Author's response to reviews

Title: Relapse under azithromycin treatment in a case of bacteremia due to Salmonella enterica Paratyphi A

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Author's response to reviews: see over
Dear Dr. Hung,

Thank you for reviewing our manuscript entitled “Azithromycin treatment failure in a case of bacteremia due to Salmonella enterica Paratyphi A” (MS: 6007824591243462).

We truly appreciate the editor and reviewers for their close attention and thoughtful comments with regard to our manuscript, and greatly appreciate their time and effort. We have taken their comments into careful consideration in preparing our revision, which we believe has helped us improve the substance and presentation of our study.

We have listed each of the reviewer’s comments below (in italics), along with our responses.

REVIEWER #1
Major Compulsory Revisions:
Comment 1
This is an interesting case of azithromycin treatment failure in a patient with a Salmonella enterica Paratyphi A infection. In this paper the authors refer to another publication about treatment failure due to possible azithromycin resistance (MIC >16 mg/L). To my opinion a different problem should be discussed in this paper; namely treatment failure in an infection with a wild type/“susceptible” isolate. This case report could be of more interest if the author would expand more on this issue. For example, isn’t it questionable that some guidelines, in the case of a Salmonella infection, advise to treat a bacteremia caused by a Gram-negative organism with an oral bacteriostatic drug? Elaborate more on the clinical studies performed with azithromycin: which dosages are used in these studies? How many studies are comparable with your treatment (500 mg daily/80 kg)? (Girgis NI et al. Antimicrob Agents Chemother. 1999, Butler T et al. J Antimicrob Chemother. 1999, Parry CM et al. Antimicrob Agents Chemother. 2007, Chinh NT et al. Antimicrob Agents Chemother. 2000, Dolecek C et al. PLoS One. 2008). Since all of these studies are performed in endemic countries, where the need for an oral drug in the treatment of enteric fever is high, the authors could discuss more if the conclusions of these studies also apply to an ill returned traveler in a developed country like Japan.

We appreciate reviewer’s insightful comments. We revised the discussion according to reviewer’s suggestion.
Comment 2
The authors should confirm the MICs of azithromycin with a reference method (broth- or agar-dilution method). It is known that E-test results may not be congruent with reference dilution test results.

We thank reviewer’s comment. We added the result of MIC values based on broth-dilution method.

Minor Essential Revisions:
Comment 3
Line 63: S. Paratyphi B and C are also possible causative pathogens of enteric fever.

We revised the sentence.

Comment 4
Line 110: Since the authors refer to reports from clinical trials, the word efficacy should be used instead of effectiveness.

We changed “effectiveness” to “efficacy”.

Discretionary Revisions
Comment 5
Line 100: Did the patient have any signs of cholelithiasis or other biliary tract abnormalities (for example, did you also perform a CT scan together with the FDG-PET)?

We performed FDG PET-CT scan as well as abdominal sonography. We revised the sentence accordingly.

Comment 6
Line 125: We recently published the MIC distribution of 354 typhoidal Salmonella isolates of ill returned travelers collected during 1999-2012 in the Netherlands (Hassing RJ et al. Emerg Infect Dis 2014). In this case series a minority of the S. Paratyphi A isolates showed an MIC of 8. This reference can be used as an example of azithromycin MIC distribution in travelers.

We thank reviewer’s comment. We included the data and reference.

REVIEWER 2
Major Compulsory Revisions
1. Well-documented cases of Salmonella Paratyphi A resistance to azithromycin are rare as are clinical treatment failures with azithromycin are rare too, reason why this report is interesting. Of note – the authors could mention the report of
Fernando (Pathogens and Global Health, 2012; 106: 366-368) as an additional case next to the report of Molloy and co-workers (authors’ reference 13). We appreciate reviewer’s comment. We added the suggested reference, and revised the discussion accordingly.

2. Clinical failure occurred with an isolate at a MIC of 8 mg/l, which is, as the authors describe, within the range that is considered effective (EUCAST), and failure occurred after full treatment with ceftriaxone. This means that other reasons for treatment failure such as “conventional” relapse (approx. 10% of patients with enteric fever) should be exploited and microbiological data should be confirmed.

As we described in the previous submission, we consider his second of bacteremia as “relapse” of the first episode which was treated by ceftriaxone for 14 days. For his “relapse” (i.e. his second time bacteremia), we treated the patient with azithromycin, which resulted in clinical (i.e. sustained fever over 7 days) as well as microbiological failure (i.e. repeated blood culture remained positive after azithromycin treatment course of 7 days). These definitions of clinical failure were used in multiple previous reports (PMID: 17145784, PMID: 18493312, PMID: 10858343). Therefore, we believe it as “clinical failure of azithromycin treatment”, not as “relapse after azithromycin treatment” (relapse was actually after ceftriaxone treatment).

-What is the clinical significance of the thickening intestinal wall of the colon on the PET scan?

We thank reviewer’s comment. We added the information to discussion section, and revised the manuscript accordingly.

- Have there been other investigations done to rule out deep-seeded infections (abscesses, aortitis…)

We added the information and revised the manuscript accordingly.

- Has the azithromycin MIC value been confirmed by a reference laboratory?

It was confirmed by a reference laboratory. We revised the result section accordingly.

In addition, as the authors state, a dose of 500mg daily for an adult patient of 80 kg is (too) low (Dolececk2008, WHO2003).

We revised the discussion section accordingly.

I suggest to re-work the case report:
- A more appropriate title could be “...relapse under azithromycin treatment”,

We respectfully disagree with reviewer.
As we described in the previous submission, we consider his second of bacteremia as “relapse” of the first episode which was treated by ceftriaxone for 14 days.
For his “relapse” (i.e. his second time bacteremia), we treated the patient with azithromycin, which resulted in clinical (i.e. sustained fever over 7 days) as well as microbiological failure (i.e. repeated blood culture remained positive after azithromycin treatment course of 7 days). These definitions of clinical failure were used in multiple previous reports (PMID: 17145784, PMID: 18493312, PMID: 10858343). Therefore, we believe it as “clinical failure of azithromycin treatment”, not as “relapse after azithromycin treatment” (relapse was actually after ceftriaxone treatment). If editor suggests to revise the title to “…relapse under azithromycin treatment”, we would do so.

- The Discussion and the Abstract should refer to the issue of correct dosage of azithromycin in typhoid fever

We revised the manuscript accordingly.

- Comments above (better description/more evidence about of ruling-out of deep-seeded infection; microbiological confirmation by reference laboratory.

We added the information, and revised the manuscript.

- Minor Essential Revisions
  1. Strictly speaking, the genus name “Salmonella” cannot be abbreviated in the case of serovar name (Salmonella Paratyphi and Salmonella Typhi).
  2. Abstract line 58: infections (add “s”)
  3. L80: “Blood culture were positive...”: replace by “Blood cultures grew with Gram-negative rods which were...”
  4. L93: “less sensitive”: replace by “showed decreased susceptibility to”
  5. L94: Biomérieux
  6. L97: delete “test”
  7. L104: “was negative”: replace by “yielded no growth”
  8. L122: replace “subspecies” by “serovars”

We appreciate reviewer’s comment. We revised the manuscript accordingly.