

Drs Damian Garcia-Olmo, Stephen Strom, and Andrzej Tarnawski
Editors-in-Chief
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16 May 2017

Dear Drs Garcia-Olmo, Strom, and Tarnawski,

Thank you for considering our manuscript "Probiotics for gastrointestinal disorders: proposed recommendations for children of the Asia-Pacific region" for publication in the *World Journal of Gastroenterology*.

The manuscript has been now been revised and the required corrections made, and a point-by-point response to these comments (shown in blue) is given below. All changes to the manuscript are highlighted yellow.

Thank you again for your time in considering our manuscript. I look forward to hearing from you soon.

Kind regards,

Prof. Donald Cameron, on behalf of all authors

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Response to Reviewer Comments

Reviewer 1

This paper proposed recommendations for the use of probiotics for pediatric gastrointestinal disorders in the Asia-Pacific countries. It is a timely contribution to the increasing research interest in probiotics. It would be great if the authors can highlight the gaps where further research will be useful. Otherwise, I have no further comments.

Author response: Thank you for your comment. We believe that the gaps where further research will be useful has been highlighted throughout the manuscript and, therefore, no additional amendments to the manuscript have been made.

Reviewer 2

This is a really timely effort to assess the situation for probiotics in Asia-Pacific region. I was delighted to read the manuscript and I appreciate it a lot. There are only minor adjustments I that I request the authors to consider and these are as follows:

1. The abstract states “adjunctive treatment” I wonder if this could be called adjunct treatment or “oral rehydration complemented with specific probiotics”

Author response: Text amended as recommended.

2. At the end of abstract I would suggest wording “Finally, specific probiotics with a history of safe use in preterm and term infants may be considered in infants for prevention of necrotizing enterocolitis.

Author response: Text amended as recommended.

3. The probiotic definition given in the introduction is “Probiotics are live microorganisms that when administered in adequate amounts confer a health benefit” which was grammatically corrected from the WHO working group by Hill and coworkers so it should be reference by ref 15 not 10.

Author response: Ref amended as highlighted by reviewer.

4. I would suggest the following wording for the sentence under the heading “Human Gut Microbiome”: “Probiotics are live microorganisms that when administered in

adequate amounts confer a health benefit”

Author response: Thank you for your comment. We do not agree that the suggested sentence is appropriate for the first sentence of the “Human Gut Microbiome” section of this paper, as probiotics are not the focus of this section. However, we have added this sentence to the beginning of the “Probiotics” section of this paper, as we believe it is appropriate to add there.

5. Probiotic chapter first sentence - please add reference 15 (Hill et al) here to emphasize the consensus definition on Probiotics.

Author response: We have amended the first sentence of the “Probiotics” section of the manuscript with the wording provided by the reviewer in comment #4. Furthermore, we have added the Hill et al reference as requested.

6. At the end of the above mentioned section I would expand on safety issues and consider the below mentioned references on safety of probiotics. Examples of some safety related publication and long term effects on probiotics in infants and children:

- Comment on safety, eg Luoto et al 10-year experience on LGG use very low birth weight infants: Luoto R, Isolauri E, Lehtonen L. Safety of Lactobacillus GG probiotic in infants with very low birth weight: twelve years of experience. Clin Infect Dis. 2010 May 1;50(9):1327-8.
- Long-term safety and efficacy: Lundelin K, Poussa T, Salminen S, Isolauri E. Long-term safety and efficacy of perinatal probiotic intervention: Evidence from a follow-up study of four randomized, double-blind, placebo-controlled trials. Pediatr Allergy Immunol. 2017 Mar;28(2):170-175.
- The report o Probiotic in hypoallergenic formula for 5 years (Scalabrin D, Harris C, Johnston WH, Berseth CL. Long-term safety assessment in children who received hydrolyzed protein formulas with Lactobacillus rhamnosus GG: a 5-year follow-up. Eur J Pediatr. 2017 Feb;176(2):217-224.

Author response: Thank you for your comment. We have expanded the safety discussion of probiotics based on your comment and added the Luoto and Lundelin reference as requested. We did not add the Scalabrin reference the manuscript, as the

use of hydrolyzed protein formulas were not discussed in the working group and this reference is out of the scope of the manuscript.