Author’s response to reviews

Title: Cefuroxime, levofloxacin, esomeprazole, and bismuth as first-line Helicobacter pylori eradication therapy in patients allergic to penicillin

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The point-by-point responses

Chao-Hung Kuo (Reviewer 4): Accept after minor essential revisions

I have raised several suggestions in my previous comments but some of them were not addressed or mentioned in your newly revised manuscript. Once again, my suggestions for your revision is the following, similar to my previous comments. To make your work more satisfying, these suggestions should be addressed or mentioned in the limitation paragraph if the data are not complete.

Comment 1
Many literatures have proved that the previous treatment experience would affect the eradication rate, probably related to secondary antibiotics resistance from previous treatment. Therefore, I suggest that in your table 1, baseline factors should include the treatment experience such as Tx-naïve or Tx-experienced. Also, this factor should be added into uni and multi variate analysis.

Responses: I strongly agree with you that the history of antibiotic use can affect the resistance, especially macrolides, quinolones and nitroimidazoles. The patients in this study were all newly diagnosed patients with Helicobacter pylori infection and no eradication treatment was performed before (all Tx-naïve).
Unfortunately, in this study we did not ask about the history of antibiotic use for other infectious diseases. The main reasons are as follows: (1) The primary objective of this study is to evaluate eradication efficacy; the secondary objectives were to determine its compliance and safety. The antibiotic resistance and influencing factors were not the main purpose, so this aspect is not included; (2) More importantly, in China, due to the relatively random use of antibiotics in patients, it is difficult for many patients to recall the history of medication, and the unified query system and monitoring records for medicine use has not been established. It is often inaccurate to ask about the use of antibiotics. Your suggestion is very good. In the future research, we can do an in-depth and accurate
evaluation and discussion on this very interesting topic. We have added a paragraph in the limitation section as below: The previous antibiotic use experience would affect the eradication rate, probably related to secondary antibiotic resistance from previous treatment. Unfortunately, in this study we did not ask about the history of antibiotic use for other infectious diseases. In the future research, we can do an in-depth and accurate evaluation and discussion on this topic.

Comment 2
In your table 3, multi-variates analysis should be expressed in your table with p value. It's more important than uni-variate analysis.
Responses: Thanks a lot. The related contents has been included in Table 3.

Comment 3
Levofloxacin has been recommended and reserved as the 2nd line therapy by many guidelines. Could you please share your thoughts on the 2nd line therapy if the patients fail with this CLEB regimen. Your point of view will affect feasibility of CLEB regimen is real-world practice.
Responses: A very good question. If the CLEB regimen fails, it will be very difficult. Tetracycline, furazolidone and rifabutin are difficult to obtain clinically, and the resistance rates of clarithromycin and metronidazole are very high. For the patients with penicillin allergy in the mainland of China, maybe three options could be chosen for the next eradication: (1) minocycline + metronidazole + PPI + bismuth (Zhi Qiang SONG & Li Ya ZHOU. Esomeprazole, minocycline, metronidazole, and bismuth as first-line and second-line regimens for Helicobacter pylori eradication. Journal of Digestive Disease 2016;17(4):260-267); (2) eradication therapy based on culture and susceptibility; (3) try to find ways to get tetracycline, furazolidone and rifabutin.
We have added a paragraph as below: If the CLEB regimen fails, it will be very difficult. Tetracycline, furazolidone and rifabutin are difficult to obtain clinically, and the resistance rates of clarithromycin and metronidazole are very high. For the patients with penicillin allergy in the mainland of China, maybe other options could be chosen for the next eradication, such as minocycline/metronidazole containing quadruple regimen or eradication therapy based on culture and susceptibility.

Comment 4
You mentioned in your discussion part, that the roughly eradication rates of clarithromycin, levofloxacin and metronidazole was 50-60%. The reference should be listed. Reference is very important.
Responses: Thanks a lot. The related contents has been added.