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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 5749

Title: Review: Second and third line treatment options for H. pylori eradication

Reviewer code: 00503464

Science editor: Gou, Su-Xin

Date sent for review: 2013-09-25 14:44

Date reviewed: 2013-09-25 17:04

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

COMMENTS TO AUTHORS: The manuscript, Mingjun Song et al. was presented for review. In this manuscript, authors summarized the current situation of Helicobacter pylori eradication therapy. The manuscript has a potential. Comment 1) Please add the following paper to the reference and discuss in more detail. Toshihiro Nishizawa1) 2), Hidekazu Suzuki2), Masayuki Suzuki1), Masahiko Takahashi1), Toshifumi Hibi2. Proton pump inhibitor-amoxicillin-clarithromycin versus proton pump inhibitor-amoxicillin-metronidazole as first-line Helicobacter pylori eradication therapy. Journal of Clinical Biochemistry and Nutrition?Vol. 51 (2012) No. 2 p. 114-116. Handa O, Naito Y, Yoshikawa T. CagA protein of Helicobacter pylori: a hijacker of gastric epithelial cell signaling. Biochem Pharmacol. 2007 Jun 1;73(11):1697-702.



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 5749

Title: Review: Second and third line treatment options for H. pylori eradication

Reviewer code: 00030962

Science editor: Gou, Su-Xin

Date sent for review: 2013-09-25 14:44

Date reviewed: 2013-09-28 18:56

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

This review focused on H. pylori re-treatment following first-line therapy failure. Data on quadruple and levofloxacin-based therapies were shortly discussed, and the role of other drugs (rifabutin, rifaximin, sitafloxacin) was also considered. **CRITICISMS.** 1. The Authors cited only data of antibiotic resistance in Korea. However, we would suggest that data on the worldwide resistance could be more interesting for the readers of an International journal as WJG (De Francesco V. J Gastrointestin Liver Dis. 2010;9:409-14). In detail, the astonishingly high amoxicillin resistance rate observed in Korea is not confirmed in all the other countries, so that such an information can not be generalized. 2. Mechanisms of H. pylori resistance as well as factors affecting therapy success have been elegantly discussed elsewhere (De Francesco V. J Gastrointestin Liver Dis. 2011;20:235-9; Zullo A. J Clin Gastroenterol 2012;46:259-61). These studies could be shortly cited. 3. It has been cited that esomeprazole is less affected by first-pass metabolism. This would appear misleading. Indeed, esomeprazole is not a "second generation" PPI, but it is simply the S-enantiomer of omeprazole with a very similar hepatic metabolism. The difference is the dosage advised (40 mg b.i.d. vs 20 mg bid). No study demonstrated that esomeprazole 40 mg is better than omeprazole 40 mg. This would appear a simply commercial "trick". Only the rabeprazole owns a distinct hepatic metabolism. 4. The "3 in 1" capsule with metronidazole, bismuth and tetracycline is not a really advantage, since several tablets 3-4 times/daily need to be taken. In addition, efficacy of such a therapy was not so impressive, being only 80% as first-line therapy (Malferttheiner P. Lancet 2011; 377:905-913). Therefore, the role of this therapy as second-line treatment is expected to poor. 5. Data on rifaximin should be considered with more caution. Indeed, several studies found a very low efficacy of such a drug in first-line therapy (Gasbarrini A. Dig Dis 2006;24:195-200; Gasbarrini A. Digestion. 2006;73 Suppl



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1:129-35; Dell'Anna A. *Eur Rev Med Pharmacol Sci.* 1999;3:105-10; De Giorgio R. *Eur Rev Med Pharmacol Sci.* 1997;1:105-10). Therefore, it would appear at least "unexpected" the result of the cited Korean study in second-line therapy. Although it is active towards *H. pylori* in vitro, less than 1% of rifaximin is adsorbed. To eradicate *H. pylori* in their peculiar "niche" an antibiotic needs to be actively secreted in the stomach and a long-term permanence in the gastric juice is required. Therefore, the role of rifaximin in *H. pylori* treatment could be marginalized. 6. Unfortunately, sitafloxacin is not worldwide available.



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 5749

Title: Review: Second and third line treatment options for H. pylori eradication

Reviewer code: 02462691

Science editor: Gou, Su-Xin

Date sent for review: 2013-09-25 14:44

Date reviewed: 2013-09-29 13:35

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

The review is well-written and provides current views on this subject for general reader of WJG. Authors may consider including the following references on levofloxacin in second-line therapy; Gisbert JP et al, Scand J Gastroenterol 2013;48:652-6 and Hsu PI et al, Helicobacter 2013 [Epub ahead of print]. References are needed for other patient factors (obesity, poor compliance, smoking) that resulted in failure. What about the role of high bacterial load? Reinfection is a significant problem in developing countries. The role of "3 in 1" capsule and rifaximin are likely to be hampered by their marginal effectiveness. Do check and correct the references.



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 5749

Title: Review: Second and third line treatment options for H. pylori eradication

Reviewer code: 00035741

Science editor: Gou, Su-Xin

Date sent for review: 2013-09-25 14:44

Date reviewed: 2013-10-01 13:16

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

This paper is a review of Second and third line treatment options for H. pylori eradication. This is interesting paper, however, two comments are listed below. 1. Authors should add subtitles of eradication regimen like rifabutin-based, sitafloxacin-based, and sequential therapy, and so on for easy understanding the content of manuscript. 2. Authors should refer the paper below about sitafloxacin-based rescue therapy. Multi-center randomized controlled study to establish the standard third-line regimen for Helicobacter pylori eradication in Japan. Murakami K, Furuta T, Ando T, Nakajima T, Inui Y, Oshima T, Tomita T, Mabe K, Sasaki M, Suganuma T, Nomura H, Satoh K, Hori S, Inoue S, Tomokane T, Kudo M, Inaba T, Take S, Ohkusa T, Yamamoto S, Mizuno S, Kamoshida T, Amagai K, Iwamoto J, Miwa J, Kodama M, Okimoto T, Kato M, Asaka M; For the Japan GAST Study Group.. J Gastroenterol. 2013 Jan 11. [Epub ahead of print] PMID: 23307042



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 5749

Title: Review: Second and third line treatment options for H. pylori eradication

Reviewer code: 00503623

Science editor: Gou, Su-Xin

Date sent for review: 2013-09-25 14:44

Date reviewed: 2013-11-05 22:46

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

Your efforts in judiciously revising this interesting article is greatly appreciated. Good job !



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 5749

Title: Review: Second and third line treatment options for H. pylori eradication

Reviewer code: 02446765

Science editor: Gou, Su-Xin

Date sent for review: 2013-09-25 14:44

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

This is a very nice review on rescue therapy after 1st line treatment failure for H. pylori.



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 5749

Title: Review: Second and third line treatment options for H. pylori eradication

Reviewer code: 01436291

Science editor: Gou, Su-Xin

Date sent for review: 2013-09-25 14:44

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

These researchers have summarised the main protocols used for the eradication of H. pylori infection with special emphasis for the second and third line of treatment. The manuscript is a useful update and only needs to be revised by someone whose mother tongue is English and some corrections: 1. "0%", i.e. zero per cent, is not correct; zero, multiplied or divided by 10, or 100 etc. is always zero. So, change it with 0. 2. Correct "Megraud" with Mégraud" (also in the ref.) 3. Page 6, modify the following phrase: "... showed that clarithromycin, levofloxacin, amoxicillin, tetracycline, rifabutin and metronidazole resistance rates were 17.5%, 14.1%, 0.7%, 0.9%, 1.1% and 34.9% respectively in 18 European countries", as follows showed that the overall prevalence of resistance, comprehensive of 18 European countries, to were". 4. Ibidem, also change "are" in "is" in the following phrase: "In regions where antibiotic resistance for key antibiotics are very high"; the overall sentence is not clear; please, rewrite it. 5. Page 7, last paragraph. The authors say: "...antibiotics work more effectively when the bacterium is undergoing replication". This is true with amoxicillin, not with the other antibiotics: since antibiotics interfering with the metabolism of dividing cells, such as amoxicillin, are more efficacious during bacterial cell division, cagA+ organisms would be more susceptible and be destroyed more rapidly than the cagA-ones, which may be in resting phase. 6. To explain the increased rates of eradication in cases of infection by strains expressing CagA, the authors may add the following sentence: CagA positive organisms stimulate the gastric mucosa to secrete proinflammatory cytokines, such as interleukin-1 β and tumor necrosis factor- α , which are potent acid inhibitors (Wang et al. 1999). High levels of pro-inflammatory cytokines in the gastric mucosa colonized by CagA+ organisms could therefore lead to a profound acid suppression (Furuta et al. 2002) and therefore in a more efficacious treatment



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(Grayson et al., 1989; Sugimoto et al, 2007). Wang M., Furuta T., Takashima M., Futami H., Shirai N., Hanai H., Kaneko E. (1999). Relation between interleukin-1beta messenger RNA in gastric fundic mucosa and gastric juice pH in patients infected with *Helicobacter pylori*. *J. Gastroenterol.* 34, 10-17. Furuta T., El-Omar E.M., Xiao F., Shirai N., Takashima M., Sugimura H. (2002). Interleukin 1beta polymorphisms increase risk of hypochlorhydria and atrophic gastritis and reduce risk of duodenal ulcer recurrence in Japan. *Gastroenterology* 123, 92-105. Grayson M.L., Eliopoulos G.M., Ferraro M.J., Moellering R.C. Jr. (1989). Effect of varying pH on the susceptibility of *Campylobacter pylori* to antimicrobial agents. *Eur. J. Clin. Microbiol. Infect. Dis.* 8, 888-889. Sugimoto M., Furuta T., Shirai N., Kodaira C., Nishino M., Yamade M., Ikuma M., Watanabe H., Ohashi K., Hishida A., Ishizaki T. (2007). Treatment strategy to eradicate *Helicobacter pylori* infection: impact of pharmacogenomics-based acid inhibition regimen and alternative antibiotics. *Expert Opin. Pharmacother.* 8, 2701-2717. 7. Pag 12; the sentence "...suggesting that rifabutin has use as salvage therapies after multiple failures." is not very clear; may be the following one is clearer: "... suggesting that rifabutin may be used as salvage drug after multiple failures". 8. Two lines further, correct the word " pantroprazole". 9. Page 13; modify the phrase "Overall, 24.37% of patients experienced side effects and 1.68% had such" as follows: "Overall, 24.37% of patients experienced side effects and 1.68% of patients had such" 10. Ibidem; correct "was" in "were" in the following sentence: " since the eradication rate would likely be higher if duration of therapy was 14 d instead ...". The authors, in fact, did not prolong the treatment up to the 14th day. 11. Page 14; correct "amoxillin". 12. Ibidem; the last paragraph, which d



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Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 5749

Title: Review: Second and third line treatment options for H. pylori eradication

Reviewer code: 01429020

Science editor: Gou, Su-Xin

Date sent for review: 2013-09-25 14:44

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

COMMENTS TO AUTHORS

The article review of Song et al critically analyzes the rationale of current second and third line therapies with some useful suggestions regarding therapeutic strategy choice. The paper is well written and structured. Minor remarks are: ? Three in 1 capsule regimen: more details may be enclosed (Company, Countries where it is available, costs) since this scheme is unknown in many parts of the world and clinical trials are very few. Is there a reason for this last point? ? Moxifloxacin: also this drug is not available everywhere. Details about its diffusion worldwide are useful. Finally, adverse events must be further emphasized since they induced some National Health Services to avoid its commercialization. ? Sequential therapy: this treatment has always been recommended as first line regimen. In this case it has shown to be superior to conventional triple therapy even if its results are unsatisfactory when A2143G point mutation in bacterial DNA occurs (De Francesco et al, Ann Intern Med, 2006). Its use as second line therapy is less effective in clinical practice and does not have a convincing rationale. ? It is surprising the effectiveness of a rifaximin rescue therapy even if confined to a single report and a series of 58 patients. More details about this experience (i. e. how the Authors explain therapeutic success of a non absorbable antibiotic which could act only by contact) are needed.



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 5749

Title: Review: Second and third line treatment options for H. pylori eradication

Reviewer code: 00073423

Science editor: Gou, Su-Xin

Date sent for review: 2013-09-25 14:44

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

The review is summarizing the potential options for second and third line Helicobacter pylori eradication regimens. The paper is well written, data are presented clearly. Overall impression is positive. I could add some suggestions to authors: 1. The authors emphasize the differences in the resistance and eradication rate in different parts of the world. There are several consensus available, which are attributable to some regions: European Consensus, Asian-Pacific consensus, South American consensus etc. Therefore it would be quite impressive if authors could summarize: what is common and what is different in those consensus? What second and third line treatments are better in some special regions? 2. Maybe it may be useful to divide the Continents in some regions: i.e. Western European countries, Southern European countries, Central and Eastern European countries..... Not every therapy is available everywhere? 3. All these summarizing could be presented in clear format: tables or pictures?