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Dear Editor,

Enclosed please find our revised manuscript "**Antimicrobial susceptibility testing before first-line treatment for *Helicobacter pylori* infection in patients with dual or triple antibiotic resistance**" by A. Cosme et al. **Ref. 32752**. All authors appreciate your rapid response and valuable reviewers' comments.

Following your recommendations, we have answered all the queries as requested. To make easier the reading, changes have now in red in the revised manuscript.

REVIEWER 02523689

Comment 1.- Sixty-eight patients with 2 or 3 antibiotic resistance were only treated. What happened to the other 59/18

Although a total of 1034 HP infected patients were included in the study (all of them from Gipuzkoa region), only those attending Donostia Hospital were selected for follow up. This is, all the HP cultures from Gipuzkoa region are centralized in our site (Donostia Hospital) and we know the dual or triple resistance for the whole region. However, we only have treatment information of those who we follow directly in our hospital. These particular group included 68 patient with dual resistance and 12 with triple resistance. In fact, it can be read in the Results section: "*A subgroup of 80*

patients (68 with dual HP-resistance, and 12 with triple HP-resistance) attending to Donostia Hospital (San Sebastián, Spain) were finally included''.

Comment 2.- Cure rate was significantly higher in naïve patients treated with OAR-10 compared to patients who had two or three previous treatment failures (83% vs 33%). This subdivision needs more details in subject and results section.

As the reviewer suggested, more details are added in subjects and results section.

Comment 3.- In abstract conclusions "eradication rate superior al 90" change "to 90%"

This typo has been corrected in the Revised manuscript.

Comment 4.- "Discusion" change to "Discussion".

This typo has been also corrected in the Revised manuscript.

Comment 5.- In the Discussion section "hibrid therapy and non-bismuth quadruple concomitant therapy (14 days) if the of dual clarithromycin" some words are missing in this statement.

In the revised manuscript, the sentence has been rewritten and not it can be read 'Quadruple sequential therapy (14 days), hybrid therapy and non-bismuth quadruple concomitant therapy (14 days) are expected to fail if the rate of dual clarithromycin and metronidazole resistant strains are > 5%, >9%, and > 15%, respectively (7)''.

Comment 6.- Figure 3: please insert explanations below the figure.

A complete explanation has been now included below Figure 3 (Figure 2 in the revised manuscript).

REVIEWER 03010025

Comment 1.- Introduction- I would remove the figure from the introduction, it is more a review format.

Figure 1 has been removed from the introduction.

Comment 2.- Methods-It is not clear why they excluded patients with type I or insulin dependent diabetes.

Generally speaking, Type I diabetes patients present multiple pathologies, being most of them under several drugs/medications. Consequently, high ratio of side effects and intolerances are developed when several antibiotics are in course. For this reason they have been excluded from the study.

Comment 3.- It is not clear why 68 patients were recruited only? Were they the only patients with dual resistance?

As explained before (responding the comment from previous reviewer) although a total of 1034 HP infected patients were included in the study (all of them from Gipuzkoa region), only those attending Donostia Hospital were selected for follow up. These were only 68 with dual resistance and 12 with triple resistance.

Comment 4.- The authors mentioned "Adherence to treatment was defined as in take of- at least 90% of the medication prescribed assessed by using a questionnaire and counting empty medication sachets returned". This is arbitrary and may affect the eradication outcome. This should be clarified more!

It is generally accepted that when patients are compliant with at least 90% of their treatment, the adherence is considered valid. All regimens included 60 pills, and we considered that if patients took least 54 pills the results of eradication would not be affected. In the revised manuscript, it can be read in the result section "75 out of 80 patients with dual or triple HP-resistance showed 100% compliance to prescribed medications. No significant differences were observed in compliance between patients with dual and triple HP-resistance (93% vs 94% respectively).

Comment 5.- In the discussion, the authors must discuss the relationship between H. Pylori antibiotic resistance and virulence factors. Previous studies have shown that certain virulence factors were associated with treatment failure eg. DupA1 and its association with antibiotic resistant by Hussein et al published in 2015 in new microbes and new infection 6, 5-10.

Now, in the revised manuscript- reference Hussein et al. 2005 has been included in the reference section (reference 22). Accordingly, it can be read: *"Different virulence factors play an important role in the pathogenesis of HP and treatment resistance. For instance, a significant association has been found between dupA1 genotype and*

A214G clarithromycin resistance mutation by Hussein et al (22). Further molecular studies are needed in order to clarify biomarkers that could causes of HP resistance”.

REVIEWER 03261349

Comment 1.- In the abstract, the acronyms OAL, OAM, OAC and OAR should be fully explained.

Achronims have been defined now also in the abstract section of the revised manuscript.

Comment 2.- Authors did not mention amoxicillin resistance. Did they find no case or did they exclude from the analysis patients with amoxicillin resistance)

We did not find any case os amoxicillin resistance. Methods section of the Revised manuscript includes now the sentence *“The rate of H. pylori amoxicillin resistance was 0%.”*

Comment 3.- In the result section, it is important to discriminate the success rates of OAM, OAC, OAL and OAR in double resistant strains. This results indeed, has been reported only in Table 1 and not in the text.

In the main text of the revised manuscript it has been now added this information *“3 with OAC and bismuth quadruple therapy, 2 with OAC, bismuth quadruple therapy and OAL, and 1 with OAC and OAL, in all cases for 10 days”*

Comment 4.- A minor linguistic revision is necessary.

Language polishing has been done in this version fo the manuscipt.

An error in Figure 2 has been corrected (OCA has been substituted by OAC).

I expect that with this revision the editorial can be published in WJG. Please do not hesitate to contact us if you further clarification.

Sincerely

A handwritten signature in black ink, appearing to be 'Luis Bujanda', with a stylized flourish at the end.

Luis Bujanda