Reviewer's report

Title: Cardiac events after macrolides or fluoroquinolones in patients hospitalized for community-acquired pneumonia: post-hoc analysis of a cluster-randomized trial

Version: 0 Date: 01 Oct 2018
Reviewer: Grant W. Waterer

Reviewer's report:

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This is a post-hoc analysis of the Dutch CAP trial published several years ago.

The findings are important because they highlight a major problem with that trial - that Erythromycin was a the major macrolide in the "dual-therapy arm" and it is well known that Erythromycin given intravenously has more cardiac problems. It is unlikely to change practice in most parts of the world as erythromycin is very much a "dead" drug in the CAP space because of its known toxicity issues.

I have a number of queries and suggestions.

1. Over 20% of patients did not have radiology confirmation of CAP. This is an important limitation acknowledged in table 5 and the text but should be referred to in the abstract.

2. Table 3 shows that there were marked differences in the beta-lactam antibiotics used with and without erythromycin. Benzpen was rarely used with the non-erythromycin macrolides. We need to see some breakdown of demographics and outcomes for the most common combinations. I would suggest pen/ery, amox/cipro and amoxyclav/cipro (could be grouped), cefuroxime/ery, ceftriaxone/azith. The large amount of benzpen with ery raises the possibility that this is not an ery effect (although I think it is), but an effect of different penicillins.

3. Another fundamental issue with the primary trial was the 40% of patients who were given dual antibiotics despite being in a monotherapy arm. It would be good to see the cardiac outcomes based on monotherapy PP, dual therapy despite monotherapy protocol and dual therapy by protocol to see if clinicians had introduced some bias here in who they
selected to overrule the monotherapy designation (that then explains the higher complication rates).

4. No pathogen data is presented - yet there is significant evidence that some pathogens are associated with worse cardiac outcomes (pneumococci and influenza). Even if they do not have sufficient data to analyse by pathogen this should be included.

5. The implications for the findings of this post-hoc study on the original publication are not discussed but need to be. Intravenous erythromycin is toxic and no longer used in most countries. However in this study the overwhelmingly most common macrolide in the "dual therapy" by protocol arm was iv erythromycin - which they have now shown is associated with worse outcomes than azithromycin or fluroquinolones which were used in the "dual therapy" patients randomised to the "monotherapy" arm. Some reflection is needed in the discussion and abstract.

6. There are some randomised trials in this space that are relevant with respect to higher side effects with erythromycin - e.g. Tamm et al Clin Microbiol Infect 2007, Vergis et al Arch Intern Med 2000,

7. The studies that have shown a benefit of macrolide combination therapy have universally NOT used erythromycin except Mufson et al. This is an important observation relevant to the findings of this study.

8. Reference 7 is misquoted. This paper showed lower cardiac events and mortality with azithromycin compared to non macrolide combinations.

9. Under potential explanations as to why erythromycin did not do as well, there is reasonable evidence that erythromycin may not be as effective an anti-inflammatory agent as the other macrolides (see for example Ersoy et al J Laryngol Otol 2018 but there are others). This may be important if the heart failure is driven by pro-inflammatory cytokines.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

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