



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 41334

Title: Second-line rescue treatment of Helicobacter pylori infection: Where are we now?

Reviewer's code: 02536252

Reviewer's country: Japan

Science editor: Ruo-Yu Ma

Date sent for review: 2018-08-07

Date reviewed: 2018-08-07

Review time: 2 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The authors need to discuss the present status in antibiotic resistance as well as resistance mechanisms for H. pylori eradication therapy in the discussion sections by citing some of followings. 1: Mori H, Suzuki H, Matsuzaki J, Masaoka T, Kanai T. Acquisition of double mutation in gyrA caused high resistance to sitafloxacin in



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Helicobacter pylori after unsuccessful eradication with sitafloxacin-containing regimens. United European Gastroenterol J. 2018 Apr;6(3):391-397. doi: 10.1177/2050640617737215. Epub 2017 Oct 8. PubMed PMID: 29774152; PubMed Central PMCID: PMC5949976. 2: Suzuki H, Mori H. World trends for H. pylori eradication therapy and gastric cancer prevention strategy by H. pylori test-and-treat. J Gastroenterol. 2018 Mar;53(3):354-361. doi: 10.1007/s00535-017-1407-1. Epub 2017 Nov 14. Review. PubMed PMID: 29138921; PubMed Central PMCID: PMC5847180. 3: Mori H, Suzuki H, Matsuzaki J, Masaoka T, Kanai T. Antibiotic resistance and gyrA mutation affect the efficacy of 10-day sitafloxacin-metronidazole-esomeprazole therapy for Helicobacter pylori in penicillin allergic patients. United European Gastroenterol J. 2017 Oct;5(6):796-804. doi: 10.1177/2050640616688995. Epub 2017 Jan 19. PubMed PMID: 29026593; PubMed Central PMCID: PMC5625875. 4: Mori H, Suzuki H, Matsuzaki J, Tsugawa H, Fukuhara S, Miyoshi S, Hirata K, Seino T, Matsushita M, Nishizawa T, Masaoka T, Kanai T. Rifabutin-based 10-day and 14-day triple therapy as a third-line and fourth-line regimen for Helicobacter pylori eradication: A pilot study. United European Gastroenterol J. 2016 Jun;4(3):380-7. doi: 10.1177/2050640615618043. Epub 2015 Nov 13. PubMed PMID: 27403304; PubMed Central PMCID: PMC4924440. 5: Nishizawa T, Maekawa T, Watanabe N, Harada N, Hosoda Y, Yoshinaga M, Yoshio T, Ohta H, Inoue S, Toyokawa T, Yamashita H, Saito H, Kuwai T, Katayama S, Masuda E, Miyabayashi H, Kimura T, Nishizawa Y, Takahashi M, Suzuki H. Clarithromycin Versus Metronidazole as First-line Helicobacter pylori Eradication: A Multicenter, Prospective, Randomized Controlled Study in Japan. J Clin Gastroenterol. 2015 Jul;49(6):468-71. doi: 10.1097/MCG.000000000000165. PubMed PMID: 24921211. 6: Nishizawa T, Suzuki H. Mechanisms of Helicobacter pylori antibiotic resistance and molecular testing. Front Mol Biosci. 2014 Oct 24;1:19. doi: 10.3389/fmolb.2014.00019. eCollection 2014. Review. PubMed PMID: 25988160; PubMed Central PMCID: PMC4428472. 7: Asaoka D,



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Nagahara A, Matsuhisa T, Takahashi S, Tokunaga K, Kawai T, Kawakami K, Suzuki H, Suzuki M, Nishizawa T, Kurihara N, Ito M, Sasaki H, Omata F, Mizuno S, Torii A, Ohkusa T, Mine T, Sakaki N. Trends of second-line eradication therapy for *Helicobacter pylori* in Japan: a multicenter study in the Tokyo metropolitan area. *Helicobacter*. 2013 Dec;18(6):468-72. doi: 10.1111/hel.12063. Epub 2013 Jun 18. PubMed PMID: 23773231.

8: Nishizawa T, Suzuki H, Matsuzaki J, Muraoka H, Tsugawa H, Hirata K, Hibi T. *Helicobacter pylori* resistance to rifabutin in the last 7 years. *Antimicrob Agents Chemother*. 2011 Nov;55(11):5374-5. doi: 10.1128/AAC.05437-11. Epub 2011 Sep 6. PubMed PMID: 21896915; PubMed Central PMCID: PMC3195021.

9: Nishizawa T, Suzuki H, Tsugawa H, Muraoka H, Matsuzaki J, Hirata K, Ikeda F, Takahashi M, Hibi T. Enhancement of amoxicillin resistance after unsuccessful *Helicobacter pylori* eradication. *Antimicrob Agents Chemother*. 2011 Jun;55(6):3012-4. doi: 10.1128/AAC.00188-11. Epub 2011 Apr 12. Erratum in: *Antimicrob Agents Chemother*. 2013 Feb;57(2):1106. PubMed PMID: 21486961; PubMed Central PMCID: PMC3101459.

10: Tsugawa H, Suzuki H, Muraoka H, Ikeda F, Hirata K, Matsuzaki J, Saito Y, Hibi T. Enhanced bacterial efflux system is the first step to the development of metronidazole resistance in *Helicobacter pylori*. *Biochem Biophys Res Commun*. 2011 Jan 14;404(2):656-60. doi: 10.1016/j.bbrc.2010.12.034. Epub 2010 Dec 11. PubMed PMID: 21147064.

11: Hirata K, Suzuki H, Nishizawa T, Tsugawa H, Muraoka H, Saito Y, Matsuzaki J, Hibi T. Contribution of efflux pumps to clarithromycin resistance in *Helicobacter pylori*. *J Gastroenterol Hepatol*. 2010 May;25 Suppl 1:S75-9. doi: 10.1111/j.1440-1746.2009.06220.x. PubMed PMID: 20586871.

12: Suzuki H, Nishizawa T, Hibi T. *Helicobacter pylori* eradication therapy. *Future Microbiol*. 2010 Apr;5(4):639-48. doi: 10.2217/fmb.10.25. Review. PubMed PMID: 20353303.

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Reviewer's code: 00001114

Reviewer's country: Japan

Science editor: Ruo-Yu Ma

Date sent for review: 2018-08-07

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<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Comments to the Author: This entitles "Second-line rescue treatment of Helicobacter pylori infection: Where are we now? " is well-written and comprehensive review about this subject. I have following one comment - I would request to add strategy for choice of second line regimen. The Maastricht V/Florence Consensus Report said that



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after a first failure, if an endoscopy is carried out, culture and standard antimicrobial susceptibility testing (AST) are recommended to tailor the treatment. What do the authors think if test-and-treat strategy is necessary before selecting second-line regimen? In Japan, PPI-containing triple therapy with metronidazole (MTZ) and amoxicillin is a standard second line regimen. Because this triple therapy is only covered under Japan's national health insurance. We clinically did not check AST but we can achieve eradication rate of around 90% because MTZ resistance rate is relatively low in Japan. I think choice of second line regimen depends on its regional factors. So I would ask the authors to give comments to readers when they select second line regimen.

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