Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5661-review.doc).

Title: *Helicobacter pylori* infection and extragastric disorders in children: a critical update

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Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:
1. Format has been updated. All corrections are marked in RED.

2. We thank the Reviewer #1 for stating that the study is important, and the manuscript will help enhance current knowledge in the field.
Following the Reviewer #1's suggestions,
2A. we have included some subheadings into the various headings;
2B. we have summarized in Table 1 the main findings of clinical and intervention studies on the association between H.pylori and iron stores in children;
2C. we have summarized in Table 2A the baseline clinical features of children with chronic idiopathic thrombocytopenic purpura;
2D. we have summarized in Table 2B data pertaining follow-up and platelet response to H. pylori eradication therapy among children with chronic idiopathic thrombocytopenic purpura.

3. We thank the Reviewer #2 for stating that the study is excellent.
Following the Reviewer #2's suggestions,
3A. the sentence "Gastroduodenal endoscop.." has been corrected (P 9, line 20);
3B. the sentence "Children who eradicated H. pylori and received.." has been corrected (P 11,lines 5-6);
3C. the sentence "This difference was not observed.." has been corrected (P 11, lines 8-10);
3D. the sentence "Bisogno et al. concluded is difficult.." has been corrected (P 17, line 31).

4. We thank the Reviewer #3 for having helped us to improve our manuscript.

Following the Reviewer #4' s "generic and specific comments",
4A. we have presented in Table 1 information about the main findings of clinical and intervention studies on the association between H. pylori and iron stores in children;
4B. we have presented in Table 2A information about baseline clinical features of children with chronic idiopathic thrombocytopenic purpura;

4C. we have presented in Table 2B data pertaining to follow-up and platelet response to H.

pylori eradication therapy among children with chronic idiopathic thrombocytopenic purpura;

4D. we have rewritten the Abstract, the core tip, and the Introduction (P 2-3 of new text) in order to clarify the aim and rationale of this review. Methods have also been briefly included (P 3 of new text, lines 23-25). In the new text, the term "manifestations" has been substituted by "disorders", while the term "extradigestive" has been changed to "extragastric". As such the title of the manuscript has also been changed;

4E. we have included (P 13 of new text, lines 3-21) the specific(and preliminary) information on the issue" Association between H.pylori infection and reduced cognitive abilities in children with iron deficiency anemia" provided in the paper of Muhsen et al. (new reference #73), along with the pertinent comment by Queiroz et al. (new reference #74);

4F. the Introduction now also includes a paragraph regarding the rationale behind the association between H. pylori infection and extragastric outcomes (P 3 of new text, lines 10-14);

4G. we have decided to not include the risk of diarrheal diseases or recurrent abdominal pain in H. pylori-infected children because the issue is beyond the scope of the manuscript.

Following the reviewer #4's comments on the section of iron deficiency anemia,
4A. we have included in the new text the most relevant articles on the association between H. pylori and iron stores that have been suggested by the reviewer (references #1,#2#3,#10,#13,#15,#18,#19,#20). The references #17 and #21 have been already included in the previous text;

4B. we have deleted the detailed results of the four meta-analyses (Previous text: beginning P 3, line 14, and ending on P 4, line 4). Indeed, the four meta-analyses included both pediatric and adult patients. This has been outlined on P 3 of new text, line 28. References #10,#13,#16,#18 ,#24 of previous text have been deleted;

4C. we have highlighted that more studies are needed to clarify the role of H. pylori virulence factors such CagA in depletion of iron stores(P 7 of new text,lines 17-19);

4D. we have updated and expanded information on biological mechanisms of the association between H. pylori and IDA (beginning P4, line 26, and ending on P5, line 31;
P 6, lines 2-8; beginning P6, line 21,and ending on P7, line 4);

4E. we have included the suggested biological explanation of the age-dependent association between H. pylori and depletion in iron stores (P 8, lines 27-29);

4F. we have highlighted (P 8,lines 3-9) that there are fewer studies evaluating the role of H. pylori in the development of ID/IDA in children undergoing gastrointestinal endoscopy (new reference #59);

4G. we have highlighted (P 11, lines 23-27) the importance of trial by Cardenas et al. (JPGN 2011), and have discussed (beginning P 4, line 26, and ending on P 5, line3) the recent findings by Sarker et al. (Helicobacter 2012);

4H. we have clarified that children enrolled in the studies by Fagan et al. (previous reference #57) and Gessner et al. (previous reference #56) were participants of the same trial (P 12,lines 14-15).

Following the reviewer #4's comments on the section of chronic idiopathic thrombocytopenic purpura,

4A. we have deleted references #62, #63,and #68;

4B. we have deleted results (previous text:P 11,lines 12-32) of the four reviews in adults with ITP and H.pylori infection (previously quoted as references #64,#65,#66,and #67);

4C.we have decided to not include the paper by Jaing TH et a.l(Ped Blood Cancer 2006)because the study is dealing with spontaneous remission(rather than acute ITP).The finding is hardly surprising, and is beyond the scope of our work;

4D. we have decided to not include the paper by Estrada-Gomez et al.(Revista de Investigation Clinica 2007) because the median age of the three H.pylori-positive patients was 53 years!!!!!!To complicate matters further, no information on the age of H.pylori-negative was provided in that paper;

4E. we have appended to the new Tables 2A and 2B the suggested paper,i.e. Wu et al. Acta Paediatrica Taiwanica 2007. However, in that paper, diagnosis of H.pylori infection was made in children whose mean age was 4.3 years(ranging from 0.2 to 13.5)by stool antigen test. The stool antigen test performs poorly in children younger than 5 years (Diagn Microbiol Infect Dis 2005;vol.52:157-160);

4F.we were unable to separate studies that assessed H.pylori infection in children with cITP from those in a control group(i.e. without cITP). All studies appended to Tables 2A and 2B included only children with cITP, with the exception of the study published in Acta Paediatrica Taiwanica 2007(Wu et al.). However,please note that in that paper from Taiwan,the control group of patients(i.e. without cITP)was based on only 30 children. Is this a sample size sufficient to assess the H.pylori prevalence rate in the "general" pediatric population from Taiwan ? To complicate matters further,the control group did not represent the general population, but rather a "control" group of children who were symptomatic and hospitalized.

4G. we have highlighted that the study by Treepongkaruna et al.(Ped.Blood Cancer 2009)was a very small trial(New text, P 16,lines 3-4);

4H.we have updated and expanded information on biological mechanisms of the association between H.pylori and cITP(beginning P13,line 30,and ending on P 15,line 22) following the suggestions of Franchini et al.(Semin Thromb Hemost 2012-new reference #84)

4I.we have clarified why results of pediatric studies on cITP are difficult to compare(P 16,lines 4-16),and have removed previous sentences(P 12: lines 13-16,and 20-23).

Following the reviewer #4's comments on the association between H.pylori infection and growth,

4A.we have given details of studies evaluating relationship between ghrelin and H.pylori infection in children(P 23 of new text,lines 8-29).We have also included the two studies on H.pylori infection,ghrelin,and leptin in children(references # 151 and #152 of new text),and have highlighted that "in our clinical setting,including children with H.pylori-associated gastritis(without atrophic changes or long-term history of gastritis), ghrelin and leptin responses appeared to be independent of one another"(P 23,lines 18-20);

4B. we have decided to not discuss the association between H.pylori infection and diarrhea because such association has yielded conflicting results(P 18 of previous text,lines 9-10).

Following the reviewer #4's comments on the section of asthma and allergic diseases,we have clarified(P 3,Introduction)why we have decided to critically address the association of H.pylori infection with asthma and allergic diseases.

Following the reviewer #4's comments on the section of Diabetes Mellitus, we have chosen to not include a pertinent Table into the revised manuscript, because there are very few data on the effects of H.pylori eradication on the control of diabetes mellitus(with conflicting results),and still more limited data on the therapeutic approach to H.pylori infection in diabetic children. In that vein a new Table would not add substantially to the overall message of the manuscript.

We again thank the Reviewers for the time invested in their constructive reviews of our manuscript. We believe that we have replied to their respective comments .

Sincerely yours,

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