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Doxycycline Versus Azithromycin for the Treatment of Community-Acquired Pneumonia in Adults: A Multi-Centre Randomised Controlled Trial

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Abstract

Background: Community-acquired pneumonia (CAP) is a leading cause of infection-related morbidity and mortality. Optimal antibiotic selection between doxycycline and azithromycin for mild-to-moderate CAP in ambulatory patients remains debated.
Objective: To compare clinical cure rates, time to symptom resolution, and adverse effects of doxycycline versus azithromycin in outpatient adults with mild-to-moderate CAP.
Methods: A double-blind, randomised controlled trial enrolled 740 adults with CAP (PSI Class I–III) across 22 primary care and emergency department sites. Participants received doxycycline 100 mg twice daily for 7 days or azithromycin 500 mg on day 1 then 250 mg daily for 4 days.
Results: Clinical cure at day 14 was achieved in 84.3% of doxycycline recipients versus 81.1% of azithromycin recipients (difference 3.2%; 95% CI –1.9 to 8.3%; p=0.22). Median time to symptom resolution was 5 days in both arms. Gastrointestinal adverse events were more frequent with azithromycin (23.8% vs 14.6%; p=0.001).
Conclusion: Doxycycline and azithromycin demonstrate comparable clinical cure rates for outpatient CAP. Doxycycline may be preferred given its lower rate of gastrointestinal adverse effects and rising macrolide resistance.

Keywords: *Doxycycline Versus, Community-Acquired, Adults.*

INTRODUCTION

Community-acquired pneumonia (CAP) affects an estimated 450 million people annually and remains a leading cause of infection-related death, particularly in the elderly and immunocompromised [1]. In high-income countries, the majority of CAP episodes are managed in the outpatient setting, where empirical antibiotic therapy is the cornerstone of treatment [2].

Current guidelines from the Infectious Diseases Society of America (IDSA) and the British Thoracic Society (BTS) recommend either a macrolide or doxycycline for ambulatory patients with CAP who lack comorbidities, citing their activity against typical bacteria (Streptococcus pneumoniae) and atypical pathogens (Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella spp.) [3,4]. Azithromycin has historically been the most prescribed macrolide in this setting due to its convenient once-daily dosing, excellent tissue penetration, and established efficacy [5].

However, rising macrolide resistance among S. pneumoniae, now exceeding 30% in some geographic regions, has raised concerns about the ongoing utility of azithromycin for empirical CAP therapy [6]. Doxycycline, a tetracycline antibiotic, retains broad activity against both typical and atypical CAP pathogens and is not subject to the same resistance pressures as macrolides. A 2021 surveillance study across 15 countries found resistance rates to doxycycline among S. pneumoniae isolates of less than 10%, compared with 28–42% for azithromycin [7].

Despite these resistance considerations, doxycycline has been less extensively studied in prospective randomised trials for CAP compared with macrolides. A 2019 Cochrane review identified only four randomised trials directly comparing doxycycline and macrolides for CAP, totalling fewer than 800 participants, and found no statistically significant difference in clinical cure rates but noted important limitations in trial quality and reporting [8].

The present trial was undertaken to provide contemporary, high-quality evidence on the comparative efficacy and tolerability of doxycycline versus azithromycin in a large, pragmatic outpatient CAP population stratified by severity using the Pneumonia Severity Index (PSI) [9]. Given evolving resistance patterns and the need for antibiotic stewardship guidance, such data are urgently needed [10,11].

MATERIALS AND METHODS

Study Design: A multi-centre, double-blind, double-dummy randomised controlled trial was conducted across 22 primary care clinics and emergency departments in five countries from March 2021 to June 2023 (NCT04895612). The trial was approved by all relevant ethics committees and registered prospectively.

Participants: Adults aged ≥18 years presenting with CAP (defined by clinical criteria plus radiographic confirmation) and PSI risk class I–III were eligible. Exclusion criteria included hospitalisation requirement (PSI IV–V), prior antibiotic use within 72 hours, allergy to doxycycline or macrolides, pregnancy or lactation, and confirmed atypical pathogen requiring alternative therapy.

Randomisation and Treatment: Participants were randomised 1:1 (stratified by PSI class and site) to oral doxycycline 100 mg twice daily for 7 days plus azithromycin-matched placebo, or azithromycin 500 mg on day 1 then 250 mg daily for days 2–5 plus doxycycline-matched placebo. Both active drug and placebo were encapsulated to maintain blinding.

Outcomes: The primary endpoint was clinical cure at day 14, defined as resolution or improvement of all CAP symptoms (cough, fever, dyspnoea, pleuritic chest pain) without requirement for additional antibiotics. Secondary endpoints included time to symptom resolution (patient diary), treatment failure, hospitalisation, adverse events, and C-reactive protein normalisation at day 7.

Statistical Analysis: The trial was powered to detect non-inferiority of doxycycline to azithromycin using a pre-specified margin of –8 percentage points (one-sided α=0.025, power=80%). The primary analysis was performed in the per-protocol population. Adverse events were analysed in all randomised participants who received at least one dose.

RESULTS

Table 1. Baseline Characteristics

Characteristic	Doxycycline (n=370)	Azithromycin (n=370)	p-value
Mean age, years (SD)	52.4 (16.8)	53.1 (17.2)	0.58
Female sex, n (%)	196 (53.0%)	198 (53.5%)	0.89
PSI Class I, n (%)	168 (45.4%)	172 (46.5%)	0.77
PSI Class II, n (%)	138 (37.3%)	134 (36.2%)	0.77
PSI Class III, n (%)	64 (17.3%)	64 (17.3%)	1.00
Diabetes mellitus, n (%)	74 (20.0%)	72 (19.5%)	0.86
Duration of symptoms before enrolment, days	3.2 (1.8)	3.3 (1.9)	0.56
CRP at baseline, mg/L (median, IQR)	48.2 (22–88)	47.6 (21–86)	0.84

SD = standard deviation; PSI = Pneumonia Severity Index; CRP = C-reactive protein; IQR = interquartile range.

Table 2. Efficacy Outcomes

Outcome	Doxycycline	Azithromycin	Difference (95% CI)	p-value
Clinical cure at day 14, n (%)	312 (84.3%)	300 (81.1%)	3.2% (–1.9 to 8.3%)	0.22
Treatment failure, n (%)	38 (10.3%)	46 (12.4%)	–2.2% (–6.4 to 2.1%)	0.31
Hospitalisation, n (%)	14 (3.8%)	18 (4.9%)	–1.1% (–3.8 to 1.6%)	0.42
Median time to resolution, days	5 (IQR 3–7)	5 (IQR 3–7)	0	0.88
CRP normalisation at day 7, n (%)	284 (76.8%)	278 (75.1%)	1.7% (–4.2 to 7.6%)	0.57
Return to normal	7.2 (3.4)	7.0 (3.2)	0.2 (–0.4 to 0.8)	0.50

activities, days				

CI = confidence interval; CRP = C-reactive protein; IQR = interquartile range.

Table 3. Adverse Events

Adverse Event	Doxycycline n (%)	Azithromycin n (%)	p-value
Any adverse event	102 (27.6%)	116 (31.4%)	0.24
Gastrointestinal events	54 (14.6%)	88 (23.8%)	0.001
Nausea	32 (8.6%)	58 (15.7%)	0.004
Diarrhoea	28 (7.6%)	44 (11.9%)	0.042
Photosensitivity	16 (4.3%)	4 (1.1%)	0.006
Headache	22 (5.9%)	18 (4.9%)	0.50
Drug discontinuation	14 (3.8%)	12 (3.2%)	0.70

All adverse events were grade 1–2 (mild-to-moderate) unless otherwise stated.

Table 1 shows well-balanced baseline characteristics across both arms. Table 2 demonstrates non-inferior clinical cure rates for doxycycline compared with azithromycin (84.3% vs 81.1%; difference 3.2%; lower bound of 95% CI –1.9%, above the pre-specified non-inferiority margin of –8%). Time to symptom resolution and CRP normalisation were comparable between groups. Table 3 reveals a significantly lower rate of gastrointestinal adverse events with doxycycline (14.6% vs 23.8%; p=0.001), though photosensitivity was more common with doxycycline (4.3% vs 1.1%; p=0.006).

DISCUSSION

This trial demonstrates that doxycycline is non-inferior to azithromycin for clinical cure of mild-to-moderate outpatient CAP, with an absolute difference of 3.2% in favour of doxycycline and a lower confidence interval bound of –1.9%, well above the pre-specified non-inferiority margin of –8%. These results corroborate and substantially extend the limited prior comparative data [8], providing the most robust evidence to date supporting doxycycline as an equivalent alternative to azithromycin for empirical outpatient CAP.

A key finding of this trial is the significantly lower rate of gastrointestinal adverse events with doxycycline (14.6% vs 23.8%), driven primarily by lower rates of nausea and diarrhoea. Azithromycin is well known for its gastrointestinal prokinetic effects mediated through motilin receptor agonism [12], which can significantly impact patient experience and adherence. The better GI tolerability profile of doxycycline may translate to improved adherence in clinical practice, though this was not formally assessed in the present study.

Photosensitivity, a class effect of tetracyclines, was more frequent with doxycycline (4.3% vs 1.1%). Although all events were mild in nature, clinicians should counsel patients receiving doxycycline to use sun protection, particularly in the summer months or in tropical climates. This adverse effect is well-characterised and generally manageable [13].

From an antibiotic stewardship perspective, the findings support a preference for doxycycline in settings with high macrolide resistance. The 2023 Global Antimicrobial Resistance and Use Surveillance System (GLASS) report documented azithromycin resistance rates in S. pneumoniae exceeding 30% in several high-income countries [6], raising concern about empirical macrolide monotherapy for CAP. Doxycycline resistance in S. pneumoniae remains substantially lower, making it a more reliable empirical choice [7].

This trial has several strengths, including its double-blind design, radiographic confirmation of pneumonia in all patients, pre-specified non-inferiority analysis, and diverse multinational population. Limitations include the exclusion of severe CAP (PSI IV–V), the lack of microbiological identification in most patients (precluding pathogen-specific subgroup analyses), and the relatively short 14-day follow-up that may have missed late recurrence.

CONCLUSION

Doxycycline is non-inferior to azithromycin for clinical cure of mild-to-moderate community-acquired pneumonia in outpatient adults, with a more favourable gastrointestinal tolerability profile. In the context of rising macrolide resistance, doxycycline should be considered a first-line empirical therapy for outpatient CAP, consistent with antibiotic stewardship principles.

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