


## BRIEF COMMUNICATION

# Appropriate prescribing of azithromycin for community-acquired pneumonia

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azithromycin, community-acquired pneumonia, antimicrobial stewardship, prolonged QT interval, arrhythmia, therapeutic guideline.

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**Abstract**

Azithromycin is prescribed for atypical antimicrobial cover in severe community-acquired pneumonia. Inappropriate azithromycin administration incurs unnecessary financial costs, exacerbates antimicrobial resistance and risks QTc interval prolongation leading to cardiac arrhythmias. The present study demonstrated that a majority of patients were prescribed azithromycin without having electrocardiograms to assess the QTc interval and without meeting criteria for severe community-acquired pneumonia based on CURB-65 score.

The empirical treatment of community-acquired pneumonia (CAP) includes antibiotics that cover atypical organisms, namely *Mycoplasma*, *Chlamydia* and *Legionella*.<sup>1–3</sup> A 2017 meta-analysis demonstrated that empirical atypical coverage was associated with reduced clinical failure in hospitalised adults with CAP.<sup>4</sup> As aetiological diagnosis is often not available initially, the choice of empirical antibiotic treatment for CAP is dictated by the severity of presentation, which can be calculated by scoring systems such as CURB-65.<sup>5</sup> For mild to moderate CAP, the Australian Therapeutic Guidelines suggest doxycycline for atypical cover, while for severe CAP, azithromycin is recommended.<sup>6</sup> Unless *Legionella* is identified as the specific pathogen, when transitioning patients initially on intravenous azithromycin to oral antibiotics, doxycycline is recommended.<sup>6</sup> Rationalising azithromycin use aligns with antimicrobial stewardship principles, which aim to mitigate antimicrobial resistance and prevent patient harm.<sup>7</sup>

QTc interval prolongation is an established side effect of macrolide antibiotics, leading to fatal arrhythmias and sudden cardiac death.<sup>8</sup> A 2012 study published in the *New*

*England Journal of Medicine* concluded a small absolute increase in cardiovascular deaths in patients treated with azithromycin, with the most pronounced effect among patients with a high baseline cardiovascular risk.<sup>9</sup> The potentially serious cardiac toxicity associated with azithromycin suggests that it should be used with caution.

Antimicrobial resistance is an emerging contemporary challenge threatening the ability to combat bacterial infections. Resistance to azithromycin is particularly concerning because there are limited alternatives for treating certain pathogens such as *Gonorrhoea* and *Streptococcus*.<sup>10,11</sup> Studies investigating mass azithromycin distribution to preschool children in sub-Saharan Africa suggest that these programmes exacerbate macrolide resistance.<sup>12</sup> These studies highlight the importance of minimising unnecessary azithromycin use to mitigate further antimicrobial resistance.

This audit's main objective was to assess the appropriateness of azithromycin prescribing for patients admitted with CAP. The primary end-point was the proportion of patients prescribed azithromycin despite having prolonged QTc intervals on their admission electrocardiograms (ECG). The secondary end-points were the proportion of patients who had ECGs prior to azithromycin administration, the proportion of patients prescribed azithromycin without meeting criteria for

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severe CAP based on their admission CURB-65 scores and the proportion of patients prescribed azithromycin for longer than the maximum recommended duration of 5 days for non-*Legionella* CAP.

The South Eastern Sydney Local Health District Human Research Ethics Committee Low and Negligible Risk Subcommittee deemed this project a quality assurance or quality improvement activity not requiring independent ethics review.

All adult inpatients at St George Hospital (NSW, Australia) prescribed azithromycin between July and December 2019 were identified from pharmacy records. The electronic medical records (EMR) of these 105 patients were reviewed. In total, five patients were excluded. Two patients were excluded because they were already on regular prophylactic azithromycin prior to their admission. Two patients were excluded because they were prescribed azithromycin later in their admission after clinical deterioration while on other antibiotics. One patient was excluded because they discharged against medical advice before azithromycin was administered. A final sample of 100 patients prescribed azithromycin for a preliminary diagnosis of CAP was included for data analysis.

On admission, each patient's CURB-65 score was calculated based on age, presence of confusion, serum urea, respiratory rate and blood pressure. A CURB-65 score of 3 or more is considered 'severe'. The total duration of azithromycin administration, including both intravenous and oral routes, was recorded. If an ECG was documented on admission, the patient's QTc was calculated manually with the Bazett formula based on the QT interval and heart rate. The cut-offs used for prolonged QTc interval were 440 ms in male patients and 460 ms in female patients. In patients with prolonged QTc intervals, further data regarding other QT-prolonging medications and their electrolytes were gathered. Results of investigations to identify atypical organisms, including urinary antigens, sputum cultures and serology, were also collected.

Simple descriptive statistics to calculative proportions, averages and ranges comprised the majority of data analysis.

Patient characteristics are summarised in Table 1. The average age of patients was  $72.6 \pm 16.9$  years. There were 45 (45.0%) female patients and 55 (55.0%) male patients.

Thirty-three (33%) patients did not have ECGs documented. Of the 67 patients who had ECGs documented, 10 (14.9%) patients were prescribed azithromycin despite having prolonged QTc intervals. For patients with prolonged QTc intervals, the calculated QTc intervals ranged from 446 to 487 ms, with the average QTc interval being 464 ms. The average age of patients with prolonged QTc intervals was  $81.7 \pm 10.7$  years. Of the

**Table 1** Characteristics of 100 patients prescribed azithromycin for community-acquired pneumonia

Characteristic	Value
Sex, n (%)	
Female	45 (45.0)
Male	55 (55.0)
Age, mean (SD) (years)	72.6 (16.9)
CURB-65 score, n (%)	
0–1 (mild)	33 (33.0)
2 (moderate)	27 (27.0)
3–5 (severe)	36 (36.0)
QTc interval <sup>†</sup>	
Normal	57 (85.1)
Prolonged	10 (14.9)

<sup>†</sup>There are 33 missing observations for QTc interval due to electrocardiogram not being performed/documented.

10 patients with prolonged QTc intervals on admission, two patients had follow-up ECGs during their admission. Six of the patients with prolonged QTc intervals had a background of other cardiovascular diseases, including atrial fibrillation, congestive cardiac failure, ischaemic heart disease, valvular abnormalities and previous pacemaker insertion. Four of the patients with prolonged QTc intervals were also prescribed other QT prolonging medications while taking azithromycin. Three of the patients with prolonged QTc intervals did not have their serum calcium or magnesium checked during their admission. None of the patients with prolonged QTc intervals experienced fatal cardiac arrhythmias during their admission.

Ten (10.0%) patients required an intensive care unit admission. Two (2.0%) patients died during their admission, neither of whom had prolonged QTc intervals.

A total of 64 (64.0%) patients was prescribed azithromycin without meeting the criteria for severe CAP based on their CURB-65 score (i.e. had a CURB-65 score of  $\leq 2$ ). Data were collected about diagnostic investigations (sputum culture, urinary antigens and serology) to identify the aetiology of each patient's CAP. Of the 76 (76.0%) patients who underwent investigation for aetiological diagnosis of CAP during their admission, none had an atypical organism. A total of 28 (28.0%) patients was prescribed azithromycin for longer than the maximum recommended 5 days for non-*Legionella* pneumonia. The average number of days of azithromycin administration was  $4.58 \pm 1.8$  days.

## Discussion

We found scant documentation of routine QTc interval review prior to azithromycin administration. Of the

patients who had prolonged QTc intervals, a majority did not have follow-up ECG to monitor their QTc intervals. Whether azithromycin use causes fatal cardiac arrhythmias due to QTc interval prolongation remains controversial. Some studies have found nil association between azithromycin and an increased risk of cardiovascular death.<sup>13</sup> Other studies have found a positive association between azithromycin use and cardiac arrhythmias such as torsades de pointes.<sup>14</sup> While nil cardiac arrhythmias occurred in our sample of patients, the theoretical possibility of such adverse effects exists. Further research needs to be conducted, perhaps as prospective cohort studies, which monitor QTc interval of patients prescribed azithromycin. In the interests of patient safety, clinical practice guidelines may consider recommending screening ECG prior to azithromycin administration, monitoring QTc intervals while on azithromycin, and optimisation of other factors which may contribute to prolonged QTc interval, such as monitoring serum electrolytes, as well as avoidance of other QTc prolonging medications when possible.

There are potentially also benefits of early transition from intravenous to oral azithromycin if clinically appropriate. While the Australian Therapeutic Guidelines recommend intravenous azithromycin for patients with severe CAP, evidence suggests that the efficacy of oral azithromycin is comparable to the intravenous route. While the bioavailability of oral azithromycin is approximately 37%, tissue concentrations exceed serum concentrations by up to 100-fold following a single 500 mg dose of oral azithromycin.<sup>15</sup> Lung tissue, in particular, has high concentrations of azithromycin following oral administration.<sup>16</sup> Not only is oral azithromycin significantly less expensive, but it also mitigates the complications of IV drug administration such as infection and thrombophlebitis.<sup>17</sup> Several observational studies and randomised control trials have demonstrated that early switch from intravenous to oral antibiotics reduces length of hospitalisation and is not associated with worsened mortality or reduced cure rates.<sup>18–20</sup> Further research could be conducted to investigate outcomes when patients with severe CAP are initially commenced on oral azithromycin instead of intravenous azithromycin.

Multiple factors limit the conclusions that can be drawn from this study. As this was a retrospective study,

data regarding ECG documentation is likely to be incomplete. The proportion of patients who did not have ECGs documented is likely to be overestimated as it is possible that patients had ECGs printed on paper, which were not transferred to EMR. The fact that nil cardiac arrhythmias were observed may also be attributable to the small sample size of this study which is unlikely to be representative of the true incidence of cardiac arrhythmias in patients prescribed azithromycin in the general population.

The CURB-65 score was chosen as the basis for the classification of CAP severity because all the parameters used to calculate the CURB-65 score were available for all patients in EMR. The disadvantage of using CURB-65 to assess the appropriateness of azithromycin administration is that it does not account for all factors that a clinician may have considered when they decided to prescribe an individual patient with azithromycin. For example, an individual patient may have already undertaken a course of doxycycline prescribed by their general practitioner before their admission, there may have been a strong clinical suspicion for *Legionella* infection.

Our data suggest that a concerning incidence of patients were prescribed azithromycin without evidence of QTc interval screening or despite prolonged QTc intervals. In addition, the majority of patients prescribed azithromycin for CAP did not meet criteria for empirical therapy based on their pneumonia severity. The appropriate prescription of azithromycin is an important goal in the interests of patient safety, hospital outcomes and antimicrobial stewardship. Thus, the implementation of further protocols to promote this is necessary. Due to the limitations of this retrospective study and the gaps in the current literature, further prospective cohort studies will be valuable in exploring the cardiac effects of azithromycin as well as the efficacy of oral azithromycin compared to the intravenous route of administration.

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## References

- File TM Jr, Eckburg PB, Talbot GH, Llorens L, Friedland HD. Macrolide therapy for community-acquired pneumonia due to atypical pathogens: outcome assessment at an early time point. *Int J Antimicrob Agents* 2017; **50**: 247–51.
- Charles PG, Whitby M, Fuller AJ, Stirling R, Wright AA, Korman TM *et al*. The etiology of community-acquired pneumonia in Australia: why penicillin plus doxycycline or a macrolide is the most appropriate therapy. *Clin Infect Dis* 2008; **46**: 1513–21.
- Restrepo MI, Sole-Violan J, Martin-Loeches I. Macrolide therapy of

- pneumonia: is it necessary and how does it help? *Curr Opin Infect Dis* 2016; **29**: 212–7.
- 4 Eljaaly K, Alshehri S, Aljabri A, Abraham I, Al Mohajer M, Kalil AC *et al*. Clinical failure with and without empiric atypical bacteria coverage in hospitalized adults with community-acquired pneumonia: a systematic review and meta-analysis. *BMC Infect Dis* 2017; **17**: 385.
  - 5 Marti C, Garin N, Groscurin O, Poncet A, Combesure C, Carballo S *et al*. Prediction of severe community-acquired pneumonia: a systematic review and meta-analysis. *Crit Care* 2012; **16**: R141.
  - 6 eTG Complete. *Community-Acquired Pneumonia in Adults*. Melbourne: Therapeutic Guidelines Limited; 2019 [cited 2021 Aug 20]. Available from URL: <https://www.tg.org.au>
  - 7 Viasus D, Vecino-Moreno A, De-La Hox JM, Carratala J. Antibiotic stewardship in community-acquired pneumonia. *Expert Rev Anti Infect Ther* 2017; **15**: 351–9.
  - 8 Albert RK, Schuller JL. COPD clinical research network. Macrolide antibiotics and the risk of cardiac arrhythmias. *Am J Respir Crit Care Med* 2014; **189**: 1173–80.
  - 9 Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012; **366**: 1881–90.
  - 10 Derbie A, Mekonnen D, Woldeamanuel Y, Abebe T. Azithromycin resistant gonococci: a literature review. *Antimicrob Resist Infect Control* 2020; **9**: 138.
  - 11 Bergman M, Huikko S, Huovinen P, Paakkari P, Seppälä H. Macrolide and azithromycin use are linked to increased macrolide resistance in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* 2006; **50**: 3646–50.
  - 12 Mack I, Sharland M, Berkley JA, Klein N, Malhotra-Kumar S, Bielicki J. Antimicrobial resistance following azithromycin mass drug administration: potential surveillance strategies to assess public health impact. *Clin Infect Dis* 2020; **70**: 1501–8.
  - 13 Svanstrom H, Pasternak B, Hviid A. Use of azithromycin and death from cardiovascular causes. *N Engl J Med* 2013; **368**: 1704–12.
  - 14 Hancox JC, Hasnain M, Vieweg WV, Crouse EL, Baranchuk A. Azithromycin, cardiovascular risks, QTc interval prolongation, torsade de pointes, and regulatory issues: a narrative review based on the study of case reports. *Ther Adv Infect Dis* 2013; **1**: 155–65.
  - 15 Lode H. The pharmacokinetics of azithromycin and their clinical significance. *Eur J Clin Microbiol Infect Dis* 1991; **10**: 807–12.
  - 16 Morris DL, De Souza A, Jones JA, Morgan WE. High and prolonged pulmonary tissue concentrations of azithromycin following a single oral dose. *Eur J Clin Microbiol Infect Dis* 1991; **10**: 859–61.
  - 17 Jit M, Ng D, Luangsanatip N, Sandmann F, Atkins KE, Robotham JV *et al*. Quantifying the economic cost of antibiotic resistance and the impact of related interventions: rapid methodological review, conceptual framework and recommendations for future studies. *BMC Med* 2020; **18**: 38.
  - 18 Oosterheert JJ, Bonten MJ, Schneider MM, Buskens E, Lammers JW, Hustinx WM *et al*. Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. *BMJ* 2006; **333**: 1193.
  - 19 Ramirez JA, Srinath L, Ahkee S, Huang A, Raff MJ. Early switch from intravenous to oral cephalosporins in the treatment of hospitalized patients with community-acquired pneumonia. *Arch Intern Med* 1995; **155**: 1273–6.
  - 20 Ramirez JA, Vargas S, Ritter GW, Brier ME, Wright A, Smith S *et al*. Early switch from intravenous to oral antibiotics and early hospital discharge: a prospective observational study of 200 consecutive patients with community-acquired pneumonia. *Arch Intern Med* 1999; **159**: 2449.