



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48679

Title: Lactobacillus rhamnosus GG in the treatment of acute pediatric diarrhea: A systematic review with meta-analysis

Reviewer's code: 03260131

Reviewer's country: Turkey

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-04-28 21:50

Reviewer performed review: 2019-05-02 11:21

Review time: 3 Days and 13 Hours

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 Grade E: Do not publish	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

SPECIFIC COMMENTS TO AUTHORS

Dear authors, This is a well documented hard study that identified the effect of LGG in children with diarrhea.



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INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48679

Title: Lactobacillus rhamnosus GG in the treatment of acute pediatric diarrhea: A systematic review with meta-analysis

Reviewer's code: 00503628

Reviewer's country: United States

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-05-01 15:29

Reviewer performed review: 2019-05-06 16:05

Review time: 5 Days

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 type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input 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 type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The study by Dr. Li and colleagues represents a meta-analysis on the use of Lactobacillus rhamnosus GG in the treatment of acute pediatric diarrhea. The study presented is well conceived, thorough and addresses an important question. The investigators searched



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the major publication databases as well as the Cochrane Central Register of Controlled trials and selected a total of 19 randomized controlled trials that describe LGG usage on acute diarrhea. Their exclusion criteria are well described and include antibiotic-associated and persistent diarrhea as well as studies with more than one strain or studies with incomplete data sets. After analysis of the findings in their study the authors reached the conclusions that better outcomes were noted in children receiving LGG > 1010 CFU at early stages, particularly if they were rotavirus-positive diarrhea cases. Interestingly, the reduction in diarrhea was noted in studies conducted in Asia and Europe, but not in other regions. This intriguing observation was not addressed in the study. Overall, this exhaustive manuscript is well written and of interest.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 48679

Title: Lactobacillus rhamnosus GG in the treatment of acute pediatric diarrhea: A systematic review with meta-analysis

Reviewer's code: 00002649

Reviewer's country: United States

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-04-28 12:29

Reviewer performed review: 2019-05-24 01:17

Review time: 25 Days and 12 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input checked="" type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input checked="" 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

MS 48679: Li et al. L. rhamnosus GG (LGG) in the treatment of acute pediatric diarrhea: a systematic review with meta-analysis. This MS analyzes RCTs which evaluated LGG treatment in children with acute diarrhea. Nineteen were selected.



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These reportedly showed that LGG reduced the duration of diarrhea—but only when given at a dose $> 10^{10}$ CFUs daily. Asian and European studies found similar results. Efficacy pertained only to studies enrolling subjects with diarrhea that started < 3 days earlier; and children rotaviral diarrhea responded the best. COMMENTS: MAJOR: 1. The MS is poorly written, with many grammatical errors and a poor discussion. The authors need an English expert to attend to this MS paragraph by paragraph. Pages are not numbered, so I did it by hand. 2. Nevertheless, the recent NEJM publication by Schnadower et al. involving > 900 patients has raised concern that this probiotic is not effective. Therefore, the publication is timely and relevant. 3. Publication bias is a clear concern, yet the discussion of figure S8 is inadequate and the figures are tiny and cannot be read. 4. Adverse effects: How many studies effectively evaluated safety of LGG, for example with diary cards, scheduled phone calls, or daily email access? 5. Risk of bias: Of 18 trials, 6 were not strictly blinded. Does this weaken the conclusions of the authors? MINOR: 1. Abstract: Results: “Nineteen RCTs ... indicated that LGG notably ameliorated diarrheal duration.” I would replace “indicated” with “showed.” 2. I do not understand why 2 significant digits or more are reported, e.g. “mean difference = 24.02 hours” and 95% CI 36.58. 3. Needs a period after 14.79. 4. “The obvious elimination of duration...” is not correct. I think they mean the “shortening of duration of diarrhea.” “Clearly” should be removed. In “reducing rotavirus diarrheal duration.” 5. Results: line 7: “participator” should be “participants.” 6. Core tip: Again there are serious grammar problems. “LGG was confirmed to be effective in reducing ...number of stools per day. LGG was particularly efficacious in the subsets of patients treated with $> 10^{10}$ CFU/day, treated at an early stage of illness, or diagnosed with rotavirus diarrhea.” 7. Similar grammar problems are seen throughout the MS. On p.3, 3rd paragraph: “shortening the duration of diarrhea and” Next sentence needs a comma after inhibitor; and



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“substantial” needs to be replaced with “the incidence of...” 8. I am not aware that the WHO feels that a gut motility inhibitor is underused. 9. What is meant by “SCFA modulate the AMP-independent cycle.” Next sentence about rotavirus diarrhea is incorrect. “Leading guidelines” refers to “leading experts.” “Schnadower et al. found no evidence...” 10. Study selection: The first 3 sentences need changes. 11. Page 7: After “The Cochrane Review Manager...” the sentence beginning with “The inverse of variance contributes... sounds like a lecture. 12. P. 7, bottom: In addition, a larger dose was suggested – actually one is in *C. difficile* prevention, not relevant. 13. Subgroup analyses: The titles should be underlined or put in italics. 14. P. 8, top paragraph. Again, serious grammar issues related to parallel structure. After Gieruszczk-Bialek concluded that...” the next title should be Site of treatment (inpatient vs. outpatient); then Vaccination status. Early administration. Publication date. 15. Bottom of p.8: A large number of trials were conducted in Europe and Asia. 16. P. 9, sentence beginning with “Inconsistency” does not make sense; and the next sentence probably means “Different criteria were used to define diarrhea among all the included studies.” 17. P. 9, bottom para: The authors are referring to duration of diarrhea before entry, I believe. Also, “Fortunately” should be replaced with “However.” 18. P. 10, 3rd line from the bottom and throughout the MS: “no less than” should be replaced with “>”. 19. Same page, bottom 2 lines: add “although there were only 3 studies with the lower dosages.” 20. P. 11: The authors say that “No studies evaluated the effectiveness of LGG in children vaccinated against rotavirus” but what about the Schnadower study? Also, this sentence should go after “(Figure 2)” 21. Please reword the last sentence on p. 11. 22. Diarrhea > 4d: 3C and 3D are not described. 23. P. 13: “David” does not need to be there; also “However” should be removed from the next sentence. 24. The Discussion is very difficult to read. Perhaps the authors should make subsections with different points to be made. One reasonable conclusion is that the original meta-analysis by



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Szajewska made the correct conclusions. I do not understand the top paragraph on p.16 that starts with “The guidelines” and goes to the end of the paragraph. 25. “Vomiting is one of the most common symptoms of diarrhea”-incorrect, authors mean “associated with diarrhea.” 26. P. 17: I am aware that probiotics benefit the immune response to viruses, but I am not aware that the “viral cycle” is impacted. This sounds like an interference with viral DNA or RNA replication. 27. P. 18, 2nd to last paragraph: I would add “Overall, our study support the previous systematic reviews which concluded that LGG if an effective treatment for children with acute diarrhea.” 28. Figure 4: What is meant by “stool times”? What is the x-axis? It is not stool number. 29. Figure 4: “frequency on day 3.” 30. Figure 5: A is duration of hospital stay? Why are hours 149, 223 reported. That is 6-10 days. Is this correct?

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