ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 5916
Title: Diagnosis before and after treatment of Helicobacter pylori infection: New approaches and treatment of the infection
Reviewer code: 01436291
Science editor: Gou, Su-Xin
Date sent for review: 2013-09-30 10:36
Date reviewed: 2013-10-03 22:35

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[Y] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ] Rejection
[ ] Grade D (Fair)		BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

These researchers reviewed the main diagnostic methods for the diagnosis of H. pylori infection and for confirmation of eradication of infection. In addition, they reassessed the main determinants related to failure to eradicate the infection. This is a comprehensive study and the treatment of the various methods is scrupulous and precise. Only minor modifications are necessary in addition to minor corrections: 1. Non-invasive methods to diagnose the infection, such as urea breath test and stool antigen test, are treated only in the section dedicated to methods to verify the eradication, following the antibiotic treatment (for a choice of the authors). This gives the incorrect impression that infection can be detected only by invasive methods. I, therefore, would suggest to move the treatment of the above reported methods to the first part of the manuscript as "non-invasive methods to establish an infection", comprehending urea breath test, stool antigen test and serology, and to retreat briefly the suitability of these techniques to verify the success of treatment. Minor errors: 1. First line of abstract: H. pylori is not an ninfection, it causes an infection. Change "is" with "causes". 2. Secon line of I paragraph of Diagnosis of infection: change "each have" with "each one has". 3. Ibidem, IV line: add "there" to "…. Are histological ….." 4. First paragraph of Histology, IV line: add neoplasia to " ….and dysplasia…." 5. First paragraph of Culture, V line: change "overproduction" with "overpresence" or similar. 6. Ibidem, last sentence: add "..preferably in broth (any kind) with 15%-20% of glycerol." after "stored at -80 °C. 7. Same pg., last but one lane. Change "media" with "medium" (it is Latin, singular name; plural is "media"). 8. Second paragraph of Polymerase ……Resistance to clarithromycin is mostly attributable to mutations in the 23S rRNA gene; just mention the efflux pumps and their role in resistance to antibiotics. 9. Ibidem, Ref. 30 deals

with microdoses of labeled urea, not minimally invasive procedures; perhaps ref 22 fits better. 10. First paragraphof Urea breath test, IV line: change "expired" with "exhaled". 11. Concomitant therapy, 3rd line: modify the sentence "… This therapy involves the administration of three antibiotics together …. " in "This therapy involves the simultaneous administration of three antibiotics …." 12. Hybridizing therapy, IV line: add for how long the treatment should be administered. 13. Ibidem, ref 41 is not correct; its title is "Current options for the treatment of Helicobacter pylori". Perhaps a different publication should be quoted. Finally, the correct name of one of the authors, Perez-Perez GI, is Pérez-Pérez GI. Similarly, Megraud should be Mégraud. I do not know whether the Journal is careful about these things.

ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
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Title: Diagnosis before and after treatment of Helicobacter pylori infection: New approaches and treatment of the infection
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ] Rejection
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		[ ] No records	

COMMENTS TO AUTHORS

The authors have revised the diagnosis and treatment of Helicobacter Pylori infection. They have done a very thorough job in describing the diagnostic techniques. Overall, the manuscript is well written and structured and the authors did a nice study that has been analyzed in the context of current literature. This revision would be of general interest to clinicians. Nevertheless, there are few details that need to be added in order to increase the quality of the manuscript: 1. Few data are available in children compared with adults. Studies specifically conducted in children should be an important aspect of this revision. They should be added.   2. I suggest include data about therapy in women who are pregnant or breastfeeding if the clinical condition of the woman requires treatment. 3. The revision of literature is exhaustive; however several references could be updated because there are a plentiful number of references on this subject in the last years.   4. Modalities of therapy such as sequential, concomitant and hybridizing therapy should be more exhaustive commented.   5 In the same line, some comments about therapy with probiotics could be informative.

ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
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Title: Diagnosis before and after treatment of Helicobacter pylori infection: New approaches and treatment of the infection
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
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COMMENTS TO AUTHORS

The Minireview of the authors describes the diagnosis before and after treatment of H. pylori infection. They divided the manuscript in three main chapters. The first chapter talks about *H. pylori* diagnosis before treatment. Here they explain the invasive diagnostic methods like histology, culture, PCR, and rapid urease test. Also serology is presented in this chapter, but only few studies are cited.

The second chapter describes diagnostic tools for H. pylori detection after eradication. Two methods for diagnosing a successful treatment are mentioned , UBT and the Stool antigen test.

In a third chapter they describe the current methods for eradication of the infection with the different therapy guide lines.

There are plenty of reviews trying to facilitate this complex problem of H. pylori diagnosis and treatment. This manuscript gives a good overview of the current status of diagnosis and treatment. However, serology could be explained more precisely, with its possibility of discrimination the infecting strain by looking at antibody responses to different virulence factors. Also, in areas where technical equipment for UBT is not available, a good serologic test is still the most efficient and affordable test for H. pylori prior to endoscopy.

In general, the authors should be more critical, especially when it comes to deviations from the current guidelines in daily routine. This is the case regarding histology, staining procedures,

indication for treatment, and assessment of antibiotic resistance…

Major points:

1. The introduction doesn't talk about the treatment of H. pylori infection. Importantly, the authors should introduce if and which diagnostic measures can be of help for deciding upon the need for treatment (i.e. histology and multiplex serology).

2. In the section describing Histology it is stated that the updated Sydney Classification is set as "gold standard" *but this approach is scarce in daily practice because of the large number of biopsies suggested*. The authors should add a conclusion/recommendation (i.e that less biopsies can lead to underestimation and sampling error, and that HE stain alone also can lead to false negatives.)

3. Fluorescent in situ hybridization: The method is only described but not judged. Again, in a review the authors should be more critical and support the reader with appraisements of the methods mentioned. In my eyes, FISH is barely used - if at all – in daily routine since it is still to technically tedious and expensive.

4. At the end of section describing culture, you state that it is less recommended to freeze gastric biopsies. Could you give a reference here? Differences in sensitivity are mentioned but not explicitly stated. Please provide parameters.

5. The authors mention the role of culture to assess antibiotic resistance, which is *mainly used to confirm the antibiotic sensitivity of the bacteria after two treatment failures.* Given the dramatically rising resistance rates in many parts of the world, the authors should critically discuss this. Can we really wait with resistance assessment until two treatments have failed? Also, this emerging situation may lead to a much broader need of culture in the future.

6. Serology: The first sentence (*In general, tests containing complex antigen mixtures…*) is rather a conclusion and should be placed at the end of the first paragraph.
I do not agree with the last sentence (*its positive predictive value is poor when used in populations with a low prevalence of infection by H. pylori [27]*.). While the authors are correct that the PPV depends on the prevalence, low PPV is only observed for tests with poor specificity. This has been overcome by tests employing multiple antigens. The authors should cite such test system, for example *Formichella et al., Clin Vaccine Immunol. 2013 Sep 4. [Epub ahead of print] A novel immuno-line assay based on recombinant virulence factors enables highly specific and sensitive*

serological diagnosis of H. pylori infection.

7. Urea breath test: It should be mentioned that corpus-predominant gastritis can produce false-negative 13C-urea breath test results, which could lead to a major mis-assessment of such patients which are in high need for endoscopy and/or eradication. This is a major drawback especially in high risk populations. Further, recent data indicate that the sensitivity and NPV of UBT is better after three months compared to six weeks.

8. Stool antigen test: sensitivity and specificity are nowhere named in the paragraph. These are highly variable. Please give numbers and examples. It should be mentioned that SAT is only recommended for diagnosis in children.

9. Treatment: *Resistance to amoxicillin and metronidazole has remained relatively stable.* I don't agree. There is no resistance to Amoxicillin, and resistance to Metronidazole has risen to >50% in many geographic areas (southern and eastern Europe, Asia, …).

10. *such as clarithromycin for respiratory ~~infections~~.* The authors should add ..or metronidazole for gastrointestinal infections.

11. *Test and treat:* This aspect should be discussed more critically: When patients with persistent dyspepsia are treated for H. pylori, only 10% benefit in the long term. The other mentioned indications require diagnosis by endoscopy, so diagnosis of H. pylori infection can be done by histology. Thus, it is unclear why UBT or SAT should be used.

12. Treatment regimens: The authors should give the eradication rates of the studies they cite (i.e. 41, 46, 48 etc.).

13. *Hybridizing therapy:* The authors cite a review but not the study itself. This should be avoided. Also, I was not able to find any study with this term. Please cite correctly.

Minor points:

1. Page 5 second paragraph "inability to obtain specimens from different areas of the stomach". Inability seems the wrong word here. It is possible and recommended to obtain specimens from different areas of the stomach, but often not performed in daily routine. This sentence should be rephrased to underscore the need of several biopsies *due to a patchy distribution of H. pylori.* Also, it should be added that the sensitivity can significantly be increased by increasing the number of biopsies and employing specific stains. Sensitivities of 53% should not occur anymore.

2. Page 5: *H. pylori*   is also observed within gastric glands.

3. Rapid urease test section: Line 3, change pH incubator to pH indicator

4. Third line treatment section: last paragraph, line 4, change "should avoid if possible" to "should be avoided"

5. Page 10, line 1: pH incubator should be pH indicator.

6. Rapid urease test: it should be mentioned that the test specificity decrease over time during incubation, since the test often becomes false positive after longer incubation.

7. Please revise (p20): This therapy is designed as sequential therapy in areas where ~~there is a~~ resistance to clarithromycin is greater than 20% and where a quadruple therapy based on bismuth is not available.

8. The manuscript contains some typos and linguistic mistakes that should be corrected. Page numbers and line numbers would facilitate proofreading.

Conclusion:

This review gives a good overview about the current status of H. pylori infection. It also shows the different guidelines for H. pylori treatment.
The section talking about serology could be more precise. The manuscript needs linguistic revision and more critical discussion.

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[ ] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[Y] Accept
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COMMENTS TO AUTHORS

The article is a theoretical review of the main diagnostic methods for the H. pylori infection and some treatment options. It is a good review, up to date, about a subject of high interest in gastroenterology due to the worldwide spread of this infection. The article is well structured, systematic, easy to read and informative, even the first part (diagnosis) is prevalent. The objectives mentioned in the aim are exposed. The references are various, up to date and appropriate cited.

In my opinion there is a good article, for general information about a subject of large interest and worth to be published.

No comments to authors.