



Outcomes of Macrolide Deescalation in Severe Community-acquired Pneumonia

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ABSTRACT

Purpose: Current data suggest potential benefits with β -lactam plus macrolide combination therapy for empiric treatment of intensive care unit (ICU) patients with severe community-acquired pneumonia (CAP). However, it is unclear whether deescalation to β -lactam monotherapy in the absence of positive results on diagnostic tests, such as the BioFire FilmArray Respiratory Panel 2 (BioFire polymerase chain reaction [PCR]), affects clinical outcomes. The purpose of this study was to compare outcomes between patients with negative BioFire PCR results deescalated to β -lactam monotherapy with those not deescalated.

Methods: This single-center, retrospective cohort study assessed the in-hospital mortality rates of critically ill adults with CAP treated for ≥ 48 h with combination β -lactam and azithromycin therapy. Additional end points included hospital length of stay (LOS), ICU LOS, duration of mechanical ventilatory support, 30-day readmission, and incidence of azithromycin-related adverse effects.

Findings: A total of 94 patients were included: 53 in the deescalation group and 41 in the nondeescalation group. No difference was observed with respect to in-hospital mortality (2.4% vs 11.3%, $P = 0.312$), although patients in the deescalated group experienced shorter ICU (1.9 vs 3.4 days, $P = 0.029$) and hospital LOS (6 vs 7 days, $P = 0.025$). No differences were found between groups with respect to additional secondary end points. Simple logistic regression confirmed that deescalation was not

associated with hospital mortality (odds ratio = 0.17, 95% CI, 0.02–1.70).

Implications: In this study of ICU patients with severe CAP and a negative BioFire PCR result, deescalation from combination β -lactam and macrolide therapy to β -lactam monotherapy was not associated with increased in-hospital mortality but was associated with decreased hospital and ICU LOS. Larger prospective studies are warranted to verify these findings. (*Clin Ther.* 2019;41:2540–2548) © 2019 Elsevier Inc. All rights reserved.

Key words: antimicrobial stewardship, antimicrobial therapy, community-acquired pneumonia, intensive care unit.

INTRODUCTION

Pneumonia continues to be a leading cause of morbidity and mortality in the United States. Combined with influenza, pneumonia is the eighth leading cause of death, with approximately 51,000 patient deaths in 2016.^{1,2} Community-acquired pneumonia (CAP) results in a high rate of hospitalization in both adult and elderly populations (649 and 846.7 per 100,000 person-years, respectively).³ Furthermore, 19% of patients are directly admitted to the intensive care unit (ICU) because of pneumonia (76 per 100,000 population

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per year), and 17% of CAP patients are readmitted within 30 days of hospital discharge.^{4,5} As a result, pneumonia provides a large economic burden on the health care system, with approximately \$13.4 billion spent annually.⁶

Although a pathogen is infrequently identified, viral and bacterial microorganisms are common causes of CAP. A recent surveillance study found that only 38% of patients with radiographic evidence of pneumonia and specimens available for bacterial and viral testing had a causative pathogen identified.⁷ Twenty-three percent identified a virus, 11% a bacterium, 3% both a virus and bacterium, and 1% a fungal or mycobacterial pathogen. The most common pathogens were human rhinovirus (9%), influenza virus (6%), and *Streptococcus pneumoniae* (5%). Other common bacterial pathogens include *Haemophilus influenzae*, *Staphylococcus aureus*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Chlamydia pneumoniae*.

Early initiation of appropriate antibiotic therapy is associated with reduced mortality in patients with CAP, and there are various diagnostic tests available to aid in the rapid identification of causative pathogens.⁸ The 2007 Infectious Disease Society of America/American Thoracic Society guidelines recommend rapid diagnostic testing, such as *Legionella* and pneumococcal urine antigen tests (UATs) for all patients admitted to the ICU.⁸ Further microbiologic workup may include blood, sputum, and endotracheal aspirate cultures via bronchoscopy, bronchoalveolar lavage, and/or protected spectrum brushes in intubated patients. Other rapid diagnostic tests, such as the BioFire FilmArray Respiratory Panel 2 (BioFire polymerase chain reaction [PCR]), can be used in addition to UATs to quickly identify common CAP pathogens and facilitate antimicrobial stewardship. The BioFire PCR can identify 17 viral and 3 atypical bacterial pathogens commonly implicated in CAP in approximately 1 h with a sensitivity and specificity of 97.1 and 99.3%, respectively.^{9–11}

The recommended empiric antimicrobial treatment regimen generally includes a β -lactam in combination with a macrolide or fluoroquinolone for patients admitted to the ICU with severe CAP and low risk of multidrug-resistant organisms.⁸ Empiric macrolide combination therapy has been associated with several improved clinical outcomes as well as mortality

benefit in severe CAP when compared with nonmacrolide regimens.^{12–18} Existing data, however, only explore the association of empiric macrolide combination therapy with these outcomes, and the significance of macrolide deescalation is unknown. Therefore, the purpose of the present study is to compare clinical outcomes, such as in-hospital mortality and length of stay (LOS), between patients with severe CAP and a negative BioFire PCR result who received empiric macrolide combination therapy (β -lactam plus azithromycin) for their full treatment duration with those who were deescalated to β -lactam monotherapy.

METHODS

This single-center, retrospective cohort study was conducted at a 1400-bed tertiary care academic medical center. Deescalation practices of macrolides and/or other antimicrobials were not determined via hospital or unit-based guidelines. Antimicrobial stewardship was performed by clinical pharmacists engaged in daily patient care rounds; however, decisions to deescalate therapy were left to physician discretion. Patients with a principal discharge diagnosis of CAP, identified using *International Classification of Diseases, Ninth Revision* (ICD-9) and *International Classification of Diseases, Tenth Revision* (ICD-10) codes, between May 2013 and 2018 were evaluated for study inclusion. Those who were ≥ 18 years of age and admitted to a medical ICU within 48 h of initial hospital presentation were included if they received at least 48 h of empiric combination β -lactam and azithromycin therapy with a negative BioFire PCR result (nasopharyngeal, tracheal, or bronchial). The BioFire PCR must have been performed within 48 h of ICU admission. Patients were excluded if they were hospitalized within the previous 30 days; were receiving long-term outpatient azithromycin treatment; had a comorbidity of cystic fibrosis, interstitial lung disease, or interstitial pulmonary fibrosis; or were immunosuppressed. Furthermore, to minimize potential confounding, patients diagnosed with a viral infection or acute respiratory distress syndrome during their hospital stay were excluded from analysis.

The primary objective of this study was to compare in-hospital mortality between patients with negative BioFire PCR results who were or were not deescalated from β -lactam and azithromycin

combination therapy to β -lactam monotherapy. Secondary outcomes included hospital LOS, ICU LOS, duration of mechanical ventilatory support (both invasive and noninvasive), and 30-day readmission rates. Safety outcomes included the cumulative incidence of *Clostridium difficile* infection, cardiac toxic effects, and liver toxic effects.

All definitions were chosen a priori with the presence of disease states identified via ICD-9 and ICD-10 codes. Deescalation was defined as the discontinuation of empiric macrolide therapy. Immunosuppression was defined as a diagnosis of autoimmune deficiency syndrome, systemic lupus erythematosus, active malignant tumor, recipient of a solid organ or bone marrow transplant, or use of long-term immunosuppression therapy. Immunosuppression therapy included methotrexate, cyclosporine, tacrolimus, sirolimus, everolimus, azathioprine, leflunomide, mycophenolate, biologic therapy, and corticosteroid use of >20 mg of prednisone or its equivalent. Furthermore, receipt of active chemotherapy within the prior 2 months was defined as immunosuppression. Long-term therapy (immunosuppression or azithromycin) was defined by the presence of a qualifying agent on the patient's home medication list for a duration of >7 days. Patients were screened for potential cardiac toxic effects via identification of those with a prolonged corrected QT interval (QTc >500 msec); elevated troponin level (>1.0 ng/mL); use of adenosine, amiodarone, or metoprolol intravenous push; or cardiac dysrhythmias, ventricular fibrillation, or acute myocardial infarction diagnosis codes. Identified patients had cardiac toxic effects related to azithromycin if, on manual medical record review, they had received azithromycin within 72 h of the development of their positive screening criteria. Hepatic toxic effects related to azithromycin followed a similar structure, with screening criteria consisting of alanine aminotransferase or aspartate aminotransferase levels >5 times the upper limit of normal or a total bilirubin level >2.0 mg/dL, followed by manual review of receipt within 72 h of any azithromycin dose.

Information on patient demographic characteristics, severity of illness, inotrope and vasopressor requirements, antibiotic-related variables, and culture-related variables was also collected. The Charlson Comorbidity Index, modified Acute

Physiology and Chronic Health Evaluation (APACHE) II score, and need for intravenous vasopressors (norepinephrine, epinephrine, phenylephrine, vasopressin, and dopamine) and inotropes (dobutamine and milrinone) were used to assess severity of illness. Microbiologic information and antimicrobial data, including drug, dose, route, frequency, and administration times, during hospital admission were also collected.

All statistical analyses were performed using SPSS software, version 25.0 (IBM Inc, Armonk, New York). Nominal data were analyzed using the Fisher exact test or the χ^2 test, as appropriate. Continuous data were analyzed using the Mann–Whitney *U* test. Simple logistic regression to determine the predictive value of deescalation on the primary end point was also used. Multivariable logistic regression was discussed as a preferred analysis; however, it was unlikely to be adequately powered with the study sample size. All analyses were 2-tailed, and $P < 0.05$ was used to represent statistical significance. The Washington University School of Medicine Human Research Protection Office, the St Louis College of Pharmacy Investigational Review Board, and the Protocol Review and Monitoring Committee granted approval for this study (approval No. 201808072).

RESULTS

Patient Demographic Characteristics

A total of 4326 adult patients were screened for inclusion after identification of ICD codes during the study period. A total of 135 patients met all other inclusion criteria. A subsequent 41 patients were excluded from the analysis. Patients were most often excluded for a comorbidity or medical exclusion ($n = 21$), followed by previous hospital admission within 30 days ($n = 16$) and long-term outpatient azithromycin use ($n = 4$). The remaining 94 patients were included in the final analysis, with 41 in the deescalation group and 53 in the nondeescalated group (Fig. 1).

Baseline characteristics were similar between groups (Table I). The median age was 56 years, and $>50\%$ of patients were African American men in the total population. More patients in the nondeescalated group required invasive mechanical ventilatory support (43.3% vs 22.0%, $P = 0.069$), although this finding was not statistically significant. More than half of the patients in each group received empiric

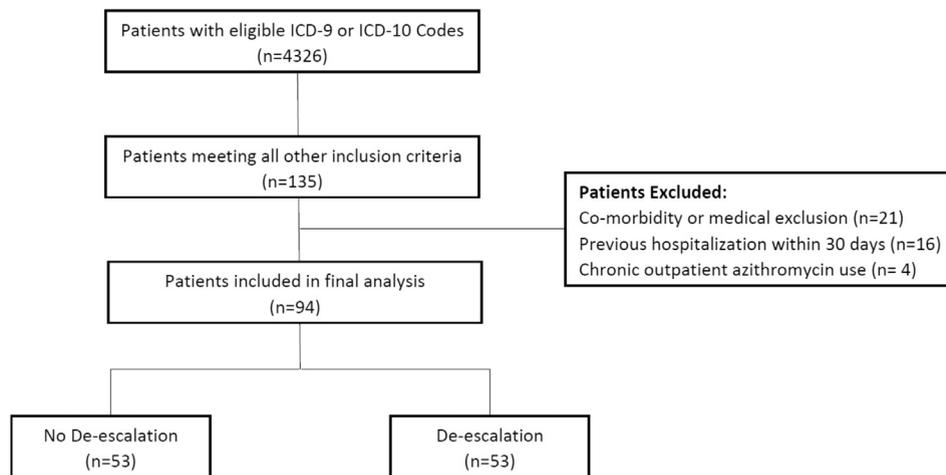


Fig. 1. Patient flow diagram. ICD-9 = *International Classification of Diseases, Ninth Revision*; ICD-10 = *International Classification of Diseases, Tenth Revision*.

antibiotic treatment with vancomycin (61.0% in the deescalated group vs 54.7% in the nondeescalated group, $P = 0.473$) and cefepime (56.1% in the deescalated group vs 56.6% in the nondeescalated group, $P = 0.094$) in addition to azithromycin. The median duration of azithromycin therapy was 2 days in the deescalation group compared with 4 days in the nondeescalated group ($P < 0.05$). A total of 13 patients (13.8%) in the cohort had a positive bacterial culture result. Of these 13 patients, Enterobacteriaceae species were the most commonly identified pathogens (57.1% in the deescalated group and 16.7% in the nondeescalated group, $P > 0.99$) followed by *Staphylococcus aureus* (14.3% in the deescalated group vs 33.3% in the nondeescalated group, $P > 0.99$). Complete culture data are reported in Table II.

Clinical Outcomes

Clinical outcomes are presented in Fig. 2 and Table III. No difference was found in the primary end point of in-hospital mortality between the 2 study groups (2.4% in the deescalated group vs 11.3% in the nondeescalated group, $P = 0.132$). Deescalated patients had shorter hospital LOS (6 vs 7 days, $P = 0.025$) and ICU LOS (1.9 vs 3.4 days, $P = 0.029$), but the rates of 30-day readmissions and duration of invasive or noninvasive mechanical

ventilatory support were not significantly different. Simple logistic regression confirmed that deescalation was not predictive of 28-day mortality (odds ratio = 0.166; 95% CI, 0.023–1.70).

Secondary safety end points were also similar between the 2 study groups (Table IV). Thirty-three percent of the total population had a diagnosis of dysrhythmia (31.8% in the deescalated group vs 34% in the nondeescalated group, $P > 0.99$) and 17% with myocardial infarction (14.6% vs 5.3%, $P = 0.0783$) within 72 h of azithromycin exposure. Twenty-eight patients (29.8%) required vasopressor support (22.0% in the deescalated arm vs 35.8% in the nondeescalated arm, $P = 0.176$). In total, 65 patients met at least 1 cardiac toxicity screening criteria within 72 h of azithromycin exposure; however, no association was observed between the deescalated and nondeescalated groups. Rates of patients who met the hepatic toxicity screening criteria were similar between groups, and no difference existed when patients were examined for receipt of azithromycin within 72 h. One patient in each group was diagnosed with *C difficile* after azithromycin administration ($P > 0.99$).

DISCUSSION

In the present study, deescalation of macrolide combination therapy was not associated with a

Table I. Baseline patient characteristics.*

Characteristic	All Patients (N = 94)	Nondeescalation (n = 53) ^a	Deescalation (n = 41) ^a	P
Age, median (IQR), y	55.9 (43.6–70.6)	55.8 (44.4–73.2)	57.4 (41.8–69.2)	0.550
Male sex	57 (60.6)	28 (52.8)	29 (70.7)	0.092
Height, median (IQR), cm	170.1 (162.6–177.8)	170.2 (161.3–180.3)	172.7 (165.1–177.8)	0.431
Weight, median (IQR), kg	79.78 (64.7–103.6)	87.2 (68.4–104.8)	76.7 (62.0–93.4)	0.187
BMI, median (IQR), kg/m ²	27.46 (23.0–35.7)	29.0 (24.3–37.7)	25.7 (21.8–32.8)	0.093
Race				
African American	48 (51.1)	27 (50.9)	21 (51.2)	0.150
White	41 (43.6)	22 (41.5)	19 (46.3)	0.674
Other	5 (5.3)	4 (7.5)	1 (2.4)	0.066
Modified APACHE II [†]	15 (12–18)	16 (14–18)	14 (11–17)	0.092
Charlson Comorbidity Index [‡]	3.0 (1.0–5.0)	3.0 (1.0–5.0)	2.0 (1.0–5.0)	0.462
Discharge disposition				
Home	43 (45.7)	24 (45.3)	19 (46.3)	0.678
Hospice	3 (3.2)	2 (3.8)	1 (2.4)	>0.99
Long-term care	41 (43.6)	25 (47.1)	16 (39.0)	0.295
Comorbidities				
COPD	22 (23.4)	15 (28.3)	7 (17.0)	0.229
Asthma	5 (5.3)	4 (7.5)	1 (2.4)	0.382
Heart failure	43 (45.7)	24 (45.3)	19 (46.3)	>0.99
ESRD	2 (2.1)	2 (3.8)	0	0.503
Polysubstance abuse	10 (10.6)	5 (9.4)	5 (12.2)	0.743
Nicotine abuse	4 (4.3)	1 (1.9)	3 (7.3)	0.315
Alcohol abuse	10 (10.6)	4 (7.5)	6 (14.6)	0.323
Cirrhosis	5 (5.3)	4 (7.5)	1 (2.4)	0.382
Azithromycin therapy, da	3.0 (2.0–4.0)	4.0 (3.0–5.0)	2.0 (1.0–2.0)	<0.001
Invasive mechanical ventilatory support	32 (34.0)	23 (43.3)	9 (22.0)	0.069
Noninvasive mechanical ventilatory support	33 (35.1)	10 (18.9)	23 (56.1)	0.070
Empiric antibiotic use				
Vancomycin	54 (57.4)	29 (54.7)	25 (61.0)	0.473
Cefepime	53 (56.4)	30 (56.6)	23 (56.1)	0.094
Ceftriaxone	26 (27.7)	17 (32.1)	9 (22.0)	0.134
Linezolid	17 (18.1)	11 (20.8)	6 (14.6)	>0.99
Meropenem	11 (11.7)	6 (11.3)	5 (12.2)	0.604
Piperacillin-tazobactam	9 (9.6)	6 (11.3)	3 (7.3)	>0.99
Ceftaroline	9 (9.6)	6 (11.3)	3 (7.3)	0.727
Metronidazole	5 (5.3)	4 (7.5)	1 (2.4)	0.048
Aztreonam	2 (2.1)	0	2 (4.9)	0.188
Ceftazidime	1 (1.1)	1 (1.9)	0	>0.99
Clindamycin	1 (1.1)	0	1 (2.4)	0.436

APACHE = Acute Physiology and Chronic Health Evaluation; BMI = body mass index; COPD = chronic obstructive pulmonary disease; ESRD = end-stage renal disease; IQR = interquartile range.

Letter 'a' represents that Data shown as n (%) or median (IQR).

* Data are presented as number (percentage) of patients unless otherwise indicated.

[†]The modified APACHE II score grades the severity of illness in critically ill patients and predicts individual survival. The modified APACHE II scores range from 0 to 100 points, with higher scores indicating more severe disease and higher risk of mortality.

[‡]Charlson Comorbidity Index categorizes comorbidities of patients based on *International Classification of Diseases* (ICD) diagnosis codes and predicts 10-year survival. The Charlson Comorbidity Index scores range from 0 to 37, with higher scores indicating a lower chance of survival.

Table II. Complete culture data of the study patients.

Culture	No. (%) of Patients			P
	All Patients (N = 94)	Nondeescalated (n = 53)	Deescalated (n = 41)	
Positive tracheal aspirate result	4 (4.3)	3 (5.7)	1 (2.4)	0.629
Positive bronchial wash/BAL result	5 (5.3)	4 (7.5)	1 (2.4)	0.382
Bacteremia	8 (8.5)	3 (5.7)	5 (12.2)	0.290
Positive bacterial culture results				
Enterobacteriaceae	13 (13.8)	6 (11.3)	7 (17.0)	>0.99
<i>Staphylococcus aureus</i>	5 (38.5)	1 (16.7)	4 (57.1)	>0.990.192
<i>Streptococcus pneumoniae</i>	3 (23.1)	2 (33.3)	1 (14.3)	0.441
<i>Pseudomonas aeruginosa</i>	2 (15.4)	1 (16.7)	1 (14.3)	>0.99
<i>Streptococcus agalactiae</i>	1 (7.7)	1 (16.7)	0	0.441
<i>Haemophilus influenzae</i>	1 (7.7)	1 (16.7)	0	0.441
	1 (7.7)	0	1 (14.3)	

BAL = bronchoalveolar lavage.

difference in hospital mortality for patients with negative BioFire PCR results and severe CAP. Although patients deescalated to β -lactam monotherapy had significantly shorter ICU and hospital LOS, there were no additional differences in 30-day readmission rates, duration of invasive or noninvasive mechanical ventilatory support, or safety outcomes, such as cardiac and hepatic toxic effects and *C difficile* infection.

Yamana et al¹⁹ retrospectively examined the effect of antimicrobial deescalation on mortality in non-

ICU patients with both culture-positive and culture-negative CAP. Antimicrobial deescalation was deemed noninferior to continued empiric therapy with respect to in-hospital mortality (8% vs 8.8%), and there were no differences observed in LOS. However, that patients in this cohort were deescalated to β -lactam monotherapy after 96 h once bacterial cultures finalized with susceptibilities, and only 33.2% of patients received combination therapy with a macrolide. The association of antimicrobial deescalation and all-cause mortality was also evaluated in a meta-analysis of patients with numerous infectious conditions, including CAP.²⁰ Authors defined deescalation as a change or discontinuation in use of an agent from the original antibiotic regimen. This meta-analysis included 2 CAP studies. With respect to all-cause mortality, nondeescalation was favored over antimicrobial deescalation in one study (96% vs 4%), whereas deescalation was favored in the other (57% vs 43%). The combined 30-day mortality between these 2 studies was significantly lower in the antimicrobial deescalation group (odds ratio = 0.50; 95% CI, 0.29–0.87); however, both investigations only included non-ICU patients and based deescalation strategies on negative culture results rather than the use of rapid diagnostic tests. Gaps in this preexisting

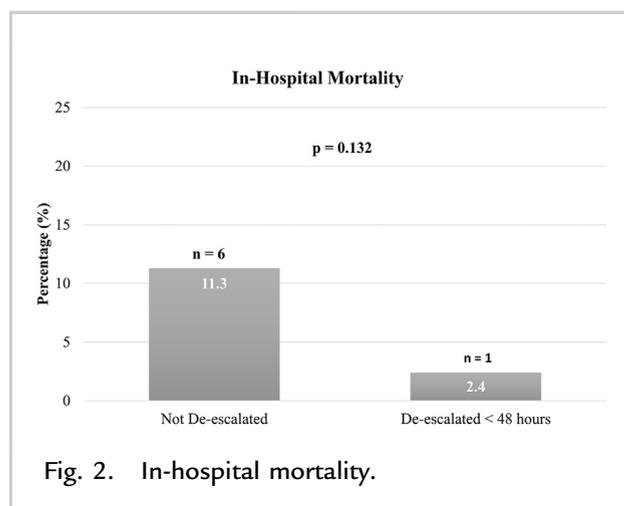


Fig. 2. In-hospital mortality.

Table III. Clinical outcomes.*

Outcome	All Patients (N = 94)	Nondeescalated (n = 53)	Deescalated (n = 41)	P
ICU length of stay, median (IQR), d	3.0 (1.6–4.9)	3.4 (1.9–5.3)	1.9 (1.2–4.0)	0.029
Hospital length of stay, median (IQR), d	7.0 (5.0–10.0)	7.0 (6.0–10.0)	6.0 (4.0–8.5)	0.025
30-Day readmission	13 (13.8)	9 (17.0)	4 (9.8)	0.378
Time to readmission, median (IQR), d	6.0 (2.0–11.50)	4.0 (2.0–8.5)	11.5 (3.5–24.8)	0.260
Any invasive mechanical ventilatory support requirement	38 (40.4)	26 (49.1)	12 (29.2)	0.060
Time spent on invasive mechanical ventilatory support, median (IQR), d	3.9 (2.7–6.8)	3.9 (2.5–5.2)	4.7 (2.8–10.6)	0.447
Any noninvasive mechanical ventilatory support requirement	36 (38.2)	20 (37.7)	16 (39.0)	>0.99
Time spent on noninvasive mechanical ventilatory support, median (IQR), d	4.2 (2.8–9.0)	3.6 (2.6–6.5)	4.5 (2.8–9.8)	0.440

ICU = intensive care unit; IQR = interquartile range.

* Data presented as number (percentage) of patients unless otherwise indicated.

literature highlight the need to describe antimicrobial deescalation strategies in critically ill populations while incorporating the use of new technologies, such as rapid diagnostic tests like the BioFire PCR.

Although the present study details a practical use of rapid microbiologic diagnostic tools, it is certainly not without limitations. The retrospective nature of this evaluation is subject to the inherent biases of its design. The rationale for antimicrobial deescalation was at the discretion of treating physicians, and it is difficult to control for confounding factors that may have influenced this decision. Similarly, ordering of BioFire PCR was at the discretion of the treating physician. The small sample size in this study not only precluded investigators from performing more advanced statistical analyses able to control for unmeasured confounding variables but also results in a study with a low power to detect meaningful differences in the primary outcome. The use of ICD-9 and ICD-10 codes to identify study population and outcomes may be influenced by inaccurate or incomplete documentation in the electronic medical record. Although the authors intended to evaluate critically ill patients with severe CAP, it is possible that the findings are attributable to an overall mild to moderate acuity of illness represented by the study

population. Inclusion and exclusion criteria were chosen to target the desired patient population, yet intrinsically resulted in a younger cohort with fewer comorbidities than expected. Importantly, however, the modified APACHE II and Charlson Comorbidity Index scores were not significantly different between the 2 study groups. In addition, authors recognize that the high study exclusion rate may limit generalizability, but most patients excluded from the analysis would have been classified as hospital- or ventilator-acquired pneumonia or CAP with multidrug-resistant risk factors for which the empiric approach to treatment is different. Similarly, generalizability may be limited by the result of Enterobacteriaceae species being the most commonly identified pathogen in this population and the median treatment duration of 4 days in the nondeescalation group.

It is also important to recognize limitations associated with the BioFire PCR test. Although this test can identify 4 atypical bacteria, it is incapable of identifying bacteria from the *Legionella* species. Only 2 of 54 *Legionella* UATs or urine cultures produced positive results for *Legionella pneumophila*, both in the nondeescalated arm, decreasing the effect of this limitation.

Table IV. Safety outcomes.*

Outcome	All Patients (N = 94)	Nondeescalated (n = 53)	Deescalated (n = 41)	P
Incidence of dysrhythmias	31 (33.0)	18 (34.0)	13 (31.8)	>0.99
Incidence of cardiac arrest/ventricular fibrillation	3 (3.2)	2 (3.8)	1 (2.4)	>0.99
Incidence of myocardial infarction	16 (17.0)	10 (5.3)	6 (14.6)	0.783
Intravenous amiodarone use	7 (7.4)	4 (7.5)	3 (7.3)	>0.99
Intravenous adenosine use	1 (1.1)	0	1 (2.4)	0.436
Intravenous metoprolol use	5 (5.3)	2 (3.8)	3 (7.3)	0.650
Maximum AST, median (IQR), mg/dL	51.5 (30.3–99.8)	56.0 (30.8–88.8)	43.0 (30.0–102.0)	0.820
AST elevated >5 times ULN	15 (16.0)	8 (15.1)	7 (17.1)	0.782
Maximum ALT, median (IQR), mg/dL	38.5 (23.0–80.00)	37.0 (23.0–71.0)	43.5 (21.0–110.0)	0.514
ALT elevated >5 times ULN	7 (7.4)	2 (3.8)	5 (12.2)	0.231
Maximum total bilirubin, median (IQR), mg/dL	0.60 (0.30–1.1)	0.60 (0.30–1.0)	0.60 (0.30–1.3)	0.754
Total bilirubin elevated >2.0 mg/dL	8 (8.5)	5 (9.4)	3 (7.3)	>0.99
Maximum troponin, median (IQR), ng/mL	0.07 (0.03–0.93)	0.08 (0.03–1.0)	0.07 (0.05–1.0)	0.229
Troponin elevated >1 ng/mL	9 (9.6)	5 (9.4)	4 (9.8)	>0.99
Maximum QTc, median (IQR), msec	479 (451–509)	471 (447–510)	483 (459–511)	0.964
Vasopressor requirement	28 (29.8)	19 (35.8)	9 (22.0)	0.176
Norepinephrine	27 (28.7)	18 (34.0)	9 (22.0)	0.253
Vasopressin	4 (4.3)	2 (3.8)	3 (7.3)	>0.990.188
Epinephrine	2 (2.1)	0	2 (4.9)	>0.99
Phenylephrine	10 (10.6)	6 (11.3)	4 (9.8)	
Inotrope requirement (dobutamine)	6 (6.4)	2 (3.8)	4 (9.8)	0.398
Incidence of <i>Clostridium difficile</i>	2 (2.1)	1 (1.9)	1 (2.4)	>0.99

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

* Data presented as number (percentage) of patients unless otherwise indicated.

CONCLUSIONS

The present study evaluated critically ill patients with severe CAP and a negative BioFire PCR result. In this cohort, no difference was found with respect to in-hospital mortality for patients who received empiric macrolide combination therapy (β -lactam plus azithromycin) for their full treatment duration compared with those who were deescalated to β -lactam monotherapy. Our results suggest that macrolide deescalation in the setting of a negative BioFire PCR result may be a reasonable approach to

antimicrobial stewardship in the severe CAP population; however, larger, prospective studies are warranted to fully explain this association.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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REFERENCES

- Centers for Disease Control and Prevention. National Center for Health Statistics. Leading causes of death. Published March 17, 2017 <https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm>. Accessed August 22, 2018.
- Centers for Disease Control and Prevention. National Center for Health Statistics. Pneumonia. Published January 20, 2017 <https://www.cdc.gov/nchs/fastats/pneumonia.htm>. Accessed August 22, 2018.
- Ramirez JA, Wiemken TL, Peyrani P, et al. Adults hospitalized with pneumonia in the United States: incidence, epidemiology, and mortality. *Clin Infect Dis*. 2017;65:1806–1812, 2017.
- Storms AD, Chen J, Jackson LA, et al. Rates and risk factors associated with hospitalization for pneumonia with ICU admission among adults. *BMC Pulm Med*. 2017;17:208.
- Olasupo O, Xiao H, Brown JD. Relative clinical and cost burden of community-acquired pneumonia hospitalizations in older adults in the United States—a cross-sectional analysis. *Vaccines (Basel)*. 2018;6:E59.
- Tong S, Amand C, Kieffer A, Kyaw MH. Trends in healthcare utilization and costs associated with pneumonia in the United States during 2008–2014. *BMC Health Serv Res*. 2018;18:715.
- Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med*. 2015;373:415.
- Mandell LA, Wunderink RG, Anzueto A, 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*. 2007;44: S27–S72.
- BioMérieux Inc. 2019. <https://www.biofire.com/products/the-filmarray-panels/filmarrayp/>.
- Rogers B, Shankar P, Jerris R, et al. Impact of a rapid respiratory Panel test on patient outcomes. *Arch Pathol Lab Med*. 2015;139:636–641.
- Martinez R, Kay HE, Scicchitano LM, Wolk DM. Implementation of non-batched respiratory virus assay significantly impacts patient outcomes in the ICU. In: *Poster presented at: The Clinical Virology Symposium, Daytona Beach, Florida*. May 2016.
- Sligl WI, Asadi L, Eurich DT, Tjosvold L, Marrie TJ, Majumdar SR. Macrolides and mortality in critically ill patients with community-acquired pneumonia: a systematic review and meta-analysis. *Crit Care Med*. 2014;42:420–432.
- Martin-loeches I, Lisboa T, Rodriguez A, et al. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. *Intensive Care Med*. 2010;36:612–620.
- Tessmer A, Welte T, Martus P, Schnoor M, Marre R, Suttorp N. Impact of intravenous β -lactam/macrolide versus β -lactam monotherapy on mortality in hospitalized patients with community-acquired pneumonia. *J Antimicrob Chemother*. 2009;63:1025–1033.
- Shorr AF, Zilberberg MD, Kan J, Hoffman J, Micek ST, Kollef MH. Azithromycin and survival in *Streptococcus pneumoniae* pneumonia: a retrospective study. *BMJ Open*. 2013;3, e002898.
- Garin N, Genné D, Carballo S, et al. β -Lactam monotherapy vs β -lactam-macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. *JAMA Intern Med*. 2014;174:1894–1901.
- Afshar M, Foster CL, Layden JE, Burnham EL. Azithromycin use and outcomes in severe sepsis patients with and without pneumonia. *J Crit Care*. 2016;32:120–125.
- Rizzato G, Montemurro L, Fraioli P, et al. Efficacy of a three day course of azithromycin in moderately severe community-acquired pneumonia. *Eur Respir J*. 1995;8: 398–402.
- Yamana H, Matsui H, Tagami T, Hirashima J, Fushimi K, Yasunaga H. De-escalation versus continuation of empirical antimicrobial therapy in community-acquired pneumonia. *J Infect*. 2016;73:314–325.
- Ohji G, Doi A, Yamamoto D, Iwata K. Is de-escalation of antimicrobials effective? a systematic review and meta-analysis. *Int J Infect Dis*. 2016;49:71–79.

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