Published in final edited form as:

J Crit Care. 2016 April ; 32: 120–125. doi:10.1016/j.jcrc.2015.12.010.

Azithromycin Use and Outcomes in Severe Sepsis Patients with and without Pneumonia

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Abstract

Purpose—Studies investigating the association between macrolides and outcomes in both pulmonary and non-pulmonary critically-ill patients are limited. We aimed to examine the association between azithromycin use and clinical outcomes in severe sepsis patients with and without pneumonia receiving mechanical ventilation.

Materials and Methods—Retrospective cohort of 105 patients admitted to an adult intensive care unit (ICU) with severe sepsis in an urban university hospital. Multivariable linear regression was performed to assess the relationship between azithromycin use and the following outcomes: 28-day ICU-free days and 28-day ventilator free days.

Results—In univariate analysis, patients receiving azithromycin had nearly six more ICU-free days on average than patients not receiving azithromycin ($p=0.005$). The increased ICU-free days remained in multivariable analysis adjusting for age, sex, race, ICU type, and presence of shock ($p=0.005$). In stratified analysis examining the association of azithromycin use in severe sepsis patients without pneumonia ($N=74$), the results were similar to the full cohort.

Conclusion—Azithromycin was associated with more ICU-free days in severe sepsis patients with and without pneumonia. Further investigations are warranted to better elicit the association of macrolide use on clinical outcomes in severe sepsis patients, especially those without pneumonia.

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Keywords

Macrolide; Severe Sepsis; Inflammation; Intensive Care Unit; Azithromycin; Mechanical Ventilation

INTRODUCTION

The use of macrolides in many acute and chronic inflammatory conditions has been associated with notable clinical benefits. For example, observational studies demonstrate that the addition of a macrolide in the treatment of community-acquired pneumonia (CAP) reduces mortality [1,2]. Similarly, in patients with acute respiratory distress syndrome (ARDS), macrolide therapy has been associated with a survival advantage and shorter duration of mechanical ventilation compared to outcomes in patients where non-macrolide antibiotics are used [3]. Beneficial associations between macrolides and outcomes have also been reported in chronic neutrophilic airway diseases including cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), and severe non-eosinophilic asthma [4–7].

The anti-inflammatory properties of macrolides are believed to drive their clinical benefit [8,9]. In the setting of sepsis, a quintessential pro-inflammatory condition, clinical and experimental studies illustrate immune modulatory properties of macrolides, including decreased neutrophil chemotaxis, adhesion, and oxidative metabolism, as well as alterations in pro- and anti-inflammatory cytokines [10,11]. Nevertheless, cytokines such as tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , IL-6, and IL-10 also play an important role in the host defense mechanisms in severe sepsis [12]. Studies aimed at investigating the impact of macrolide therapy on outcomes in sepsis have reported benefits mainly in patients with pneumonia, with the most benefit in the subgroup of severely ill patients with severe sepsis and septic shock [1,13,14]. In these severely ill patients, higher levels of pro-inflammatory mRNAs were observed, in contrast to non-critically ill bacteremic patients or healthy controls [15], implying that macrolides may be less important when inflammation is not as robust. Observations in patients with CAP support this argument, illustrated in a meta-analysis of 23 studies that did not demonstrate a mortality benefit when macrolides were used in all CAP patients [16]. However, when these same investigators performed a separate meta-analysis focusing on critically ill patients with CAP, a crude mortality benefit was observed with 18% relative risk reduction for mortality between the macrolide and non-macrolide groups [13]. These conflicting reports pose the question of what threshold of disease severity or inflammation related to sepsis may benefit most from macrolide therapy.

Data regarding associations between macrolides and clinical outcomes in both pulmonary and non-pulmonary critically-ill patients are limited. We aim to examine the association between azithromycin use and clinical outcomes in intensive-care unit (ICU) patients with severe sepsis receiving mechanical ventilation, some of whom had pneumonia. We hypothesize that critically ill patients receiving a macrolide will benefit with shorter stays in the ICU and shorter time receiving mechanical ventilation. In addition, we hypothesize that these results will persist in the group of patients without pneumonia.

METHODS

Environment and Patient Selection

Records from a retrospective cohort of patients admitted to medical and surgical ICUs at the University of Colorado with an initial diagnosis of severe sepsis between September 2010 and March 2012 were examined. Manual chart review occurred for 838 patients (C.L.F.) from the hospital's electronic medical records system (Epic Hyperspace, 2010), and 135 patients required additional paper chart review for antibiotic administration records and vital signs. The Institutional Review Board of the University of Colorado approved this study with waiver of consent and Health Insurance Portability and Accountability Act authorization.

Severe Sepsis Definition

The following International Classification of Diseases, Ninth Revision, Clinical *Modification* codes were used to identify patients with sepsis: 003.1, 027.0, 036.2, 038.X, 041.3, 348.31, 599.0, 785.52, 790.7, 995.91, 995.92, and 996.62. Patient selection by similar methods was previously described in large epidemiologic studies of sepsis [17,18]. Severe sepsis was defined using Surviving Sepsis Campaign guidelines as sepsis plus an organ dysfunction or tissue hypoperfusion [19]. The degree of hypoxemia was measured as the ratio of partial pressure arterial oxygen and fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$). This was measured as an ordinal variable by decreasing intervals of 100 beginning at 300. The following definitions were used for an organ dysfunction: lactate greater than 2 mmol/L in the first 72 hours; bilirubin > 2 mg/dL without normalization in the first 24 hours of ICU admission and no recorded history of alcohol abuse or liver disease; acute kidney injury with a creatinine increase by 1.5 fold in the first 72 hours of ICU admission; thrombocytopenia with platelet count below 100,000/uL in the first 72 hours of admission; ratio of partial pressure arterial oxygen and fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) < 250 in absence of pneumonia; ($\text{PaO}_2/\text{FiO}_2$) in presence of pneumonia; and refractory hypotension requiring vasopressor therapy. In patients with shock, the severity of shock was measured by the cardiovascular parameters from the Sequential Organ Failure Assessment (SOFA) at admission, 24 hours, 48 hours, and 72 hours after admission.

Inclusion Criteria

Patients were between the ages of 18 and 85 and treated for at least three days in an ICU for an initial diagnosis of severe sepsis (Figure 1). Pregnant women or those who had an operation within 30 days of admission were excluded. Other exclusion criteria were a history of solid organ or bone marrow transplant positive HIV status active receipt of chemotherapy at the time of diagnosis of sepsis use of long-term corticosteroids (> 6 months of use) or recent corticosteroid use at a dose greater than the equivalent 5mg of oral prednisone daily; or receipt of immunomodulation drugs for an autoimmune condition (medications classified as disease modifying anti-rheumatic drugs (DMARDs)). These patients with pre-existing immunosuppression were also excluded to avoid confounding the potential immunosuppressive effect of late-stage sepsis. Patients with cancer who did not receive chemotherapy in the past six months, patients with autoimmune diseases not on a DMARD or taking corticosteroids as above, and diabetic patients were included in the

cohort. Finally, patients who received protein synthesis inhibitor (PSI) class of antibiotics later than seven days into their hospitalization were also excluded.

Exposure and Covariates

Azithromycin was the only macrolide administered. Patients received azithromycin within the first four days of ICU admission and for a minimum duration of 48 hours. Receipt of a PSI other than a macrolide was recorded, including aminoglycosides, tetracyclines, lincosamides, rifampin, and linezolid [20]. Baseline clinical variables including demographics, comorbidities, and physiologic parameters were collected. Types and duration of antibiotics administered, sources of infection, and all available culture data were also recorded. Severe sepsis with pneumonia was identified as patients diagnosed by the attending physician with any type of pneumonia including community, aspiration, and healthcare-associated.

Analytic Approach

The primary outcome was 28-day ICU-free days, defined as the number of days patients were both alive and discharged from the ICU out of the first 28 days. Because death biases toward fewer ICU days, participants who died prior to day 28 were assigned as having zero ICU-free days²¹. Secondary outcomes were 28-day ventilator-free days and in-hospital death. 28-day ventilator-free days were defined as the number of days of unassisted breathing for 48 consecutive hours between days 1 and 28 from onset of mechanical ventilation. Patients discharged before day 28 were assumed alive and not on a ventilator [21]. Macrolide use was evaluated in our primary analysis as a dichotomous variable. Baseline characteristics were presented as medians with interquartile ranges. Unadjusted comparisons of two or more proportions were performed using a chi-square test or Fisher's exact test and continuous variables were performed using the Kruskal-Wallis one-way analysis of variance. Cardiovascular SOFA scores (range 0–4) were compared between groups with the Wilcoxon-Mann-Whitney test. We used simple linear regression to evaluate unadjusted associations, and multivariable linear regression for adjusted associations. Covariables included in the model for adjustment were age, sex, race, ICU type, and presence of shock requiring a vasopressor. These were previously shown to be strong predictors for ICU length of stay and prolonged mechanical ventilation [22]. Number of organ dysfunctions was evaluated and excluded from the final model because it was not significant at the 25% level and did not improve overall model fit (R^2). We assessed regression models with the link test and plotting residuals against predicted values, and influence using Cook's distance. Two-way interactions were tested including azithromycin use with vancomycin use, beta-lactam use, other protein synthesis inhibitors, and azithromycin with pneumonia status. Analysis was performed using SAS Version 9.4 (SAS Institute, Cary, NC). A p-value 0.05 was set for statistical significance.

RESULTS

Between September 2010 and March 2012, 105 patients with severe sepsis who received mechanical ventilation met inclusion criteria for analysis (Figure 1). Over 70% (N=74) of the patients had severe sepsis without pneumonia. The majority of patients were cared for in

the medical ICU as opposed to the other ICUs, and a low proportion had comorbid conditions (Table 1). Slightly less than half (44%) of the patients received PSIs of any type. Of these patients who received PSIs, the most common agent received was azithromycin (29/47) for a median of 4 days (interquartile range (IQR) 2–6 days).

When the 105 patients were analyzed according to whether or not they received azithromycin, there were no significant differences between the azithromycin and non-azithromycin groups with regard to age, sex, race, , ICU type, and Glasgow Coma Score (Table 1). However, chronic liver disease was present only in the non-azithromycin group. The large majority of patients who received azithromycin had pneumonia as an admitting diagnosis ($p<0.001$), with a lower baseline $\text{PaO}_2/\text{FiO}_2$ ratio ($p=0.01$). Nearly 90% ($N=26$) of the patients receiving azithromycin had $\text{PaO}_2/\text{FiO}_2 \geq 200$. Other baseline markers of organ function, including lactic acidosis, acute kidney injury, thrombocytopenia, and hyperbilirubinemia recorded anytime in the first 72 hours of hospitalization were not significantly different between groups. The majority of patients had two or less organ dysfunctions ($N=57$) and no difference in number of organ dysfunctions was demonstrated between groups ($p=0.97$). In addition, no differences in SOFA cardiovascular scores were found between groups at admission ($p=0.61$), 24 hours ($p=0.51$), 48 hours ($p=0.54$), or 72 hours ($p=0.79$) after admission. More patients who had received azithromycin ultimately had a positive microbiologic cultures ($p=0.002$), although the overall percentage of Gram(+) and Gram(−) infections did not vary between groups based on azithromycin administration. Notably, receipt of β -lactam or vancomycin antibiotics did not differ significantly between azithromycin and non-azithromycin groups. Comparisons between severe sepsis patients with and without pneumonia are shown in Supplemental 1. The distribution of antibiotic type between severe sepsis patients with and without pneumonia is illustrated in Figure 2.

The median hospital length of the stay in patients who survived and received azithromycin was not significantly different from patients without azithromycin treatment (11 [IQR 8–14] vs. 13 [IQR 8–25], $p=0.20$). The distributions for both 28-day ICU-free days and 28-day VFD are shown in Supplemental 2A and 2B. In univariate analysis for 28-day ICU-free days, patients receiving azithromycin had 5.47 more ICU-free days on average than patients not receiving azithromycin (Regression coefficient 5.47 (standard error (SE) 1.99), $p=0.005$). The increased ICU-free days remained in multivariable analysis adjusting for age, sex, race, ICU type, and presence of shock ($p=0.005$) (Table 2). Subgroup analysis without the chronic liver disease patients ($N=10$) continued to demonstrate more ICU-free days on average in the azithromycin treatment group than their counterparts not receiving azithromycin (5.1 days, $p=0.01$). No significant interactions existed between azithromycin use and other classes of antibiotics including vancomycin, beta-lactams, and other PSIs. No significant interaction existed with azithromycin use and pneumonia status. In the analysis for 28-day ventilator-free days, no difference was noted with azithromycin use (Regression coefficient 3.71, SE 2.10, $p=0.08$), and a trend for more ventilator-free days was observed in patients receiving azithromycin in adjusted analysis ($p=0.06$) (Table 2). The case-rate for in-hospital death for the full cohort was 13.3% ($N=14$) and only one patient in the azithromycin group died. No significant difference was found for in-hospital death in patients receiving azithromycin (data not shown).

In stratified analysis examining the association of azithromycin use in severe sepsis patients without pneumonia (N=74), the results were similar to the full cohort. In univariate analysis for 28-day ICU-free days, the azithromycin group had 6.61 more ICU-free days on average than the non-azithromycin group ($p=0.036$). In adjusted analysis, the number of ICU-free days was similar (6.46 ICU-free days, $p=0.047$). No significance difference in 28-day ventilator-free days or in-hospital death was found (data not shown).

DISCUSSION

A considerable amount of evidence is available from observational studies on macrolide use in critically ill patients with CAP [13]. In certain studies, a greater benefit was shown in more severely ill patients, possibly reflecting the macrolides' effect on the robust inflammatory response in severe sepsis [3,23]. Our cohort of ICU patients supports a clinical benefit for the use of azithromycin in critically ill patients, including those without CAP. In a case-mix of severe sepsis, patients receiving azithromycin had more ICU-free days, and similar results remained in the sub-group of severe sepsis patients without pneumonia.

Studies aimed at investigating the immunotherapy of sepsis with macrolides have mainly focused on patients with pneumonia, with severe sepsis patients having better clinical outcomes on macrolide therapy [1]. Many of these studies used an endpoint of mortality. Our work focuses on understanding the impact of macrolides on 28-day ICU-free days, another important clinical and economic outcome [24] as sepsis mortality declines [25]. Recently, more randomized controlled trials (RCTs) have investigated outcomes from macrolide use in severe sepsis, specifically in patients with ventilator-associated pneumonia, but clinical equipoise remains in clinical trials. For example, one recent RCT found no mortality benefit in patients with gram-negative sepsis treated with clarithromycin [14], while another study of severe sepsis patients with ventilator-associated pneumonia reported decreased risk of death from septic shock and multiple organ dysfunctions associated with the same agent [26]. Our study in severe sepsis patients found that early use of azithromycin for at least 48 hours, independent of other risk factors and accounting for organ dysfunction and presence of shock, was associated with six more days free of ICU care compared to the group not receiving azithromycin. Furthermore, our cohort was mainly comprised of severe sepsis patients without pneumonia and we identified a beneficial outcome from azithromycin use in these patients as well, which few studies have previously reported. A trend for diminished number of days requiring ventilator support was also observed, potentially limited by sample size and high variability, as other studies have shown shorter times to successful discontinuation of mechanical ventilation with a macrolide in severe sepsis patients [26]. Further investigations are warranted to clarify the association of macrolide use on clinical outcomes in different phenotypes of critically ill patients, especially severe sepsis patients without pneumonia.

Over 80% of our cohort received a β -lactam and/or vancomycin. Our investigation into effect modification by other classes of antibiotics did not show any additional benefit on 28-day ICU-free days. These results parallel separate investigations in ARDS and CAP patients where fluoroquinolone and cephalosporin antibiotics did not improve clinical outcomes whereas macrolides did [2,3], suggesting effects beyond the antimicrobial properties of

macrolides. One consideration for the differences on outcomes found in our cohort is azithromycin restores the balance between pro- and anti-inflammatory mediators leading to improved outcomes, including patients without pneumonia. Nevertheless, the benefit of increased ICU-free days may be due to residual confounding from other patient characteristics or risk factors. Studies are needed targeting the innate immune response of azithromycin in this phenotype of patients before clear associations can be made with outcomes.

The immunomodulatory action of macrolides is targeted to neutrophils with reduced neutrophil adhesion and increased neutrophil apoptosis contributing to an anti-inflammatory state. Macrolides also block extracellular signal-regulated kinase (ERK)1/2 phosphorylation and inactivate the inhibitor of κ B phosphorylation, important components of intracellular signaling. These effects lead to diminished levels of TNF- α , IL-1 β , IL-8, and IL-6 further contributing to an anti-inflammatory state. Accordingly, translational studies have reported that long-term treatment with azithromycin is efficacious in chronic neutrophil mediated airway diseases including CF, post-transplant bronchiolitis obliterans syndrome, and COPD [5,6,27–29]. The role of azithromycin in acute neutrophil-mediated conditions such as ARDS may be clinically important as well. Animal models have confirmed this by demonstrating the immunomodulatory effects in different models of lung injury [30–34]. Although we did not assess ARDS in our cohort, nearly all the patients receiving azithromycin had P/F ratios <200, a much larger proportion than the non-azithromycin group.

Mortality could not be adequately addressed in our analysis because only one patient died in the azithromycin group. The comorbidities and age of our cohort was healthier and younger than other ICU populations, with many patients having single organ dysfunction which may account for the lower than expected case-fatality rate in severe sepsis [35–37]. However, in a recent sepsis population study, the mortality rate in severe septic patients without comorbidities was identical to our case-fatality rate at 13% [25]. Nevertheless, identification of septic patients was retrospective using administrative claims data which represents treated incidence and could have introduced a misclassification bias [38]. Furthermore, nearly 70% of the cases did not have positive microbiology culture data. Exact information about compliance with early goal-directed therapy was not available; however, data originated from a single academic medical center where severe sepsis guidelines are in place in both the emergency department as well as in ICUs, including provision of early antibiotics and early goal-directed therapy. The retrospective nature of the study and single center design limit the ability to generalize our results to a broader population.

In conclusion, azithromycin was associated with a beneficial effect on 28-day ICU-free days in severe sepsis patients, including patients without pneumonia. Currently, guidelines recommend the use of a macrolide in ICU patients with pneumonia [39]. Additional consideration should be given for the administration of a macrolide in all ICU patients, including the more critically ill without pneumonia. Further investigations are warranted to explore the benefit of macrolide use in other phenotypes of severe sepsis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by NIH Grant Number R24 AA019661 (ELB). Supported by NIH/NCATS Colorado CTSI Grant Number UL1 TR001082 (ELB). We thank Elizabeth J. Kovacs, Ph.D., for her revisions and comments. Contents are the authors' sole responsibility and do not necessarily represent official NIH views.

ABBREVIATIONS

CAP	community acquired pneumonia
ICU	intensive care unit
RCTs	randomized controlled trials
ARDS	acute respiratory distress syndrome
CF	cystic fibrosis
COPD	chronic obstructive pulmonary disease
PaO₂/FiO₂	ratio of partial pressure arterial oxygen and fraction of inspired oxygen
DMARDS	disease-modifying anti-rheumatic drugs
PSI	protein synthesis inhibitor

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Figure 1.
CONSORT

Figure 2.

Distribution of Antibiotics in Severe Sepsis with Pneumonia (N=31) and Without Pneumonia (N=74)

*Other protein synthesis inhibitors (PSI) include aminoglycosides, tetracyclines, lincosamides, rifampin, and linezolid. Macrolide is not included in the other PSI group.

Table 1

Clinical Characteristics and Outcomes

Characteristic	Total (105)	No Azithromycin (76)	Azithromycin (29)	P-value
Age years, mean (SD)	55.2 (16.4)	54.6 (17.2)	56.5 (14.5)	0.60
Sex (male), n (%)	63 (60.0)	42 (55.3)	21 (72.4)	0.11
Black, n (%)	21 (20.0)	12 (15.8)	9 (31.0)	0.31
Hispanic, n (%)	12 (11.4)	9 (11.8)	3 (10.3)	
Other, n (%)	8 (7.6)	7 (9.2)	1 (3.5)	
Smoker, n (%) (n=99)	31 (31.3)	21 (29.6)	10 (35.7)	0.55
Alcohol Use Disorder	21 (20.8)	16 (21.9)	5 (17.9)	0.65
Co-Morbidities				
Cancer, n (%)	6 (5.7)	5 (6.6)	1 (3.5)	0.86
Chronic Liver Disease, n (%)	10 (9.5)	10 (13.2)	0 (0.0)	n/a
Autoimmune, n (%)	4 (3.8)	3 (4.0)	1 (3.5)	0.99
ICU Bed				
MICU, n (%)	96 (91.4)	68 (89.5)	28 (96.6)	
TBICU, n (%)	4 (3.8)	3 (4.0)	1 (3.5)	0.43
CICU, n (%)	5 (4.8)	5 (6.6)	0 (0.0)	
Organ Dysfunction				
Hyperbilirubinemia, n (%)	58 (55.2)	44 (57.9)	14 (48.3)	0.38
Thrombocytopenia, n (%)	22 (21.0)	16 (21.1)	6 (20.7)	0.97
Acute Kidney Injury, n (%)	21 (20.0)	16 (21.1)	5 (17.2)	0.66
Lactic Acidosis, n (%)	60 (57.1)	44 (57.9)	16 (55.2)	0.80
Septic Shock, n (%)	15 (14.3)	13 (17.1)	2 (6.9)	0.22
Oxygenation Ratio(n=99)				
PO ₂ /FiO ₂ 300, n (%)	10 (9.5)	8 (11.4)	2 (6.9)	
PO ₂ /FiO ₂ 201–300, n (%)	13 (12.4)	12 (17.1)	1 (3.5)	0.01
PO ₂ /FiO ₂ 101–200, n (%)	47 (44.8)	36 (51.4)	11 (37.9)	
PO ₂ /FiO ₂ 100, n (%)	29 (27.6)	14 (20.0)	15 (51.7)	
Pneumonia, n (%)	31 (29.5)	13 (17.1)	18 (62.1)	<0.001
Lactate clearance (Yes)*	60 (57.1)	44 (57.9)	16 (55.2)	0.80
Culture Positive ^, n (%)	31 (29.5)	16 (21.1)	15 (51.7)	0.002
Gram (+), n (%) (n=64)	40 (62.5)	31 (62.0)	9 (64.3)	0.88
Gram (–), n (%) (n=60)	26 (43.3)	22 (46.8)	4 (30.8)	0.63
Vancomycin, n (%)	91 (86.7)	68 (89.5)	23 (79.3)	0.17
β-lactam, n (%)	102 (97.1)	73 (96.1)	29 (100.0)	0.28
Protein Synthesis Inhi, n (%)	47 (44.8)	18 (23.7)	29 (100.0)	<0.001
Glasgow Coma Score, mean (sd) (n=90)	12.8 (3.7)	12.5 (3.9)	13.7 (3.2)	0.17
28-day Ventilator-Free Days, mean (SD)	16.3 (9.7)	15.3 (10.4)	19.0 (7.3)	0.49
28-day ICU-Free Days, mean (SD)	15.4 (9.4)	13.8 (9.9)	19.6 (6.4)	0.02
In-Hospital Death	14 (13.3)	13 (17.1)	1 (3.5)	0.07

PO_2/FiO_2 = ratio of partial pressure arterial oxygen and fraction of inspired oxygen. Pneumonia = any type of pneumonia including community, aspiration, and healthcare associated. Organ dysfunction include the following: lactate greater than 2 mmol/L in the first 72 hours; bilirubin > 2 mg/dL without normalization in the first 24 hours of ICU admission and no history of alcohol or liver disease; acute kidney injury with a creatinine increase by 1.5 fold in the first 72 hours of ICU admission; thrombocytopenia with platelet count decreasing below 100,000/uL in the first 72 hours of admission. Septic shock = refractory hypotension requiring vasopressor therapy for greater than 24 hours *Lactate improved from > 2mg/dL to 2mg/dL over 72 hrs from q admission

[^] Includes urine, sputum, and blood culture.

Protein synthesis inhibitor = azithromycin, aminoglycosides, tetracyclines, lincosamides, rifampin, and linezolid

Table 2

Association between azithromycin use and outcomes (N=105)

Adjusted 28-Day ICU--Free Days	Regression coefficient	Standard Error	P-value
Age	0.09	0.05	0.09
Sex (Male)	−1.96	1.84	0.29
Race (White)	−1.68	1.84	0.29
ICU (Medical)	−4.28	3.21	0.19
Presence of Shock	−2.43	2.60	0.35
Azithromycin Use	5.83	2.03	0.005
Adjusted 28-Day Ventilator-Free Days			
Age	0.07	0.06	0.20
Sex (Male)	−2.66	1.95	0.17
Race (White)	−1.59	1.94	0.42
ICU (Medical)	−4.04	3.40	0.24
Presence of Shock	−2.44	2.72	0.37
Azithromycin Use	3.94	2.16	0.07

Adjusted linear regression model includes age, sex, race, ICU type, and presence of shock. Regression coefficient represent days with azithromycin use.