

CORRESPONDENCE

Open Access

Probiotics can Cause D-Lactic Acidosis and Brain Fogginess: Reply to Quigley et al.

Satish S. C. Rao, MD, PhD¹, Siegfried Yu, MD¹, Eula P. Tetangco, MD¹ and Yun Yan, MD, PhD¹

We thank the authors for their interest in our article. As they would appreciate, the realm of probiotics in health and disease is important to understand mechanistically and from a precision medicine perspective. Clearly, some people benefit from probiotics, others are unaffected, while still others have unexpected deleterious effects. Our research focused on a group of patients with unexplained brain fogginess, gas and bloating, and to determine the underlying mechanism(s). We have identified probiotics as one plausible factor in the pathogenesis of their problem among others. The report has received both praise and criticism from manufacturers of probiotics, as well as from Dr Quigley and colleagues, who have significant personal and scientific interests in probiotics. We are happy to respond to these criticisms, especially when approached from the perspective of average effects in average populations, and clarify what was clearly demonstrated in the subset of patients who experienced “brain fogginess”.

1. “Probiotics are safe”: Studies on probiotics have inadequate record of safety assessment, as concluded by the Agency for Healthcare Research and Quality¹, or carry risks^{2,3}. Hence, more safety studies are needed. 2. “Probiotics and SIBO are not equally culpable”: We found evidence for SIBO in 68% with either duodenal aspirate or breath test in a group of patients with brain fogginess (BF) and significant gas/bloating, all of whom took probiotics, compared to 28% in a control group without BF. Duodenal aspirates grew lactobacilli incriminating probiotics, among other bacteria. Because distal small bowel was not evaluated, where colonization is more likely, we may have detected fewer subjects. Thus, probiotics cause SIBO, but not all SIBO is from

probiotics. 3. “Bifidobacteria don’t produce D-lactate”: They quote a 1968 paper as evidence⁴, in which the authors did not measure D-lactate, because “Bifidobacterium did not produce CO₂”, and substantiate this with an unpublished observation⁴. In contrast, *Bifidobacterium longum* subsp. *infantis* does produce D- and L-lactate, but in lower amounts compared to *Lactobacillus rhamnosus*⁵. Thus, Bifidobacteria produce D-lactate, albeit less than Lactobacillus⁶. 4. “D-lactic acidosis can be treated by probiotics”: The authors describe a recent case report, but there are other case reports where D-lactic acidosis was treated with antibiotics and probiotics but these authors were unsure which treatment conferred benefit^{7,8}. In another report, D-lactic acidosis was provoked twice by probiotics⁹. Hence, probiotics should be avoided in D-lactic acidosis. 5. “Rao and colleagues equate all probiotics which is misleading”: We found that 15/30 patients took OTC generic probiotics (Walmart, Walgreens, CVS etc) and 15 took named brands (Culturelle®, Jarodophilus®, VSL#3®, Align®, Nature’s®, Colonsense®, Ultimate Care®). Our study was not designed to address which probiotic or its contents either caused SIBO or was safer, but to identify why our patients developed debilitating gastrointestinal symptoms and BF. 6. “Is it D-Lactic acidemia or acidosis?": D-Lactic acidosis describes elevated D-lactic acid levels with neurocognitive symptoms, and misdiagnosis is common¹⁰. In our series, 23/30 patients with BF had elevated D-lactic acid with mild to moderate symptoms, and BF was reproduced in 20/30 (66%) patients, but not severe enough for hospitalization. Thus, it is a matter of semantics. 7. “Patient’s response to antibiotic and probiotic cessation is not conclusive”: Our scientific paper was intended to raise awareness that probiotics may colonize small bowel and cause SIBO. If so, because they

Correspondence: Satish S. C. Rao (srao@augusta.edu)

¹Division of Neurogastroenterology/Motility, Department of Medicine, Augusta University Medical Center, Augusta, GA, USA

© The Author(s) 2018



Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. If you remix, transform, or build upon this article or a part thereof, you must distribute your contributions under the same license as the original. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-sa/4.0/>.

produce D-lactic acid (especially *Lactobacillus* and *Streptococcus* sp.), they may cause BF and clinicians should recognize this association and treat appropriately. We intend conducting future studies using more validated parameters for BF, and testing for SIBO and D-lactate resolution. 8. “Questionable diagnosis of SIBO especially with mild increased counts”: The methodology we used for identifying SIBO with either glucose breath test or duodenal aspirate/culture conforms with the recommendations of the North American Consensus¹¹. Hence, the diagnosis was accurate and based on current established criteria.

Acknowledgements

Guarantor of the article:

Satish S.C. Rao.

Financial support: None to report.

Potential competing interests: None to report.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Specific author contributions: All authors wrote the letter.

Received: 21 September 2018 Revised: 10 October 2018 Accepted: 21 October 2018

Published online: 19 November 2018

References

1. Hempel S. et al. Safety of probiotics used to reduce risk and prevent or treat disease. *Evid. Rep. Technol. Assess.* **200**, 1–645, PMID 23126627 (2011).
2. Doron, S. & Snyderman, D. R. Risk and safety of probiotics. *Clin. Infect. Dis.* **60** (Suppl. 2), S129–S134 (2015).
3. Koretz, R. L. Probiotics in Gastroenterology: How Pro Is the Evidence in Adults? *Am. J. Gastroenterol.* **113**, 1125–1136 (2018).
4. de Vries, W. & Stouthamer, A. H. Fermentation of glucose, lactose, galactose, mannitol, and xylose by bifidobacteria. *J. Bacteriol.* **96**, 472–478 (1968).
5. Munoz, J. A. et al. Novel probiotic *Bifidobacterium longum* subsp. *infantis* CECT 7210 strain active against rotavirus infections. *Appl. Environ. Microbiol.* **77**, 8775–8783 (2011).
6. Ewaschuk JB et al. D-lactate in human and ruminant metabolism. *J. Nutr.* **135**, 1619–1625 (2005).
7. Uchida, H. et al. D-lactic acidosis in short-bowel syndrome managed with antibiotics and probiotics. *J. Pediatr. Surg.* **39**, 634–636 (2004).
8. Gavazzi, C. et al. Confusion after antibiotics. *Lancet* **357**, 1410 (2001).
9. Ku, W., DCY, Lau & KF, Huen Probiotics provoked D-lactic acidosis in short bowel syndrome: case report and literature review. *Hong. Kong J. Paediatr.* **11**, 246–254 (2006).
10. Petersen, C. D-lactic acidosis. *Nutr. Clin. Pract.* **20**, 634–645 (2005).
11. Rezaie, A. et al. Hydrogen and methane-based breath testing in gastrointestinal disorders: The North American Consensus. *Am. J. Gastroenterol.* **112**, 775–784 (2017).