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Kirby, A (2015) Comment on: Clinical cure rates in subjects treated with azithromycin for community-acquired respiratory tract infections caused by azithromycin-susceptible or azithromycin-resistant Streptococcus pneumoniae: analysis of Phase 3 clinical trial data. Journal of Antimicrobial Chemotherapy, 70 (11). 3170 - 3170. ISSN 0305-7453

https://doi.org/10.1093/jac/dkv212

Title: Comment on: Clinical cure rates in subjects treated with azithromycin for community-acquired respiratory tract infections caused by azithromycin-susceptible or azithromycin-resistant *Streptococcus pneumoniae*: analysis of Phase 3 clinical trial data.

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Running title: *S. pneumoniae* azithromycin MICs and clinical outcome.

Comment on: Clinical cure rates in subjects treated with azithromycin for community-acquired respiratory tract infections caused by azithromycin-susceptible or azithromycin-resistant *Streptococcus pneumoniae*: analysis of Phase 3 clinical trial data.

Zhanel *et al*. report that *Streptococcus pneumoniae* azithromycin MICs ≥2mg/L, compared to <0.5mg/L, predict worse outcomes in azithromycin treated *S. pneumoniae* respiratory tract infections.[1] This relationship between MIC and outcome is not a linear dose (MIC) response relationship. Whilst an MIC ≥2mg/L predicts worse outcomes, outcomes are no different if the *S. pneumoniae* MIC is 2-8mg/L, ≥16 or ≥ 64mg/L. The absence of a linear dose (MIC) response relationship is not explained and raises the possibility that the MIC is not causally related to outcomes.[2] Defining if an MIC is causally related to outcome is important to ensure the maximal benefit from azithromycin treatment can be obtained. Given this non-linear dose response relationship I suggest further analysis is required to understand the study findings. Specifically, an analysis of individual patient factors should be completed. It may be that patient factors e.g. age, co-morbidities, previous episodes of respiratory tract infection or macrolide treatment, are associated with both treatment failure and azithromycin MICs. A study by Moreno *et al*. supports this possible explanation, they showed nosocomial acquisition of a *S. pneumoniae* infection was a risk factor for macrolide (erythromycin) resistance.[3] Data from Holmes *et al*. has also shown that raised MICs are not always causally related to outcomes. Holmes *et al*. investigated outcomes from *Staphylococcus aureus* bacteraemia in relation to vancomycin MICs.[4] A multivariate analysis determined that raised vancomycin MICs were associated with poorer clinical outcomes, even in the absence of vancomycin treatment. Might a raised *S. pneumoniae* azithromycin MIC also be a predictor of a poorer outcome, but not one related to a reduced efficacy of azithromycin treatment? A multivariate analysis is required to determine if patient factors may explain the observed association between azithromycin resistance and outcome in the treatment of *S. pneumoniae* respiratory tract infection. Such analyses have been completed for penicillin treated *S. pneumoniae* respiratory tract infections. One such analysis by Pallares *et al*. showed that after adjusting for co-morbidities the odds ratio for mortality in patients with penicillin-resistant, compared to penicillin sensitive strains, was 1.0.[5] If patient factors do explain the association between MICs of ≥2mg/L and clinical failure, MIC criteria defining resistance for azithromycin treatment of *S. pneumoniae* respiratory tract infections may be unhelpful in predicting an individuals risk of treatment failure.

Transparency declarations: None to declare

References

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