Clinical Infectious Diseases

MAJOR ARTICLE

Effectiveness of Beta-Lactam plus Doxycycline for Patients Hospitalized with Community-Acquired Pneumonia

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Background. Despite clinical practice guideline recommendations to use doxycycline as part of combination therapy for some patients hospitalized with pneumonia, there is minimal evidence supporting this recommendation. Our aim was to examine the association between beta-lactam plus doxycycline and mortality for patients hospitalized with community-acquired pneumonia.

Methods. We identified patients >65 years of age admitted to any US Department of Veterans Affairs hospital in fiscal years 2002–2012 with a discharge diagnosis of pneumonia. We excluded those patients who did not receive antibiotic therapy concordant with the 2019 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) clinical practice guidelines. Using propensity score matching, we examined the association of doxycycline with 30- and 90-day mortality.

Results. Our overall cohort was comprised of 70 533 patients and 5282 (7.49%) received doxycycline. Unadjusted 30-day mortality was 6.4% for those who received a beta-lactam plus doxycycline versus 9.1% in those who did not ($P < .0001$), and 90-day mortality was 13.8% for those who received a beta-lactam + doxycycline versus 16.8% for those who did not ($P < .0001$). In the propensity score matched models, both 30- (odds ratio 0.72, 95% confidence interval [CI], .63–.84) and 90-day (0.83, 95% CI, .74–.92) mortality were significantly lower for those who received doxycycline.

Conclusions. In this retrospective observational cohort study, we found that doxycycline use, as part of guideline-concordant antibiotic therapy, was associated with lower 30- and 90-day mortality than regimens without doxycycline. While this supports the safety and effectiveness of antibiotic regimes that include doxycycline, additional studies, especially randomized clinical trials, are needed to confirm this.

Keywords. pneumonia; doxycycline; antimicrobial therapy; mortality; length of stay.

Community-acquired pneumonia (CAP) continues to be one of the leading causes of morbidity and mortality. In the United States, there are up to 10 million cases of CAP with 1.1 million hospitalizations and >50 000 deaths every year [1, 2]. There has been a continued increase in the age-adjusted death rate over the last 5 years [1]. These numbers are expected to continue to increase as the population ages and more individuals develop comorbid conditions [3].

There is concern regarding the potential for diminished effectiveness of the frequently used empiric antibiotics for CAP, including macrolides, given the rising incidence of antibiotic resistance amongst the organisms commonly associated with CAP [4, 5]. Recent data suggest that there is now resistance to macrolides in up to 50% of *Streptococcus pneumoniae* and *Mycoplasma* strains, 2 of the more common bacteria causing CAP [5, 6]. Growing antibiotic resistance in addition to other modifiable (diabetes, smoking) and nonmodifiable risk factors (age, genetic disorders) pose a significant challenge and have become important contributors towards rising disease burden globally including the United States.

The 2019 American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) guidelines recommended that for inpatients with CAP, not in the intensive care unit (ICU), empiric antibiotic therapy consist of a beta-lactam and macrolide, an anti-pneumococcal fluoroquinolone, or beta-lactam and doxycycline for those with contraindications to the alternatives [7]. Unfortunately, there is limited evidence supporting the combination use of beta-lactams and doxycycline in hospitalized CAP patients and the guidelines stated there is a "need for higher-quality evidence in support of the use of combination therapy with a beta-lactam and doxycycline" [7].

The aim of this study was to examine the association between doxycycline, as a part of combination antibiotic therapy, with clinical outcomes including 30- and 90-day mortality for veterans hospitalized with CAP in the Department of Veterans Affairs Health Care System (VA). Our a priori hypothesis was that receipt of doxycycline, as part of guideline-concordant empiric antibiotics, would be associated with similar 30- and

Received 22 May 2021; editorial decision 16 September 2021; published online 9 November 2021.
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Clinical Infectious Diseases® 2022;75(1):118–24

https://doi.org/10.1093/cid/ciab863

90-day mortality, after adjusting for potential confounders, compared to other guideline-concordant therapies.

METHODS

We conducted a retrospective cohort study using clinical and administrative databases of the Department of Veterans Affairs Health Care System. These databases are the repositories of clinical data from all of the national VA hospitals and outpatient clinics [8]. This study was approved by the VA North Texas Institutional Review Board. More detailed information regarding the databases can be found in prior publications [9, 10].

Inclusion Criteria

We included patients who met the following criteria:

a) Hospitalization between 1 October 2001 and 30 September 2012.
b) 65 years or older on the date of admission.
c) Discharged with a diagnosis of pneumonia defined as either a primary diagnosis of pneumonia (ICD-9 codes 480.0–483.99 or 485.0–487.0) or a secondary diagnosis of pneumonia with a primary diagnosis of respiratory failure (ICD-9 code 518.81) or sepsis (ICD-9 code 0.38xx).
d) Had at least 1 dose of antimicrobial therapy within the first 48 hours of admission.
e) Were not in an ICU during the admission.
f) Had at least 3 or more VA outpatient clinic visits in the year preceding admission to ensure that clinical variables and medications were appropriately captured.
g) Received at least 1 outpatient medication from a VA pharmacy within 90 days prior to admission, thereby ensuring that the patients were receiving medications from VA pharmacies [9].
h) Received antibiotic therapy concordant with the 2019 ATS/IDSA guidelines for community-acquired pneumonia [11] within the first 48 hours of admission. Prior studies have consistently demonstrated that the use of non-guideline concordant antibiotics is associated with increased mortality [12, 13]. Therefore, patients will have received either a respiratory fluoroquinolone (eg, levofloxacin), appropriate beta-lactam + azithromycin, or beta-lactam + doxycycline.

For patients who had multiple pneumonia-related hospitalizations during the study period, we included only their first hospitalization.

Data Sources and Definitions

We used inpatient and outpatient demographic, utilization, and comorbidity data from the National Patient Care Database and the Corporate Data Warehouse. Pharmacy data were extracted from the Decision Support System National Data Extracts and the Corporate Data Warehouse. Vital status information was obtained from the Vital Status file, which incorporates data from veterans' death benefits claims, inpatient deaths, Medicare Vital Status files, and the Social Security Administration's death master file. Encrypted patient identifiers linked information across these databases.

We controlled for race and ethnicity categories (White, Black, and Hispanic), tobacco use (ICD 9 codes 305.1 and V15.82, smoking cessation clinic use, and/or use of medications for the treatment of nicotine dependence such as zyban, nicotine replacement, or varenicline), alcohol abuse (ICD-9 codes 291, 303, 305.0), and illicit drug use (ICD-9 codes 292, 304, 305, excluding 305.0-0.1). The number of outpatient clinic visits, excluding lab or pharmacy in the year prior to admission were also included as a potential confounding factor. We also included whether patients received noninvasive ventilation (eg, bilevel positive airway pressure) based on CPT codes. We also used the Charlson-Deyo comorbidity system to identify preexisting comorbid conditions [14], and the VA priority status for socioeconomic status [15].

Potential confounding medications were controlled for by using a count of unique drugs in each of the following classes for outpatient prescriptions filled within 90 days prior to presentation: antiplatelet agents, antipsychotics, statins, angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, cardiac antiarrhythmics, beta-blockers, calcium channel blockers, diuretics, nitrate antianginal medications, other cardiac medications, diabetic medications, other lipid-lowering medications, beta-agonist bronchodilators, other bronchodilators, oral corticosteroids, and prior outpatient antibiotics.

We classified a patient as having used doxycycline if they received at least 1 dose of doxycycline along with an appropriate beta-lactam (eg, ceftriaxone) during the first 48 hours after admission.

Outcomes

The primary outcomes of this study were all-cause mortality within 30 and 90 days of admission. Death was identified using the VA Vital Status file, which has a 98% accuracy in identifying mortality [16]. The length of hospital stay, in days, was a secondary outcome.

Statistical Analysis

For the primary analyses, we used propensity score matching to balance measured confounders between groups (doxycycline users vs non-users). Logistic regression was used to create the propensity score and then nearest-number matching with a caliper of 0.01 with no replacement performed [17]. We selected candidate variables that we believed would be potentially associated with severity of illness (eg, use of noninvasive mechanical ventilation), outcomes (eg., age, nursing home residence), or individual comorbid illnesses that may impact severity or outcomes (eg, cardiovascular disease, dementia.) Variables included in the propensity score are displayed in Table 1. Odds ratios were

Table 1. Comparison of Doxycycline-Users and Non-users Hospitalized with Pneumonia

Demographics	N (%)	N (%)	*P* Value
Age, mean (SD)	78.1 (7.4)	77.9 (7.4)	.1
Male	5155 (97.6)	64115 (98.3)	.001
Married	2697 (7.3)	2585 (7.7)	.08
Race			
White	4177(79.1)	53487 (82.0)	.0001
Black	454 (8.6)	7257 (11.1)	.0001
Hispanic	375 (7.1)	3600 (5.5)	.0001
Outpatient visits in year prior, mean (SD)	16.7 (13.8)	16.1 (14.1)	.005
Nursing home residence	70 (1.3)	914(1.4)	.7
Socioeconomic proxies			
VA priority group 1	1158 (21.9)	13458 (20.6)	.08
VA priority groups 2–6	3590 (68.0)	45082 (69.1)	
VA priority groups 7–8	534 (10.1)	6711 (10.3)	
Characteristics of hospitalization			
Noninvasive ventilation	67 (1.3)	1222 (1.9)	.002
Comorbid conditions			
Tobacco use	2276 (43.1)	27807 (42.6)	.5
Alcohol abuse	244 (4.6)	2950 (4.5)	.8
Illicit drug abuse	90 (1.7)	908 (1.4)	.07
Myocardial infarction	372 (7.1)	4391 (6.7)	.4
Heart failure	1313 (24.9)	16347 (25.1)	.8
Peripheral vascular disease	840 (15.9)	10722 (16.4)	.3
Stroke	900 (17.0)	12252 (18.9)	.002
Chronic obstructive pulmonary disease	2796 (52.9)	34474 (52.8)	.9
Rheumatologic disease	143 (2.7)	1919 (2.9)	.3
Mild liver disease	48 (0.9)	554 (0.9)	.7
Peptic ulcer disease	151 (2.9)	1996 (3.0)	.4
Dementia	204 (3.9)	3256 (5.0)	.0001
Diabetes	1709 (32.4)	22308 (34.2)	.007
Diabetes with complications	554 (10.5)	6935 (10.6)	.8
Moderate liver disease (“liver failure”)	23 (0.4)	269 (0.4)	.8
Hemiplegia	66 (1.3)	777 (1.2)	.7
Renal disease	905 (17.1)	10550 (16.2)	.07
Any prior malignancy	1245 (23.6)	16202 (24.8)	.04
Metastatic solid tumor	171 (3.2)	2625 (4.0)	.005
Hematologic malignancy	122 (2.3)	1721 (2.6)	.15
HIV	4 (0.1)	61 (0.1)	.7
Other medications			
Antipsychotic agents	288 (5.4)	4190 (6.4)	.08
Antiplatelet agents	476 (9.0)	5882 (9.0)	.7
Statins	2011 (38.0)	23933 (36.7)	.007
ARBs	337 (6.4)	4049 (6.2)	.2
ACE inhibitors	1730 (32.8)	21291(32.6)	.003
Antiarrhythmics	206 (4.0)	1843 (2.8)	.0001
Beta blockers	1798 (34.0)	22711 (34.8)	.4
Calcium channel blockers	1296 (25.4)	16592 (25.3)	.3
Diuretics	2553 (48.3)	31564 (48.4)	.9
Other lipid lowering medications	234 (4.5)	3016 (4.6)	.8
Nitrate antianginal medications	776 (14.7)	10533 (16.1)	.02
Other cardiac medications	1189 (22.5)	14324 (22.0)	.5
Diabetic medications	1191 (22.5)	15414 (23.6)	.4
Beta-agonist bronchodilators	1934 (36.6)	23213(35.6)	.0001
Other bronchodilators	1862 (35.2)	21998 (33.7)	.0001
Corticosteroids	1086 (20.6)	12873 (19.7)	.03
Antibiotics within 90-days prior to hospitalization	1472 (27.9)	17061 (26.1)	.006

Abbreviations: ACE, Angiotensin converting enzyme; ARB, Angiotensin receptor blockers; HIV, human immunodeficiency virus; ICU, intensive care unit; VA, Veterans affairs.

calculated to determine the association between doxycycline use and the outcomes, using conditional logistic regression.

To analyze time-to-event for mortality and cardiovascular outcomes by receipt of doxycycline, we used Kaplan-Meier plots adjusted for the same potential confounders as in the propensity score to display the survivor functions and assessed statistical significance using the log-rank test.

For secondary analyses, we used generalized linear mixed-effect models to examine the association of doxycycline use with 30- and 90-day mortality in the following predefined subgroups: (1) the entire cohort of those who met the inclusion/exclusion criteria, (2) those patients who did not receive antipneumococcal fluoroquinolone therapy, and (3) those who did not receive antibiotics prior to admission. We also used linear regression models to examine the association of receipt of doxycycline with the length of hospital stay. These models were adjusted for all of the covariates in the propensity score as well as adjusted for admitting hospital (for the generalized linear mixed effect models).

Statistical significance was defined as a 2-tailed *P*-value of < .05. All analyses were performed using STATA 17 (College Station, Texas, USA).

RESULTS

Of the 70 533 patients who were eligible, 5282 (7.4%) were given doxycycline containing regimes and 65 251 (92.5%) were given alternative guideline-concordant regimes. The mean age of patients was 77.9 (standard deviation [SD] [18] of 7.4) years, and 98.2% were male. Table 1 demonstrates the breakdown by receipt of doxycycline. Although there were several statistically significant differences between receipt versus nonreceipt of doxycycline-containing regimes, there were no clinically significant differences >3% between groups. Unadjusted 30-day mortality was 6.4% for those who received a beta-lactam plus doxycycline versus 9.1% in those who did not ($P < .0001$), and 90-day mortality was 13.8% for those who received doxycycline versus 16.8% for those who did not ($P < .0001$). Unadjusted length of stay was 5.5 days (SD 6.8) for those who received doxycycline versus 5.84 days (SD 9.50) for those who did not ($P = .01$).

Propensity Matched Cohort

We matched 5278 patients who received doxycycline containing therapy to 5278 patients who received other guideline-concordant regimes. Table 2 shows the balance between key variables after propensity matching. There were no statistically significant differences between groups for any of the key characteristics after matching.

Primary Outcomes

Both 30- (OR 0.72, 95% CI, 0.63–0.84) and 90-day (OR 0.83, 95% CI, 0.74–0.92) mortality were significantly lower for those who received a beta-lactam + doxycycline.

Figure 1, an adjusted Kaplan-Meier plot, demonstrates that while mortality was statistically significantly lower ($P < .001$) it had unclear clinical significance.

Secondary Analyses

For the entire cohort (n = 70 533), in a multilevel regression model receipt of beta-lactam + doxycycline was associated with lower 30- (odds ratio [OR] 0.76, 95% confidence interval [CI], .66–.86) and 90-day (OR 0.86, 95% CI, .79–.95) mortality. For those who did not receive antibiotics prior to admission, receipt of beta-lactam + doxycycline was also associated with lower 30- (OR 0.75, 95% CI .65–.87) and 90-day (OR 0.86, 95% CI, .77–.96) mortality. Length of hospital stay was not statistically different in those who did and did not receive doxycycline guideline-concordant regimes (coefficient −0.26, 95% CI, −.51 to .002).

DISCUSSION

Our retrospective observational study based on national VA healthcare data elderly demonstrates that for patients hospitalized with CAP the empiric use of a beta-lactam plus doxycycline was associated with reduced 30- and 90-day mortality, compared to other guideline-concordant regimens, and with similar length of stay. Our results support the ATS/IDSA recommendations for the use of doxycycline in combination with beta-lactams for the treatment of patients with CAP.

Per the ATS/IDSA guidelines, doxycycline can be used in combination with beta-lactams as empiric therapy for hospitalized CAP patients [7]. It has several advantages when used as part of guideline-concordant CAP treatment. Doxycycline has high activity toward many respiratory pathogens including anaerobes and atypical organisms [19]. This broad-spectrum coverage is complemented by its rapid absorption, high bioavailability (up to 90%), and ability to concentrate in lung tissues, notably into alveolar macrophages [19]. Also, doxycycline has a lower risk of *Clostridium difficile* infections (CDI) as compared to fluoroquinolones [20, 21]. Two of the most common antibiotics used for CAP, beta-lactams and fluoroquinolones, are frequently associated with CDI [22], so the use of doxycycline as part of CAP treatment may reduce this risk. In addition, recently the Food and Drug Administration (FDA) updated its warning on fluoroquinolones in terms of mental health side effects and adverse reactions related to low blood sugar levels [23]. Fluoroquinolones and macrolides are associated with corrected QT interval prolongation, whereas doxycycline has a lower tendency to cause QT prolongation as compared to these agents. Doxycycline is also rarely associated with psychological side effects [24, 25] unlike fluoroquinolones, which the FDA recently updated its warning on regarding mental health side effects [23].

Our study suggests that doxycycline may be efficacious as empiric treatment in combination with a beta-lactam such as

Table 2. Comparison of Propensity Matched Doxycycline-Users and Nonusers Hospitalized With Pneumonia

Variables	Doxycycline (N = 5,278) N (%)	No Doxycycline (N = 5,278) N (%)	*P* Value	Standardized Difference
Demographics				
Age, mean (SD)	78.1 (7.4)	78.1 (7.4)	.8	0.0060
Men	5141 (97.6%)	5137 (97.3%)	.4	−0.0169
Race				
White	4177(79.1%)	4128(78.2%)	.2	−0.01857
Black	453(8.6%)	466 (8.8%)	.7	0.0087
Hispanic	372 (7.1%)	349 (6.8%)	.6	−0.0097
Married	2694 (51.0%)	2585 (49.0%)	.9	−0.0019
Outpatient visits in year prior, mean (SD)	16.7 (13.8)	16.5 (15.5)	,6	−0.0092
Nursing home residence	70 (1.3%)	63 (1.2%)	.5	−0.0012
Socioeconomic proxies				
VA priority group 1	1158 (21.9%)	1136 (21.5%)	.6	0.0196
VA priority groups 2–6	3586(67.9%)	3578 (67.8%)		
VA priority groups 7–8	534 (10.1%)	564 (10.7%)		
Characteristics of hospitalization				
No-invasive mechanical ventilation	66 (1.3%)	71 (1.4%)	.7	0.0084
Comorbid conditions				
Tobacco use	2275 (43.1%)	2253 (42.7%)	.7	−0.0084
Alcohol abuse	244 (4.6%)	242 (4.6%)	.9	−0.0018
Illicit drug abuse	90(1.7%)	83 (1.6%)	.6	−0.0104
Myocardial infarction	370 (7.0%)	376 (7.1%)	.8	0.044
Heart failure	1311 (24.8%)	1319 (25.0%)	.9	0.0035
Peripheral vascular disease	839 (15.9%)	811(15.4%)	.6	0.0088
Stroke	898 (17.0%)	945 (17.9%)	.2	0.0235
Chronic obstructive pulmonary disease	2794 (52.9%)	2768 (52.4%)	.6	−0.0099
Rheumatologic disease	143 (2.7%)	147 (2.8%)	.8	0.0046
Mild liver disease	48 (0.9%)	45 (0.8%)	.8	−0.0061
Peptic ulcer disease	151 (2.9%)	160 (3.0%)	.6	0.0101
Dementia	203 (3.9%)	219 (4.2%)	.4	0.0155
Diabetes	1708 (32.4%)	1695(32.1%)	.8	−0.0057
Diabetes with complications	553 (10.5%)	562 (10.7%)	.8	0.0056
Moderate liver disease	23 (0.4%)	27 (0.5%)	.6	−0.0110
Hemiplegia	66(1.3%)	68 (1.3%)	.9	0.0034
Renal disease	904 (17.1%)	929 (17.6%)	.5	0.0125
Any prior malignancy	1244 (23.6%)	1215 (23.0%)	.5	−0.0130
Metastatic solid tumor	171 (3.2%)	184 (3.5%)	.4	0.0137
Hematologic malignancy	122 (2.3%)	128 (2.4%)	.7	0.0075
HIV	4(0.1%)	4 (0.1%)	1.0	0.0000
Outpatient Medications				
Antipsychotic agents	288 (5.5%)	283 (5.5%)	.5	−0.0110
Antiplatelet agents	476 (9.0)	479 (9.1%)	.5	0.0013
Statins	2009 (38.0%)	1998(37.9%)	.7	−0.0033
ARBs	337(6.5%)	380 (7.2%)	.2	−0.0312
ACE inhibitors	1730 (32.8%)	1680 (31.8%)	.5	−0.0021
Antiarrhythmics	203 (3.9%)	192 (3.6%)	.7	−0.0099
Beta blockers	1797(34.0%)	1795 (34.0%)	.9	0.0098
Calcium channel blockers	1296 (24.6%)	1368 (25.8%)	.1	0.0363
Diuretics	2551 (48.3%)	2510 (47.8%)	.7	−0.0091
Nitrate antianginal medications	774 (14.7%)	749 (14.2%)	.6	−0.018
Other lipid lowering medications	234 (4.4%)	244 (4.6%)	.7	0.0070
Other cardiac medications	1190 (22.5%)	1145 (21.7%)	.3	−0.0120
Diabetic medications	1190 (22.5%)	1181 (22.3%)	.8	0.016
Beta agonists bronchodilators	1932 (36.6%)	1992(37.7%)	.3	0.0110
Other bronchodilators	1860 (35.2%)	1910 (36.2%)	.6	0.0059
Oral corticosteroids	1086 (20.6%)	1102 (20.9%)	.3	0.0022
Antibiotics within 90-days prior to hospitalization	1471 (28.0%)	1486 (28.2%)	.8	0.0059

Abbreviations: ACE, Angiotensin converting enzyme; ARB, Angiotensin receptor blockers; HIV, human immunodeficiency virus; SD, standard deviation; VA, Veterans affairs.

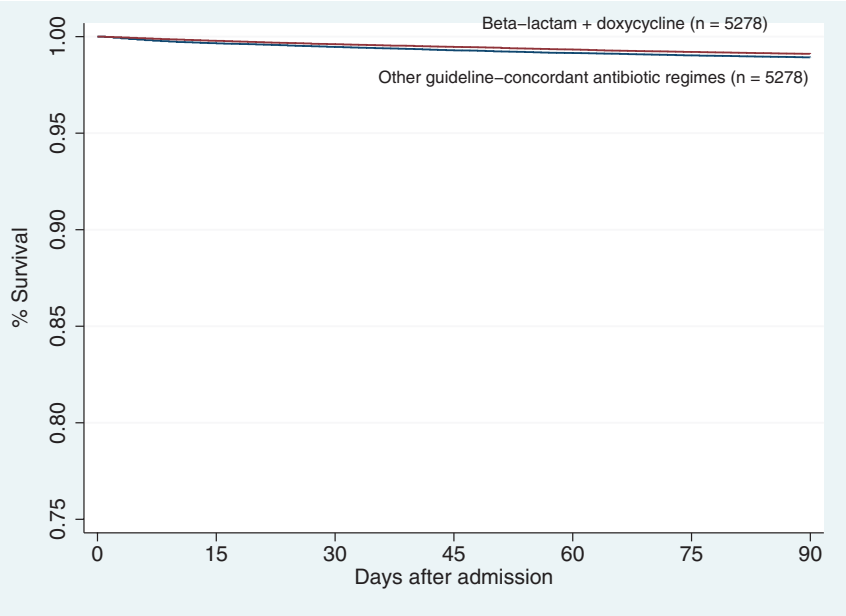

Figure 1. Kaplan-Meier plot showing differences in survival between beta-lactam and doxycycline versus other guideline-concordant CAP regimens after adjustment for potential confounders. Abbreviation: CAP, community-acquired pneumonia.

ceftriaxone. From an antibacterial perspective, doxycycline targets both typical and atypical organisms and can be instrumental in combatting the increasing levels of resistance to macrolides or fluoroquinolones [19, 26]. Furthermore, because this study looked at adults >65 years old, doxycycline is favorable in terms of the side effect profile compared to macrolides or fluoroquinolone, specifically related to QT prolongation [24, 25].

The findings in our study are concordant with prior studies that assessed the effectiveness of doxycycline in combination with beta-lactams [11, 20, 26–30]. Although the literature is observational, it suggests that combination therapy with beta-lactam plus doxycycline is associated with improved clinical outcomes compared to empiric antibiotic therapy of a beta-lactam and macrolide or an anti-pneumococcal fluoroquinolone for CAP [11]. Flanders et al found that ceftriaxone and doxycycline were associated with reduced inpatient mortality and 30-day mortality with no changes in length of stay or readmission rates [26]. A study by Teh et al found that a beta-lactam with macrolide versus beta-lactam with doxycycline regimen for CAP showed similar outcomes when it was due to a typical or atypical organism [29]. Other studies demonstrated that oral doxycycline has similar effectiveness as levofloxacin alone or in combination with ceftriaxone in non-ICU patients with CAP [28]. Unfortunately, the use of doxycycline remains unsettled due to the lack of strong randomized clinical trial evidence as well as concerns regarding potential adverse effects and bacterial resistance [27, 29].

Our study has the following limitations: Medication allergy data were not available so we are unable to examine whether patients who were prescribed doxycycline containing regimes had macrolide or fluoroquinolone allergies. Being a study based on data from the VA healthcare system, it predominantly had a male patient population, with only a small number of female patients (1.8%). The analyses were restricted to those ≥ 65 years of age as this is the primary population at risk for CAP, so the results do not provide information on those <65 years. In addition, due to the observational nature of the study, it remains possible that some important confounders may not have been accounted for in our models. Also, at the time that the study database was created, reliable microbiology data were not available in the national administrative VA databases, so we were unable to examine the impact of doxycycline use on *Clostridium difficile* infections or specific organisms that cause CAP. Finally, we did not examine specific causes of death, because previous studies demonstrated an extremely poor correlation between death certificate data and actual cause(s) of death [31].

A strength of this study is the large sample size of the study with good matching for the propensity scores. The VA healthcare system allows excellent and consistent follow-up with patients to document 30- or 90-day mortality, which allowed us to ascertain the effect of the treatment under study. The generalizability of the results is promising, as in 2010, 71% of hospitalized patients with CAP were older than 65 [28]. In addition, we were able to look at different comorbid conditions, such as tobacco use, *chronic obstructive pulmonary disease (*COPD), and peripheral vascular disease.

With growing antibiotic resistance to frontline agents, there is an urgent need for exploring and promoting newer

antibacterial regimens to address the escalating burden of CAP. Our study suggests that an empiric regimen of beta-lactam and doxycycline is associated with similar, or better, outcomes compared to other guideline concordant empiric therapies. Randomized control trials are needed to confirm this finding and to identify the best therapies for patients hospitalized with CAP.

Notes

Author Contributions. M. U. and T. M. contributed to the interpretation of data for the work, drafting the manuscript and revising it for the final approval of the version submitted for publication. M. M., A. A., and C. A. contributed to analysis and interpretation of data for the work, provided critical inputs for important intellectual content and final approval of the version submitted for publication. E. M. contributed substantially to the conception or design of the work, acquisition, analysis and interpretation of the data, drafted and revised the manuscript critically for important intellectual content, and approved the final version for submission. All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial support. This work was supported by grant number R01NR010828 from the National Institute of Nursing Research.

Potential conflicts of interest. C. A. A. reports research grants paid to Texas Tech from Merck and Boehringer Ingelheim and participation on an Advisory Board for Bayer Pharmaceuticals. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or Department of Veterans Affairs. This material is the result of work supported with resources and the use of facilities at the VA North Texas Health Care System. The funding agencies had no role in conducting the study, or role in the preparation, review, or approval of the manuscript. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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