pneumonia severity index risk class of I, II or III,

while patients with severe disease had a risk class of IV or V. In-hospital all-cause mortality was defined as the total mortality during the entire hospitalization. The 30-day mortality outcome was defined as death within 30 days of admission. Length of stay, in days, was calculated as the day of discharge minus the day of hospitalization. Patients who died during hospitalization were attributed 14 days for their length of stay outcome. Time to clinical stability was evaluated over the first seven days after admission. Criteria defining clinical stability were the 2001 ATS criteria for switch from intravenous to oral antibiotic therapy: 1) improvement in cough and shortness of breath; 2) afebrile status for ≥8 h (<37.8°C); 3) normalizing leukocyte count by at least 10% from the previous day; and 4) adequate oral intake.[6]

Statistics

Data were prepared as frequencies with proportions and means with standard deviations (SD) or medians with interquartile ranges (IQR). Bivariate analyses were applied to categorical variables, which were compared using χ^2 test or Fisher's Exact Test, while continuous variables were compared using the Student's t-test or the Mann-Whitney U-test. Unadjusted comparisons between study group with respect to length of stay and time to clinical stability were calculated using Kaplan Meier curves, and statistical significance was determined using the Log-Rank test. The PSI was modeled using a restricted cubic spline as it was not expected to linearly predict all outcomes.

To compare the adjusted effect of each study group on length of stay and time to clinical stability, accelerated failure time survival models were computed using lognormal distributions.

Adjusted survival plots were created from each model. To compare the adjusted effect of each study group on mortality, Poisson Regression models were used. Since the outcomes were binary and the assumptions for the Poisson models were not met, robust error variance estimators were applied to the results to correct the standard errors.[7] This approach allowed us to compute risk ratios (RR) and 95% confidence intervals (CI). The effect estimates were adjusted for need for ICU immediately upon admission, chronic obstructive pulmonary disease history, pneumonia severity index, and human immunodeficiency virus infection. These confounders were selected based on previous literature.[8] A *P* value of <0.05 was considered statistically significant. Statistical analyses were performed using R, version 3.2.2. (R foundation for statistical computing, Vienna, Austria).

Results

The total number of CAPO database patients reviewed was 7789. Among those, 5181 patients had blood cultures taken, of whom 549 patients were positive with a CAP-related pathogen; 247 (45%) in the macrolide group and 302 (55%) in the non-macrolide group. A patient with Salmonella bacteremia and another with a non-tuberculous mycobacterium bacteremia were excluded. Patient demographics are in Table 1.

Table 1

Demographics of patients with CAP treated with a macrolide or a non-macrolide antibiotic regimen.

Variable	Macrolide	No Macrolide	P-value
GENERAL			
Total (%)	247 (45)	302 (55)	
Age, Median (IQR*)	59 (30.0)	64.5 (35.8)	0.244
Sex, n (%)	141 (57)	180 (60)	0.602
ICU admission, n (%)	53 (21)	95 (31)	0.009
Nursing home resident, n (%)	9 (4)	23 (8)	0.066
Antibiotics in prior 30 days, n (%)	23 (9)	40 (13)	0.179
Pneumonia Severity Index, Median (IQR)	86 (46.5)	94.5 (49.8)	0.004
COMORBIDITIES			
Congestive Heart Failure, n (%)	43 (17)	42 (14)	0.286
COPD, n (%)	35 (14)	58 (19)	0.137
Diabetes, n (%)	45 (18)	55 (18)	>0.999
HIV, n (%)	31 (13)	61 (20)	0.021
Liver Disease, n (%)	20 (8)	30 (10)	0.551
Neoplastic Disease, n (%)	22 (9)	31 (10)	0.664
Pleural effusion, n (%)	68 (28)	97 (32)	0.262
Renal Disease, n (%)	27 (11)	39 (13)	0.511
VITAL SIGNS			
Temperature, Median °F (IQR)	100.9 (3.4)	100.4 (3.7)	0.218
Systolic blood pressure, Median mmHg (IQR)	116 (28.8)	119 (36)	0.655

Heart rate, Median beats/min (IQR)	110 (28)	110 (24.8)	0.457
Respiratory Rate, Median respirations/min (IQR)	24 (9)	24 (12)	0.372
Altered mental status on admission, n (%)	33 (14)	58 (19)	0.083
LABORATORY VALUES			
Blood Urea Nitrogen, Median mg/DL (IQR)	33 (39.9)	31 (34.2)	0.831
Hematocrit, Median % (IQR)	38 (6.5)	36.3 (9.3)	0.05
PaO2, Median mmHg (IQR)	63 (19.1)	61 (23.6)	0.453
pH, Median (IQR)	7.442 (0.06)	7.425 (0.12)	0.033
Serum glucose, Median mg/DL (IQR)	112 (40.5)	114 (47.5)	0.882
Serum sodium, Median mmol/L (IQR)	135 (7)	135 (7)	0.634

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IQR, interquartile range

* All IQRs are given as the difference between the 1st and 3rd quartiles.

The number of patients in each world region were: US/Canada 233 (42%) patients, Europe 175 (32%) patients and Central/South America 141 (26%) patients. The pathogens infecting patients included primarily *Streptococcus pneumoniae*, but also *Staphylococcus aureus* (Table 2).

Table 2

Pathogens identified in 549 patients with CAP.

Pathogen	**Macrolide (%)**	**No Macrolide (%)**
Streptococcus pneumoniae	184 (75)	219 (73)
Staphylococcus aureus	6 (2)	3 (<1)
MRSA	7 (3)	20 (7)
MSSA	13 (6)	15 (5)
Escherichia coli	5 (4)	15 (5)
Haemophilus influenzae	8 (4)	11 (4)
Pseudomonas aeruginosa	6 (2)	7 (2)
Moraxella catarrhalis	5 (2)	3 (<1)
Streptococcus pyogenes	2 (<1)	2 (<1)
Klebsiella pneumoniae	3 (1)	2 (<1)
Acinetobacter spp.	1 (<1)	2 (<1)
Proteus spp.	2 (<1)	0
Enterobacter spp.	0	(<1)

MRSA – Methicillin resistant *Staphylococcus aureus*, MSSA – Methicillin sensitive *Staphylococcus aureus*

The antimicrobial regimens prescribed to all the patients are in Table 3. The most common regimens were a β-lactam with or without a macrolide, and a fluoroquinolone with or without a

β-lactam. In the ICU, 89 of 148 (60%) patients received a β-lactam with or without a fluoroquinolone, while 42 of 148 (28%) received a β-lactam plus a macrolide.

Table 3

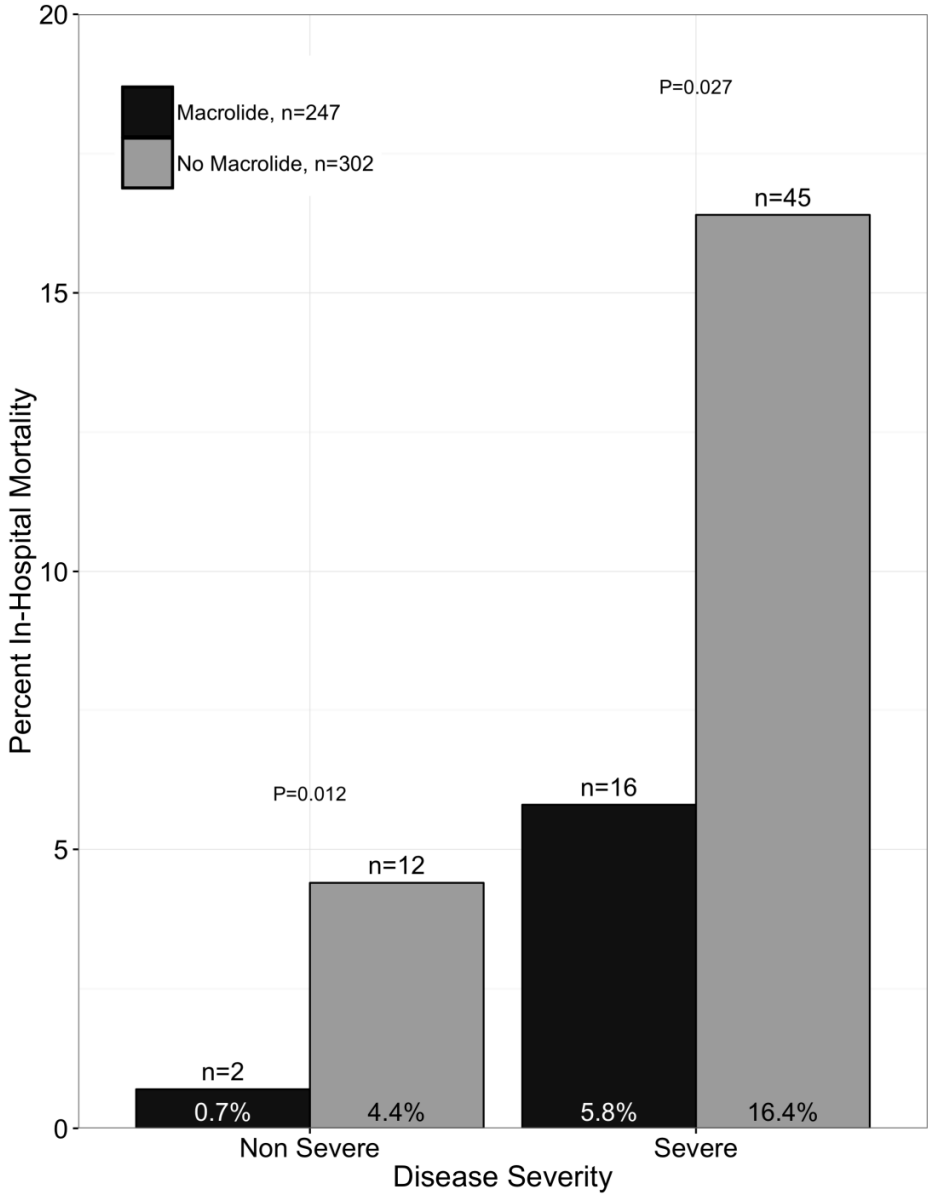
Antimicrobial regimen categories prescribed to patients with CAP.

Macrolide Containing Regimen	**No. (%)**	**Non-macrolide Containing Regimen**	**No. (%)**
β-lactam + Macrolide ± other*	220 (40)	β-lactam ± other*	145 (26)
Fluoroquinolone + β-lactam +Macrolide ± other*	1 (<1)	Fluoroquinolone ± other*	75 (14)
Fluoroquinolone + Macrolide ± other*	6 (1)	Fluoroquinolone + β-lactam ± other*	91 (17)
Macrolide ± other*	5 (<1)	Other*	4 (<1)

* Other excludes a β-lactam, a macrolide and a fluoroquinolone, and may or may not include one or more of the following: amikacin, atovaquone, clindamycin, colistimethate, gentamicin, metronidazole, oseltamivir, pentamidine, primaquine, rifampin, trimethoprim/sulfamethoxazole, tobramycin, and vancomycin.

In-hospital mortality for the macrolide group was 7.3%, and for the non-macrolide group was 18.9%; $P<0.001$. Data is presented for severe and non-severe patients (Figure 1). The adjusted risk of in-hospital mortality was 46% lower for patients with a macrolide compared to those without; RR 0.54, 95% CI 0.30-0.98; $P=0.043$. Those who received a macrolide had significantly decreased in-hospital mortality regardless of severity. There were fewer patients to evaluate for 30-day mortality than in-hospital mortality (432 patients instead of 549) because of missing data. The 30-day mortality for the macrolide group was 18.4%, and for the non-macrolide group was 29.6%; $P=0.011$. The adjusted risk of 30-day mortality was 19% lower for patients with a macrolide compared to those without; RR 0.81; 95% CI 0.50-1.33; $P=0.41$. The difference in length of stay and time to clinical stability is depicted in Figures 2 and 3, respectively. Although the length of stay was two days shorter in the macrolide group and the time to clinical stability was 0.7 days shorter, the differences were not significantly different.

287 **Figure 1**



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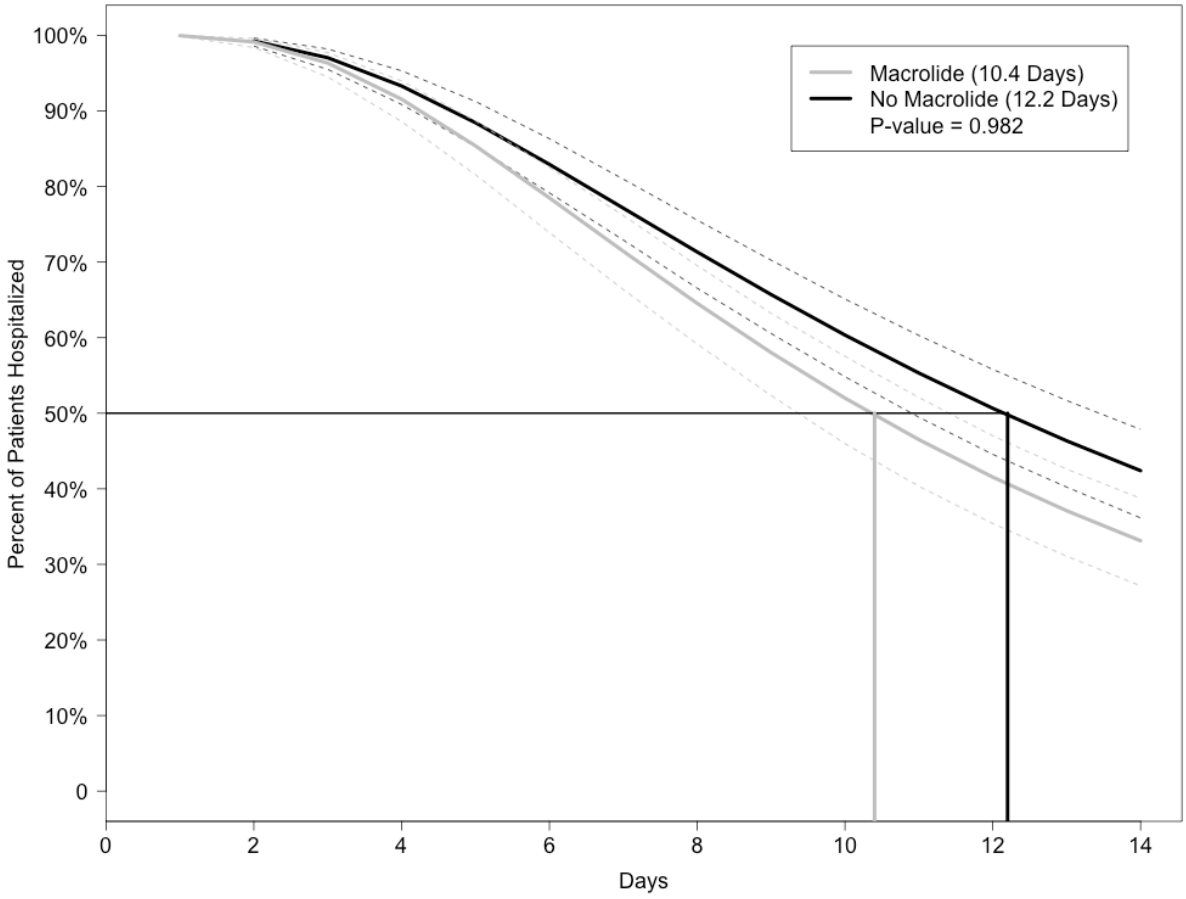
289 **Figure 1** In hospital mortality for severe and non-severe community-acquired pneumonia

290 patients treated with and without a macrolide.

291

292 **Figure 2**



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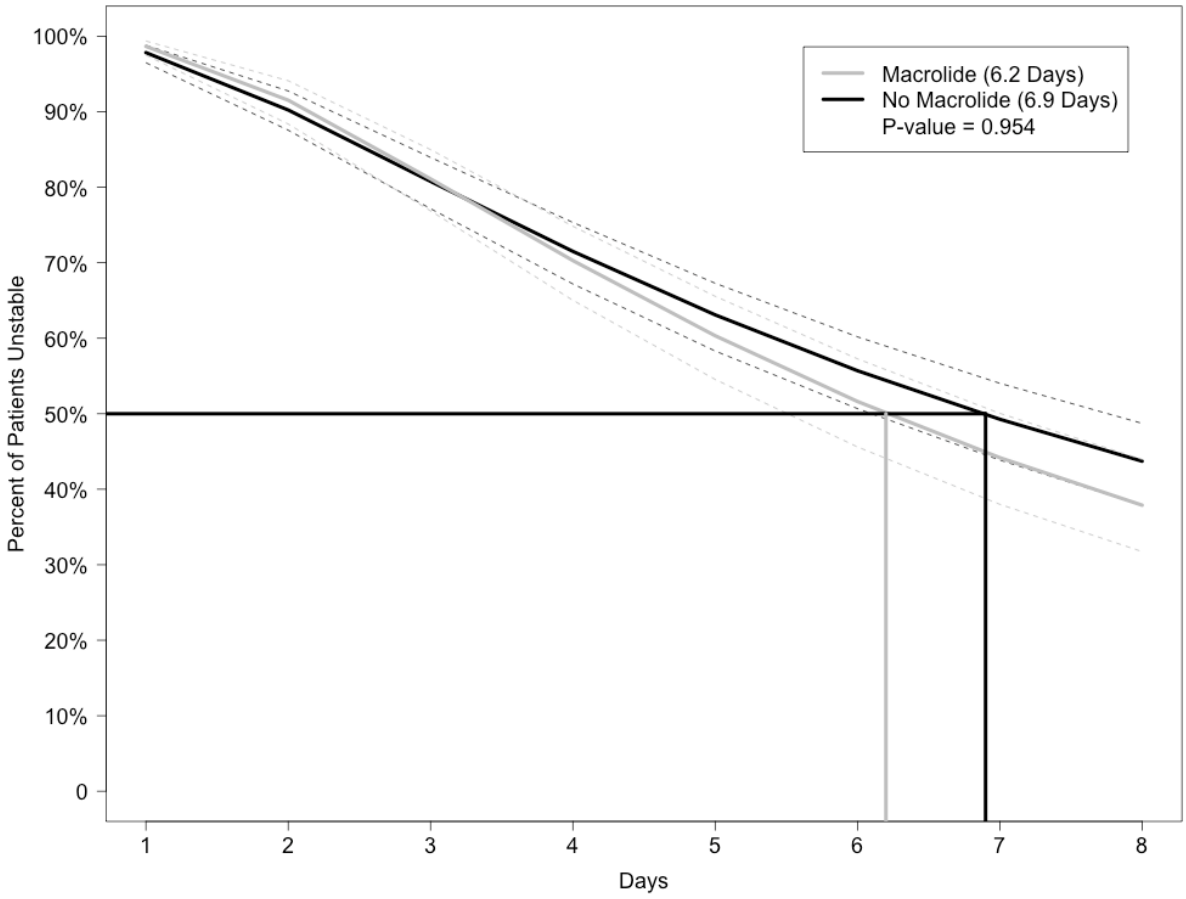
294 **Figure 2** Kaplan Meier curve (adjusted) for length of stay in community-acquired
295 pneumonia patients with and without a macrolide. The darker dashed lines accompany the
296 darker line, while the lighter dashed lines accompany the lighter line.

297

298

299 **Figure 3**



300

301 **Figure 3**

302 Kaplan Meier curve (adjusted) for time to clinical stability in community-acquired
303 pneumonia patients with and without a macrolide. The darker dashed lines accompany the
304 darker line, while the lighter dashed lines accompany the lighter line.

305

Discussion

The most striking finding of this study was the statistically significant difference for in-hospital mortality in CAP patients with bacteremia who received a macrolide compared to those who did not. Certainly, mortality has multiple factors contributing to it, but the difference for those patients with and without a macrolide is striking. The antibacterial property of a macrolide is a reasonable first explanation for the favorable difference, but 95% of the entire population (macrolide recipients as well as non-macrolide recipients), had an appropriate empiric antimicrobial regimen when comparing it to the ultimate pathogen isolated (data not shown). A second potential explanation is if patients had a dual infection with an undiagnosed atypical pathogen, but the antimicrobial benefit of a fluoroquinolone, which also covers atypical pathogens and part of the non-macrolide group treatment, would oppose that theory. A third factor that may be attributed to the difference is the immunomodulatory property of a macrolide. One study found a much lower mortality among patients with CAP due to *S. pneumoniae* who received a macrolide – even among those who were resistant to a macrolide.[9] A fourth possible explanation is residual bias, particularly indication bias.

The decreased mortality among the macrolide group was most apparent when considering patients with severe CAP. The non-macrolide group had mortality that was >10% higher than the macrolide group. This supports that there may be a greater benefit among patients with severe CAP than those with mild to moderate CAP. Since the dosing is the same regardless of severity, future research may address whether severe patients benefit more from

immunomodulation because they are suffering from a greater immune response or some other reason.

Several beneficial immunomodulatory properties of a macrolide have been studied. Specific favorable immunomodulatory effects on host inflammation and immunity that could be attributed to a macrolide include affecting neutrophil function and cytokine levels in patients with CAP.[10] Macrolides may have the ability to suppress production of systemic pro-inflammatory chemokines and cytokines [2] while allowing more local pulmonary inflammation.[11] They may also interfere with the attachment of bacteria to respiratory epithelial cells [3] and favor apoptosis over necrosis in the presence of neutrophils.[4]

There have been studies that found a benefit from a macrolide, but were limited primarily to pneumococcal bacteremia. In one study, over 2200 CAP patients had bacteremia due to a variety of bacteria including *S. pneumoniae*, other streptococci, *S. aureus*, *E. coli* and other bacteria.[12] A multivariable analysis found that a macrolide was independently associated with a decreased in-hospital mortality (OR 0.59 (95% CI 0.40-0.88); *P*=0.01), 30-day mortality and 30-day readmission rate. A meta-analysis by Nie *et al*. included 12 reviews of which five represented over 4500 CAP patients with bacteremia.[13] Each of the five studies found a statistical difference in improved mortality in patients who received a macrolide.[12,14-17] Overall, Nie *et al*. found a significant association between use of a β-lactam plus a macrolide and decreased mortality risk (OR 0.57 (95% CI 0.35-0.94); *P*=0.03).

There have been many more studies of patients with CAP, in which bacteremia was not an inclusion criterion, and conclusions were mixed. A cluster-randomized, crossover trial using three antimicrobial regimens was tested evaluating a β-lactam alone for non-inferiority against a β-lactam with a macrolide, and against a fluoroquinolone.[18] ICU patients were excluded, and the mean pneumonia severity index was 84 for each group (risk class III 71-90). Outcomes included 90-day mortality, length of stay and time to starting oral therapy. The mortality for β-lactam use alone was 9% (59 of 656 patients), for a β-lactam with a macrolide was 11% (82 of 739 patients) and for a fluoroquinolone was 9% (78 of 888). The time to oral therapy was four days, except for the fluoroquinolone group, which was three days. All groups had an average length of stay of six days. The use of β-lactams was concluded to be non-inferior to the other to regimens.

A retrospective, multicenter study on hospitalized patients with CAP, using a hospital-claims database, studied 44,814 patients who received a backbone antimicrobial (penicillin, ceftriaxone, other cephalosporin, or fluoroquinolone) with or without a macrolide.[19] For each treatment, length of stay, cost and mortality were better if a macrolide was added as part of the regimen. However, a sub-analysis of each antimicrobial regimen based on four classes of severity only showed a significant difference when a macrolide was paired with ceftriaxone compared to ceftriaxone alone. The present study and some other studies of both ward and ICU patients have shown an association with macrolide use and decreased 30-day mortality. [20, 21] One study even showed a benefit of macrolide use with 90-day mortality. [9]

370 There have been at least five meta-analyses in the last five years addressing antimicrobial
371 therapy in patients with CAP in which macrolide *vs*. non-macrolide treatment was compared.
372 Three detected a difference in mortality with macrolide use while two did not. [13,22-25] There were
373 84 individual manuscripts reviewed; with 19 in more than one review. The three meta-analyses
374 that favored macrolides included in-patients and reviewed a total of 54 articles; 45 were
375 retrospective studies, five were randomized controlled trials (RCTs), and four were prospective
376 cohort studies. [13,22,23] The two meta-analyses that did not find a difference between antimicrobial
377 groups reviewed 32 studies; all RCTs – and included out-patients. [24,25] Populations with CAP in
378 RCTs have been shown to have a lower overall mortality rate (~4%) than the usual 8-10%
379 mortality reported in observational studies. [26] This suggests that the populations in the RCTs
380 mentioned above may be different from the populations in the observational studies, hence
381 explaining the inconsistent conclusions of the reviews.

382

383 The major implication of the present study is that it should provoke further research into the
384 potential benefit of a macrolide for CAP preferentially over a non-macrolide regimen (*e.g.*,
385 fluoroquinolone alone). Despite multiple studies having been published of antimicrobial therapy
386 in CAP patients, there are differing conclusions whether a macrolide is beneficial or not.
387 Regarding studies addressing macrolide use in patients with CAP, there are some generalities
388 that can be made about RCTs finding no difference and observational studies finding a
389 difference, but the few observational studies evaluating CAP patients with bacteremia, and the
390 present study, all favor groups who received a macrolide. The present study should prompt one
391 to consider obtaining blood cultures if they have a suspicion for bacteremia. Positive blood
392 culture data already help create local antibiograms and treatment guidelines. There are two

reasons to study macrolide use in CAP patients with bacteremia. First, the immunomodulatory properties of macrolides that enhanced gastro-motility in patients without CAP show that they have at least one clinical impact, and second, it is unknown how those properties might be relevant in CAP.[27]

Limitations

This study was limited by its retrospective nature and recording of antimicrobial treatment in an observational manner. And although it had over 500 confirmed pneumonia patients with bacteremia, the data were short of finding a significant difference between the more subtle outcomes such as length of stay and time to clinical stability. As in any observational study there is possible bias despite our choice of statistical methods, including residual bias. Patients included in the database were randomly selected by each site, and did not represent consecutive cases of hospitalized patients with CAP. In-hospital mortality is prone to biases that are prevented in 30-day mortality. We did not perform competing risk analysis using 'discharge alive' as the competing event. This manuscript was strengthened by its inclusion of multiple international sites, and a mortality rate consistent with previous reports making it generalizable to a broad audience. Having bacteremia and abnormal pulmonary imaging served to confirm the diagnosis of pneumonia.

Conclusions

413 The profound difference for in-patient mortality between the macrolide and non-macrolide
414 groups in the present study, combined with the findings from other studies in slightly different
415 populations, including pneumococcal bacteremia patients, the elderly, ICU patients and veterans,
416 make a larger argument for using a macrolide as empiric therapy in hospitalized patients with
417 CAP and bacteraemia. Our data were associated with a macrolide-containing regimen resulting
418 in lower in-hospital mortality. Our findings are consistent with guideline recommendations for
419 using a macrolide when treating CAP.

420

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Highlights

Patients with community-acquired pneumonia and bacteremia have a high mortality

Mortality was significantly lower among patients who received a macrolide

The association was more significant among patients with severe pneumonia

Conflicts of Interest

Macrolide Therapy is Associated with Lower Mortality in Community-Acquired Pneumonia

Forest W. Arnold – Conflicts of interest:none

Gustavo Lopardo – Conflicts of interest:none

Timothy L. Wiemken – Conflicts of interest:none

Robert Kelley – Conflicts of interest:none

Paula Peyrani – Conflicts of interest:none

William A. Mattingly – Conflicts of interest:none

Charles Feldman has been on the advisory board and/or received honoraria for talks presented for pharmaceutical companies that manufacture and/or market macrolide antibiotics (Abbott, Aspen-GSK, Pfizer, Sandoz).

Martin Gnoni – Conflicts of interest:none

Rosemeri Maurici – Conflicts of interest:none

Julio A. Ramirez – Conflicts of interest:none