

**Reviewer #1:**

We thank the reviewer for his/her positive comments on our manuscript.

**Comment 1:** The abstract is inconsistent with the content of the text. For example, neurological, dermatological, hematologic, ocular, cardiovascular, metabolic, allergic, pancreatic, hepatobiliary, colorectal, and urologic diseases were mentioned in the abstract but there is no description about pancreatic, hepatobiliary, colorectal, and urologic diseases in the text.

**Response:** We agree with the reviewer's comment and we have now made it clear that in this review we focused on neurological, dermatological, hematologic, ocular, cardiovascular, metabolic, allergic and hepatobiliary diseases. This information appears in the Abstract section, page 2, line 4<sup>th</sup> and in the core tip section, page 2, line 6<sup>th</sup>

**Comment 2:** The content of Table 1 is not reflected” Prevalence”

**Response:** Per the reviewer's request, the title of the table has now been changed into: “Literature reports in favour of (pro) or against (con) *H. pylori* involvement in a number of extra-gastric conditions”.

**Reviewer #2:**

We thank the reviewer for his/her positive comments on our manuscript.

**Comment 1:** The review by Dr. Gravina and colleagues represents an excellent summary of the role of *H. pylori* infection in extra-gastric conditions. It is well presented with a thorough inclusion of pertinent studies. It is also presented in an unbiased perspective. Although a nice table is appended, the manuscript could have benefitted from at least one or two illustrations showing mechanistic relationships between infection and disease.

**Response:** Because of the reviewer's request we have now added to the manuscript a figure which illustrates the possible mechanisms linking *H. pylori* infection to iron deficiency anemia, vitamin B12 deficiency and idiopathic thrombocytopenic purpura, the only extragastric manifestations for which there is a strong evidence for a clinically relevant association with *H. pylori* infection. This is now Figure 1 of the revised manuscript.

**Comment 2:** Overall, it is a high quality review. A few typographical errors or fused words could be corrected.

**Response:** We took care of typos and fused words as indicated by the reviewer.

**Reviewer #3:**

We thank the reviewer for his/her positive comments on our manuscript.

Major comments

**Comment 1.** The review should summarize the current state of research and provide some possible interpretations or explanations when different groups reach disparate conclusions. There isn't quite enough analysis in this review and coverage of some diseases is far more in depth than for other diseases.

**Response:** Because of the reviewer's concern and suggestion, we have now provided some possible explanations when different groups reached different conclusions. This appears in most of the paragraphs where discordant results were presented. Also, the coverage of some diseases, in

particular neurological, dermatological and ocular diseases, is far more in depth compared to the previous version of the manuscript.

**Comment 2.** The English is not acceptable, particularly for a review article. Some sections are fairly well-written, but others require significant editing for language and clarity.

**Response:** Because of the reviewer's concern, the manuscript has been edited by American Journal Experts as also requested by the editorial office of the Journal for articles written by non-native English speakers.

**Comment 3.** The Parkinson's disease section does not accurately reflect the range of published literature on the associations between *H. pylori* and PD.

**Response:** Because of the reviewer's suggestion we have examined more thoroughly the literature in this field and we have included the results of a recent (2017) meta-analysis dealing with the problem of *H. pylori* infection and PD and also a population study published in 2018. This appears in page 5, line 3<sup>rd</sup> and the related references are refs 36 and 37 of the revised manuscript.

**Comment 4.** Campylobacter should be mentioned in the Guillain-Barre section, since it is a known risk factor and closely related to Helicobacter.

**Response:** We agree with the reviewer's comment and we have mentioned Campylobacter in Guillain-Barre. This information appears in page, 5<sup>th</sup> line of Guillain-Barre paragraph in the section of neurological diseases.

**Comment 5.** Certain terms, such as telangiectasia, should be defined since many readers will not have medical backgrounds.

**Response:** We agree with the reviewer's comment and the term telangiectasia has now been explained (2<sup>nd</sup> line of rosacea paragraph in the dermatological diseases section, page 6)

**Comment 6.** Only two references are cited in the psoriasis section, even though there is considerable controversy over the role of *H. pylori* in psoriasis. Some have found no association with Helicobacter and others suggest it is associated with severity, not prevalence. Each section should reflect the current state of the field. If you conclude that *H. pylori* does influence psoriasis, you should offer suggestions as to why some studies failed to find an association.

**Response:** To the reviewer's request, we have now expanded the paragraph dealing with *H. pylori* infection and psoriasis. In particular, we also reported data from an interventional study demonstrating that eradication of the infection led to an improvement of the disease. This further supports a pathogenic role for *H. pylori* in psoriasis. This information appears in page 6, line 2<sup>nd</sup> and 6<sup>th</sup> in the psoriasis paragraph and the related references are refs 50, 51, 54 and 55 of the revised version of the manuscript.

**Comment 7.** Liver disease should have its own section and not be combined with metabolic disease

**Response:** We agree with the reviewer's comment and we have added a section entitled "Hepatobiliary disease" which appears in page 13.

**Comment 8.** With regard to allergies, one must consider the hygiene hypothesis and associations between pet ownership and reduced allergic disease. *H. pylori* infection is associated with poor hygiene and low socioeconomic status. Such populations may also have greater exposure to other bacteria or antigens that reduce the risk of allergic disease. Epidemiologic studies of Helicobacter must control for other factors in order to differentiate among the various possibilities.

**Response:** We agree with the reviewer's comment and because of his suggestion we have now discussed the role of low socioeconomic conditions and poor hygiene conditions as possible

confounding factors in the interpretation of the association between *H. pylori* infection and allergies. This information has been added to the Allergic Disease section, page 12, line 28<sup>th</sup>.

**Comment 9.** The conclusion section is a bit unsatisfying. It would be useful to mention which diseases have the strongest associations with *H. pylori*.

**Response:** We have modified the conclusions according to the reviewer's suggestion making it clear that to date the only conditions in which *H. pylori* infection should be searched for and eradicated are hematologic conditions

Minor comments

**Comment 1.** There are numerous typographical errors, such as missing spaces

**Response:** typos and missing spaces have been taken care of

**Comment 2.** "Et al" should be italicized throughout and in some cases, the "et" is missing.

**Response:** this is also been taken care of

**Comment 3.** Since most references are several years old, it isn't clear whether the authors considered the most recent publications.

**Response:** Unfortunately most of the literature on *H. pylori* and extragastric diseases is dated, however, we have now added in the reference list more recent study which of course have also been discussed in the text

**Comment 4.** The authors might consider associations with extragastric cancers

**Response:** The relationship between extra-gastric cancer and *H. pylori* infection is extremely rarely been reported. Most of the reports are related to liver cancer, and this has now been discussed in the new section dealing with hepatobiliary diseases.