HHS Public Access

Author manuscript

Gastroenterology. Author manuscript; available in PMC 2018 January 04.

Published in final edited form as:

Gastroenterology. 2017 June ; 152(8): 1817–1819. doi:10.1053/j.gastro.2017.04.027.

Probiotics for prevention of *Clostridium difficile* infection in hospitalized patients: is the jury still out?

Krishna Rao, MD, MS[1] and **Vincent B. Young, MD, PhD**[2]

[1]Assistant Professor, Division of Infectious Diseases, Department of Internal Medicine, University of Michigan, Ann Arbor, MI

[2]Professor, Division of Infectious Diseases, Department of Internal Medicine, Department of Microbiology and Immunology, University of Michigan, Ann Arbor, MI

The incidence of *Clostridium difficile* infection (CDI) has increased in the past decade, despite intensified efforts at prevention including infection control and antimicrobial stewardship.[1] This has led to the exploration of additional means to reduce the incidence of primary CDI, including vaccines,[2] fecal microbiota transplantation (FMT),[3] isolation of colonized patients,[4] and probiotics. Probiotics are an attractive option since they are widely available, inexpensive, and administered easily.

The recent publication of the negative results of the PLACIDE trial,[5] a large randomized controlled trial (RCT) examining the role of probiotics in CDI prevention, had cooled interest in probiotics for this indication. This study also followed the lack of a recommendation for the use of probiotics for routine prophylaxis in the most recently published CDI guidelines.[6] Prior to the PLACIDE trial, earlier systematic reviews and meta-analyses have suggested probiotic use during antibiotic exposure can reduce incident CDI.[7–9] Furthermore, a real-world implementation study at a single center also suggested a benefit exists to CDI prophylaxis with probiotics.[10] Prior reviews may have been compromised by methodological inconsistencies, and they did not focus on hospitalized patients taking antibiotics, a population at high risk of CDI. Additionally, the PLACIDE trial had a low overall risk of CDI (0.8–1.2%), suggesting that there was insufficient power to detect an effect and/or that the results do not generalize to a higher incidence setting.

The recent systematic review and meta-analysis by Shen et al.[11] focuses on RCTs evaluating probiotics for the prevention of CDI in hospitalized patients taking antibiotics. This study was rigorously conducted according to PRISMA guidelines. The authors included 19 trials with 6261 patients (3277 on probiotics and 2984 controls), including the PLACIDE trial. There was no evidence of publication bias and the heterogeneity was low. Despite this, the authors still made the conservative decision to use a lower power mixed model with random effects for the meta-analysis. The relative risk (RR) of the primary outcome of incident CDI

Correspondence: Vincent B. Young, MD, PhD. 1150 W. Medical Center Drive, 1520B MSRB1, Ann Arbor, MI 48109. youngvi@umich.edu. Phone: 734-764-2237. Fax: 734-615-5534.

Disclosures: all authors have nothing to disclose.

Author contributions: KR and VBY—drafting of the manuscript; critical revision of the manuscript for important intellectual content.

in patients who received a probiotic was 0.42, with a number needed to treat (NNT) of only 43, given the baseline incidence of 4% in the control groups. One major issue not previously addressed by prior analyses was the missing outcome data in ten of the 19 trials. However, even when the authors conservatively assumed a five-fold higher incidence of CDI in the missing data compared to the non-missing data, the RR of incident CDI while on probiotics only rises to 0.6 (NNT 63 if control group incidence remains at 4%). As a comparison, a commonly advocated practice of heparin for prophylaxis of venous thromboembolism in hospitalized patients has a NNT of 250.[12] Overall, the methodology in this study was sound and the analysis decisions made were conservative, including the use of a random effects model and the attention to missing data.

The only subgroup analysis that was significant was the timing of probiotic initiation in relation to the start of antibiotics. Each day of delay in initiation of probiotics resulted in an 18% increase in the log odds of incident CDI. This finding is interesting in that the PLACIDE trial was an outlier, allowing probiotics to be administered as late as seven days following antibiotics. Nevertheless, the association with timing of probiotics and incident CDI persisted when this trial was excluded in a sensitivity analysis. This suggests that future trials testing probiotics to prevent CDI should be designed to start probiotic administration soon after the initiation of antibiotics.

How is a clinician to interpret the results of the Shen et al. study? While we still do not believe we can wholeheartedly recommend probiotics for prevention of CDI, this study suggests that the case is far from closed: further trials would be helpful and should be conducted. One omission of the current analysis that could be explored is the effect of specific antibiotic classes on CDI risk in the setting probiotic use, since certain antibiotics confer significantly higher risk of CDI.[13, 14] Additionally, not all of the included trials excluded patients on yogurt and recent data suggest that kefir is a potentially useful agent for treatment of recurrent CDI.[15] Finally, we are still left with questions about what probiotic species and formulations are most effective. We do not know whether single agent probiotics are the best option vs. probiotic communities or even FMT. As this was a meta-analysis, a variety of different agents were used in the 19 trials included in the study.

Many of the excluded patients in the trials were immunocompromised, were in an intensive care unit (ICU), or had inflammatory bowel disease. These patients are among those at the highest risk of incident CDI; the efficacy of probiotics in these important populations is still undetermined. Safety remains a concern, especially among the aforementioned excluded patients. A prior trial of probiotic use following acute pancreatitis in an ICU population actually measured increased mortality in the probiotic group.[16] Other reported complications include septicemia[17] and infective endocarditis,[18] warranting caution in patients with central venous catheters and immune compromise. The utility and safety of probiotics in these populations is unknown without further studies specifically targeting these patients.

In conclusion, the study by Shen et al. is rigorous in its execution and conservative in its analysis and interpretation of the data, while still measuring a net beneficial effect in the use of probiotics for prevention of CDI in hospitalized patients on antibiotics. Despite this, the generalizability to the excluded populations, the safety / efficacy in those populations, how

the differential CDI risk of certain antibiotic classes modulates any protective effect, and whether probiotic communities offer greater benefit remain open areas for investigation that limit broad recommendations for clinical practice. In addition to addressing these issues, future RCTs should aim to initiate probiotics early after antibiotics are started and should also consider whether a cohort selection strategy that accounts for non-antibiotic contributors to CDI risk, such as baseline colonization status,[19] would be more effective. Such knowledge could lead to probiotics being incorporated as part of a larger CDI prevention bundle and finally buck this decade-long trend in CDI incidence.

Acknowledgments

Grant support: This work was supported by grants from the National Institute of Allergy and Infectious Diseases at the National Institutes of Health [grant numbers R21-AI120599 and U01-AI124255].

Abbreviations

CDI	*Clostridium difficile* infection
FMT	fecal microbiota transplantation
ICU	intensive care unit
NNT	number needed to treat
RCT	randomized controlled trial
RR	relative risk

References

1. Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, Farley MM, Holzbauer SM, Meek JI, Phipps EC, Wilson LE, Winston LG, Cohen JA, Limbago BM, Fridkin SK, Gerding DN, McDonald LC. Burden of *Clostridium difficile* infection in the United States. N Engl J Med. 2015; 372:825–34. [PubMed: 25714160]
2. Martin J, Wilcox M. New and emerging therapies for *Clostridium difficile* infection. Curr Opin Infect Dis. 2016; 29:546–554. [PubMed: 27753689]
3. Lofgren ET, Moehring RW, Anderson DJ, Weber DJ, Fefferman NH. A Mathematical Model to Evaluate the Routine Use of Fecal Microbiota Transplantation to Prevent Incident and Recurrent *Clostridium difficile* Infection. Infection Control and Hospital Epidemiology. 2013; 35:18–27. [PubMed: 24334794]
4. Longtin Y, Paquet-Bolduc B, Gilca R, Garenc C, Fortin E, Longtin J, Trottier S, Gervais P, Roussy JF, Levesque S, Ben-David D, Cloutier I, Loo VG. Effect of Detecting and Isolating *Clostridium difficile* Carriers at Hospital Admission on the Incidence of *C difficile* Infections: A Quasi-Experimental Controlled Study. JAMA Intern Med. 2016
5. Allen SJ, Wareham K, Wang D, Bradley C, Sewell B, Hutchings H, Harris W, Dhar A, Brown H, Foden A, Gravenor MB, Mack D, Phillips CJ. A high-dose preparation of lactobacilli and bifidobacteria in the prevention of antibiotic-associated and *Clostridium difficile* diarrhoea in older people admitted to hospital: a multicentre, randomised, double-blind, placebo-controlled, parallel arm trial (PLACIDE). Health Technol Assess. 2013; 17:1–140.
6. Debast SB, Bauer MP, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection. Clin Microbiol Infect. 2014; 20(Suppl 2):1–26.

7. Lau CS, Chamberlain RS. Probiotics are effective at preventing *Clostridium difficile*-associated diarrhea: a systematic review and meta-analysis. Int J Gen Med. 2016; 9:27–37. [PubMed: 26955289]
8. McFarland LV. Probiotics for the primary and secondary prevention of *C. difficile* infections: a meta-analysis and systematic review. Antibiotics. 2015; 4:160–178. [PubMed: 27025619]
9. Johnston BC, Ma SSY, Goldenberg JZ, Thorlund K, Vandvik PO, Loeb M, Guyatt GH. Probiotics for the Prevention of *Clostridium difficile*–Associated Diarrhea: A Systematic Review and Meta-analysis. Annals of Internal Medicine. 2012; 157:878–888. [PubMed: 23362517]
10. Maziade PJ, Andriessen JA, Pereira P, Currie B, Goldstein EJ. Impact of adding prophylactic probiotics to a bundle of standard preventative measures for *Clostridium difficile* infections: enhanced and sustained decrease in the incidence and severity of infection at a community hospital. Curr Med Res Opin. 2013; 29:1341–7. [PubMed: 23931498]
11. Shen NT, Maw A, Tmanova LL, Pino A, Ancy K, Crawford CV, Simon MS, Evans AT. Timely use of Probiotics in Hospitalized Adults Prevents *Clostridium difficile* Infection: a Systematic Review with Meta-Regression Analysis. Gastroenterology. 2017
12. Qaseem A, Chou R, Humphrey LL, Starkey M, Shekelle P. Venous thromboembolism prophylaxis in hospitalized patients: A clinical practice guideline from the american college of physicians. Annals of Internal Medicine. 2011; 155:625–632. [PubMed: 22041951]
13. Dubberke ER, Yan Y, Reske KA, Butler AM, Doherty J, Pham V, Fraser VJ. Development and validation of a *Clostridium difficile* infection risk prediction model. Infect Control Hosp Epidemiol. 2011; 32:360–6. [PubMed: 21460487]
14. Kuntz JL, Smith DH, Petrik AF, Yang X, Thorp ML, Barton T, Barton K, Labreche M, Spindel SJ, Johnson ES. Predicting the Risk of *Clostridium difficile* Infection upon Admission: A Score to Identify Patients for Antimicrobial Stewardship Efforts. Perm J. 2016; 20:20–5. [PubMed: 26845084]
15. Bakken JS. Staggered and tapered antibiotic withdrawal (STAW) with administration of Kefir for recurrent *Clostridium difficile* infection. Clinical Infectious Diseases. 2014
16. Besselink MGH, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, Nieuwenhuijs VB, Bollen TL, van Ramshorst B, Witteman BJM, Rosman C, Ploeg RJ, Brink MA, Schaapherder AFM, Dejong CHC, Wahab PJ, van Laarhoven CJHM, van der Harst E, van Eijck CHJ, Cuesta MA, Akkermans LMA, Gooszen HG. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. The Lancet. 2008; 371:651–659.
17. Herbrecht R, Nivoix Y. *Saccharomyces cerevisiae* fungemia: an adverse effect of *Saccharomyces boulardii* probiotic administration. Clin Infect Dis. 2005; 40:1635–7. [PubMed: 15889361]
18. Kato K, Funabashi N, Takaoka H, Kohno H, Kishimoto T, Nakatani Y, Matsumiya G, Kobayashi Y. *Lactobacillus paracasei* endocarditis in a consumer of probiotics with advanced and severe bicuspid aortic valve stenosis complicated with diffuse left ventricular mid-layer fibrosis. Int J Cardiol. 2016; 224:157–161. [PubMed: 27657466]
19. Kagan S, Wiener-Well Y, Ben-Chetrit E, Kashat L, Aouizerats J, Bdolah-Abram T, Yinnon AM, Assous MV. The risk for *Clostridium difficile* colitis during hospitalization in asymptomatic carriers. J Hosp Infect. 2017