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Research Article

Clinical Effectiveness and Outcomes of Azithromycin versus Doxycycline Containing Regimen in Inpatients with Community Acquired Pneumonia: A Retrospective Cohort Study

Alaa S. Babonji,[1] **Sara J. Alshehri**,[2] **and Abdulrahman M. Alturaiki**[3]

[1]*Internal Medicine Clinical Pharmacist, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, (Formerly King Abdulaziz University Hospital-Jeddah), Jeddah, Saudi Arabia*
[2]*King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia*
[3]*Consultant Internal Medicine Clinical Pharmacist, Program Director Internal Medicine Clinical Pharmacy, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia*

Correspondence should be addressed to Alaa S. Babonji; babonjial@mngha.med.sa

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Background. Community acquired pneumonia (CAP) is a common serious infection that is usually treated with a macrolide with a β-lactam while doxycycline is considered an alternative due to limited evidence. Hence, we aimed to evaluate azithromycin versus doxycycline containing regimen in achieving clinical stability for inpatients with CAP. *Materials and Methods*. a retrospective cohort of inpatients with CAP receiving either azithromycin or doxycycline combined with a β-lactam. The primary endpoint was the percentage of patients who achieved clinical stability within 3 days, while secondary endpoints were the average days required to achieve clinical stability. *Results*. A total of 447 were included of which 379 received azithromycin while 68 received doxycycline containing regimen. The average age of the study population was 65.4 ± 21.1, of which 49% were females. Ceftriaxone was the most prescribed β-lactam. Majority of this cohort had a length of hospital stay of 5 days or less. Total percentage of patients who achieved clinical stability within 3 days were 257 (57.5%), of which 222 (58.6%) were in azithromycin group versus 35 (51.5%) in doxycycline containing regimen group; $p = 0.275$. While the average day required to achieve clinical stability in both groups was 3.8 ± 3.2, in which 3.8 ± 3.3 in azithromycin versus 3.9 ± 2.7 in doxycycline containing regimen; (95% CI −0.98–0.68; $p = 0.727$) *Conclusions.* These findings support that doxycycline is comparable in efficacy to macrolides with a β-lactam for inpatients with CAP as supported by current guideline recommendations.

1. Introduction

Community acquired pneumonia (CAP) is a common serious infection of the pulmonary parenchyma acquired outside the hospital or a long-term-care facility. It is considered to be the ninth leading cause of death in the United States (US) that results in significant morbidity, hospitalization, and mortality globally. It is also associated with substantial costs of care with an annual cost of over $17 billion in the United States, [1–3] more than 1 million emergency department visits [4] and a mortality rate of 30.6% within 1 year for inpatients [5].

Clinical features of CAP infection include fever, chills, cough with sputum production, and pleuritic chest pain, along a physical examination that may revels tachycardia, tachypnea, egophony, and dull percussion, accompanied by acute infiltrate on a chest radiograph consistent with pneumonia. A diffuse parenchyma is more likely related to *Legionella* or viral pneumonia, while a lobar consolidation, cavitation, and pleural effusion suggests a bacterial cause. Several complications are associated with CAP including hypotension, plural effusion, sepsis, and respiratory failure, all of which might be life threatening [6].

CAP can be due to several microbial organisms, including typical organisms, commonly due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or atypical organisms, due to *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* or *Legionella* species, as well as *Staphylococcus aureus* and respiratory viruses [7]. Atypical pneumonia is responsible for 8–63% of all CAP cases globally [8]. Around 20% of CAP cases were found to have mixed infections of both bacterial and viral species and are associated with a more severe course than those with bacterial infection alone [9]. Despite advances in diagnostic tools, majority with CAP do not have organisms detected [10].

Empiric therapy for CAP depends on the common causative organisms with atypical coverage being routinely recommended to be added by all CAP guidelines [11–13]. Based on the latest American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) guideline, the panel recommended empiric therapy for hospitalized nonsevere patients to include a macrolide (azithromycin or clarithromycin) in combination with a β-lactams, or the use of a respiratory fluoroquinolone (moxifloxacin, levofloxacin). Due to the relatively limited evidence of small numbers of patients, doxycycline was considered an alternative to macrolide in case of contraindications such as documented allergies, clinical failure, cardiac arrhythmia, safety concerns, and increased drug resistance. Therefore, the ATS/IDSA guideline has emphasized on their latest update on the need for high-quality evidence to support the use of this combination.

Azithromycin is a broad-spectrum macrolide that is associated with gastrointestinal adverse effects, development of *Clostridioides difficile* infection, but to a lower extent compared to other common antimicrobial classes, and rarely hepatotoxicity [14]. Like other macrolides, it can cause QT prolongation and has been associated with torsades de pointes. It is generally regarded to have fewer cardiac adverse effects than other macrolides. Per the U.S. Food and Drug Administration (FDA) drug safety communication, individualswho are at high risk for cardiovascular events with this drug include preexisting QT prolongation, arrhythmias, bradycardia, hypokalemia, hypomagnesemia, or the use of certain drugs used for the treatment of arrhythmias [15].

Doxycycline which is a member of the tetracycline class is regarded as an effective and inexpensive therapy that is generally well tolerated, especially compared with older tetracyclines. Common side effects include gastrointestinal symptoms, teeth discoloration, benign intracranial hypertension, photosensitivity, and photo-onycholysis [16].

Many practitioners consider doxycycline to be favorable when it comes to the risk of QT prolongation compared to macrolides or fluoroquinolones. Nevertheless, there is lack of evidence for outcomes and efficacy when combining doxycycline compared to macrolides with β-lactams. Therefore, we aimed in this study to evaluate azithromycin versus doxycycline containing regimen in terms of achieving clinical stability in adult hospitalized patients diagnosed with CAP at a tertiary care hospital in Saudi Arabia.

2. Ethical Approval

Ethical approval was obtained from King Abdullah International Medical Research Center (KAIMRC).

3. Materials and Methods

This was a retrospective cohort study that was conducted at King Abdulaziz Medical City (KAMC) in Riyadh. Adult inpatients admitted at medical wards diagnosed clinically and radiologically with CAP who received either azithromycin or doxycycline as part of their empiric regimen from Jan 2017 to Feb 2020 were included. We excluded pregnant women, children, and patients who were admitted to intensive care units (ICUs), had a concomitant diagnosis with acute decompensated heart failure or acute pulmonary embolism or were on oxygen at home. During study period, patients were screened and data were collected using Excel sheet. The study site had no specific protocol developed for the treatment of CAP during study period and empiric therapy was decided by the treating physician.

4. Endpoints

Primary endpoint was to compare percentage of patients who achieved clinical stability as per IDSA criteria within 3 days, which included temperature $\leq$37.8°C, heart rate $\leq$100 beats/min, respiratory rate $\leq$24 breaths/min, systolic blood pressure $\geq$90 mm·Hg, arterial oxygen saturation $\geq$90% on room air, ability to maintain oral intake, and normal mental status [11, 17, 18]. Secondary endpoints were the average days required to achieve clinical stability, length of hospital stay, total duration of antibiotic, and percentage of patient required antibiotic escalation.

5. Statistical Analysis

Baseline characteristics and outcome variables were compared between the two study groups. A descriptive analysis was conducted for all independent variables. *T*-test was used to compare continuous data, while the chi-square test was used to compare categorical variables. We presented continuous variables as mean and standard deviation (SD) and categorical variables as number (percentage). The 95% confidence intervals (CI) were reported as appropriate. No imputation was made for missing data as the cohort of patients in our study was not derived from random selection. The SPSS software version 23 was used for all statistical analyses.

6. Results

2628 patients were identified during the study period and were screened for eligibility. A total of 447 were included of which 379 received azithromycin while 68 received doxycycline containing regimen (Figure 1). Overall, patients had similar baseline characteristics except for the percentage of patients who had normal kidney function and those who had a detected pleural effusion on X-ray (Table 1). In terms of concomitant β-lactam use, ceftriaxone was the most

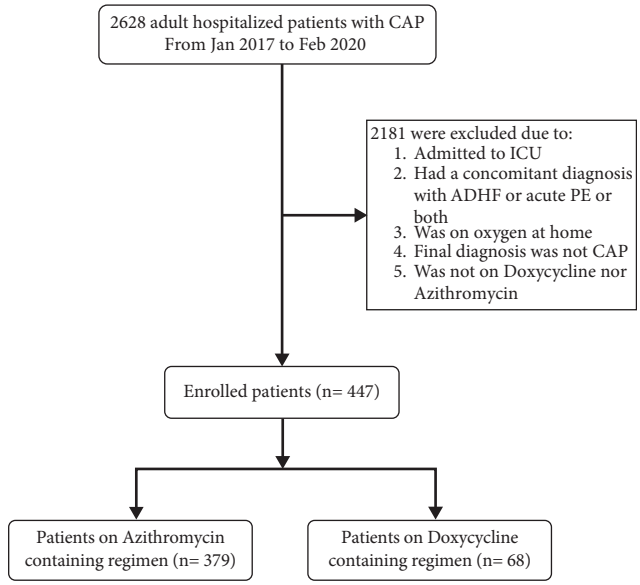

Figure 1: Study flowchart.

Table 1: Summary of patients' characteristics.

	Total $n = 447$	Azithromycin $n = 379$	Doxycycline $n = 68$
Age (years)	65.4 ± 21.1	64.5 ± 21.7	70.2 ± 17.1
Male	228 (51%)	191 (50.3%)	37 (54.4%)
CURB-65 score	1.4 ± 1	1.4 ± 1.05	1.6 ± 0.9
Pneumonia severity index (PSI) score	96.9 ± 38.5	94.7 ± 38.5	109.5 ± 35.6
Comorbidities			
DM	261 (58.4%)	213 (56.2%)	48 (70.5%)
HTN	273 (61.1%)	221 (58.3%)	52 (76.4%)
HF	41 (9.2%)	29 (6.5%)	12 (2.7%)
Asthma	101 (22.6%)	90 (23.7%)	11 (16.1%)
DLP	123 (27.5%)	100 (26.3%)	23 (33.8%)
Cancer	27 (6%)	22 (4.9%)	5 (1.1%)
Antimicrobials received			
Ceftriaxone	311 (69.6%)	265 (70%)	46 (67.6%)
Meropenem	17 (3.8%)	14 (3.7%)	3 (4.4%)
Piperacillin/tazobactam	195 (43.6%)	162 (42.7%)	33 (48.5%)
Required antibiotic escalation	163 (36.4%)	136 (35.8%)	27 (39.7%)
Culture detected	126 (28.1%)	100 (26.3%)	26 (38.2%)
Baseline labs			
WBC ($\times 10^9$/L)	12.7 ± 12.6	12.6 ± 11.4	13.2 ± 17.7
Serum creatinine (mmol/L)	128.1 ± 164.3	126.4 ± 169.1	137.2 ± 135
eGFR (mL/min/1.73 m^2)			
>90	169 (38.3%)	155 (35.1%)	14 (3.2%)
89–60	132 (29.9%)	107 (24.2%)	25 (5.7%)
59–30	85 (19.3%)	67 (15.3%)	18 (4%)
29–15	25 (5.7%)	18 (4.1%)	7 (1.6%)
<15	30 (6.8%)	26 (5.8%)	4 (1%)
Pleural effusion on X-ray	181 (40.5%)	156 (35%)	25 (5.5%)
Temperature (C°)	37.6 ± 0.9	38 ± 4.1	37.6 ± 1
Heart rate (bpm)	101.1 ± 21.5	102.1 ± 21.6	96 ± 20.8
Respiratory rate (bpm)	25 ± 5.2	25 ± 5	25.4 ± 6.3
Systolic blood pressure (mm·Hg)	128.7 ± 26.2	128 ± 26.5	132 ± 24.4
Oxygen saturation (%)	92.1 ± 4.9	92.1 ± 5	92.5 ± 5
30 days mortality	7 (1.6%)	7 (1.8%)	0

Data are presented in n (%) or mean (SD).

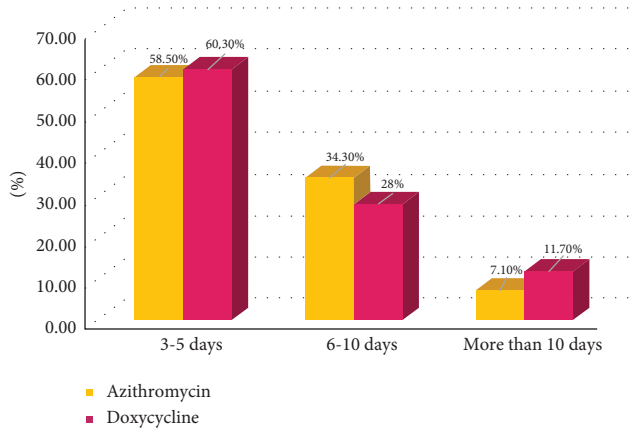

Figure 2: Length of hospital stay.

Table 2: Days till vital signs stability were achieved.

	Total $n = 204$	Azithromycin $n = 136$	Doxycycline $n = 68$	p-value	95% CI
Temperature ≤37.8 C	1.7 ± 1.4	1.7 ± 1.4	1.7 ± 1.4	0.967	(−0.37–0.36)
Heart rate ≤100 bpm	2.2 ± 2.0	2.2 ± 2.0	2.2 ± 2.2	0.884	(−0.49–0.57)
Respiratory rate ≤24 bpm	2.3 ± 1.8	2.3 ± 1.7	2.4 ± 1.9	0.544	(−0.61–0.32)
Systolic blood pressure ≥90 mm·Hg	1.1 ± 0.7	1.1 ± 0.6	1.2 ± 1.2	0.588	(−0.25–0.14)
Oxygen saturation ≥90%	2.8 ± 3.2	2.8 ± 3.3	2.5 ± 2.3	0.564	(−0.59–1.08)
Ability to maintain oral intake	1.4 ± 1.4	1.39 ± 1.2	1.8 ± 2.2	0.026	(−0.79–−0.05)
Normal mental status	1.0 ± 0.8	1.0 ± 0.7	1.2 ± 1.1	0.038	(−0.43–−0.01)
Days to have achieve clinical stability	3.8 ± 3.2	3.8 ± 3.3	3.9 ± 2.7	0.727	(−0.98–0.68)
Length of hospital stay	5.8 ± 3.5	5.8 ± 3.4	6.0 ± 4.0	0.597	(−1.16–0.67)
Total duration of antibiotics (days)	5.6 ± 2.8	5.6 ± 2.8	5.6 ± 2.7	0.994	(−0.73–0.73)

Data are presented in mean (SD).

prescribed in 30.4% and 69.6% for azithromycin and doxycycline, respectively. Cultures and respiratory multiplex PCR were obtained, in which, cultures were detected in about 28% of our study population. Majority of our cohort had length of hospital stay of 5 days or less (Figure 2). Total percentage of patients who achieved clinical stability within 3 days were 257 (57.5%), in which, 222 (58.6%) in azithromycin versus 35 (51.5%) in doxycycline containing regimen; $p = 0.275$. As viewed in (Table 2), the average days required to achieve clinical stability in both groups were 3.8 ± 3.2, in which, 3.8 ± 3.3 in azithromycin versus 3.9 ± 2.7 in doxycycline containing regimen; (95% CI–0.98–0.68; $p = 0.727$), which indicates no significant difference in primary nor in secondary endpoints between the two groups (Figure 3). All of our study population's predefined clinical stability parameters have improved from their baseline. Both groups had similar total duration of antibiotics use as displayed in (Figure 4).

7. Discussion

The findings of this observational retrospective cohort study support that using either doxycycline or macrolide containing regimen were comparable in achieving clinical stability within at least 3 days. Few studies have assessed the relative efficacy of doxycycline versus macrolide containing regimen in CAP. A large prospective study by Teh et al. evaluating 855 patients on doxycycline versus macrolides for the treatment of CAP has found that patients with CAP due to "atypical" bacterial pathogens and β-lactam plus doxycycline was at least comparable in outcomes and possibly superior in terms of reduced LOS compared to β-lactam plus macrolide ($p < 0.001$) [19]. A retrospective cohort study of mortality among CAP patients which used azithromycin for 5 days had an increased risk of cardiovascular death (HR, 2.88; 95% CI, 1.79 to 4.63; $p < 0.001$) and death from any cause (HR, 1.85; 95% CI, 1.25 to 2.75; $p = 0.002$), it is worth mentioning that it was evident more in patients who had a high risk of cardiovascular disease [20]. In another retrospective cohort study by Flanders et al. of 341 adult hospitalized patients with CAP treated with ceftriaxone plus doxycycline or other empiric regimens, ceftriaxone plus doxycycline resulted in lower inpatient mortality (OR 0.26, 95% CI: 0.08–0.81) and 30-day mortality (OR 0.37, 95% CI: 0.17–0.81) [21]. Another cohort retrospective study comparing azithromycin with other antibiotics in elderly hospitalized with CAP found a lower risk of 90-day mortality but a smaller increased risk of myocardial infarction [22]. *Clostridium difficile* infection (CDI) is a well-known cause of antibiotic-associated diarrhea, and doxycycline has possibly been less potentially to cause CDI. A large cohort study of hospitalized patients found that incidence of CDI was lower by 27% for each day for those who received doxycycline compared to those who received other antibiotics (HR, 0.73;

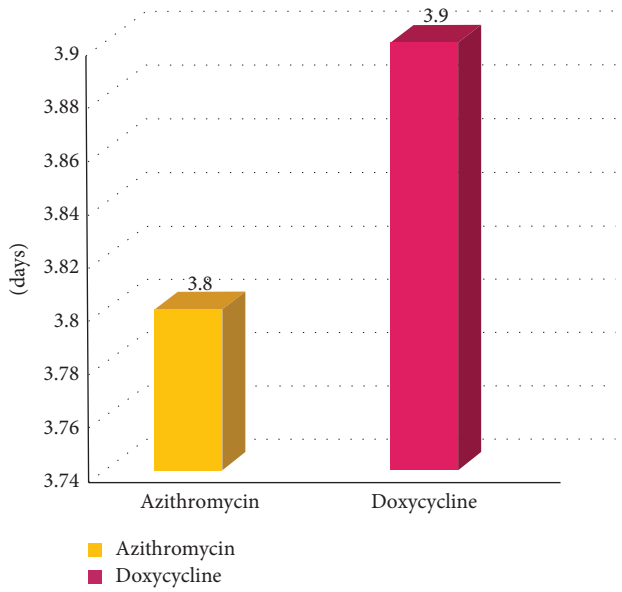

Figure 3: Average days required to achieve clinical stability.

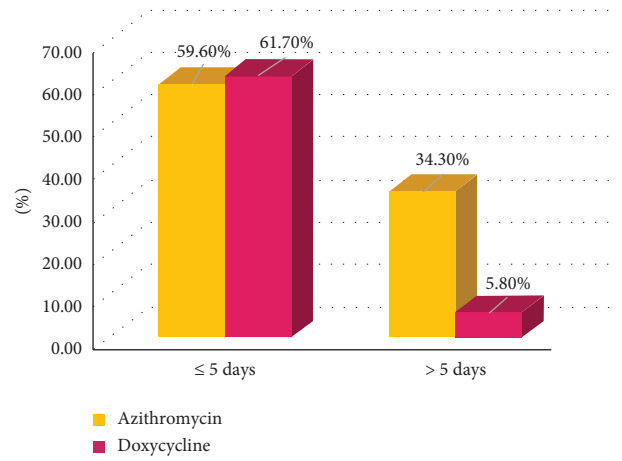

Figure 4: Total duration of antibiotics.

95% CI 0.56–0.96, p value 0.03) [23]. A recently published retrospective cohort study by Uddin et al. found that all-cause mortality within 30 and 90 days of admission were significantly lower for patients who received concurrent therapy with doxycycline compared to other guideline directed therapies (OR 0.72, 95% CI, 0.63–0.84) and (OR 0.83, 95% CI, 0.74–0.92), respectively [24].

Current literature along with our study results affirms that doxycycline appears to be a proper alternative to macrolides, in combination with a β-lactam for nonsevere inpatients with CAP as supported by current (ATS/IDSA) guideline recommendations. These findings would be of importance to those interested in cost difference, risk of *Clostridium difficile* rate, cardiovascular mortality, and the persistent increase of macrolide-resistance towards important respiratory pathogens [23, 25–29]. Practitioners should outweigh the risk versus benefit when choosing between these agents.

8. Limitation

We believe our study is limited due to being retrospective and noninterventional with selection of empiric therapy being decided by the treating physician based on patient's comorbidities. Also, cultures were not reported in most of the patients which could have impact choice of empiric therapy. Indeed, large randomized controlled trials are needed to compare doxycycline containing regimens versus other guideline therapy to ascertain these results.

Data Availability

The data supporting this study are available from the corresponding authors upon request.

Additional Points

Impact Statements. (1) Doxycycline has been regarded as an alternative to macrolide due to the limited evidence. (2) Doxycycline appears to be comparable to azithromycin when combined with β-lactam in achieving clinical stability for CAP. (3) Findings of this study would be of importance to those interested in cost difference, risk of *Clostridium difficile* rate, cardiovascular mortality, and the persistent increase of macrolide-resistance towards important respiratory pathogens.

Conflicts of Interest

The authors declare that they have no conflicts of interest in preparing this article.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Alaa Babonji, Sara Alshehri, and Abdulrahman Alturaiki. The first draft of the manuscript was written by Alaa Babonji and all authors commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

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