



Is primary prevention of *Clostridium difficile* infection possible with specific probiotics?

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SUMMARY

Background: The efficacy of probiotics for the prevention of *Clostridium difficile* infection (CDI) is highly controversial, particularly with regard to the prevention of recurrent CDI. We hypothesize that primary prevention of CDI among patients receiving antibiotics might be a more achievable goal for probiotics than prevention in patients with previous CDI where the host flora is markedly altered.

Methods: We conducted a literature search for randomized, placebo-controlled efficacy studies of probiotic use among adults receiving antibiotics, in which CDI was one of the outcomes measured. In addition, we conducted meta-analyses of probiotics that were included in more than one randomized trial.

Results: Eleven studies were identified; most were seriously underpowered to determine the efficacy of probiotics in the prevention of CDI. Two showed significantly lower rates of CDI among the probiotic recipients. A meta-analysis of three studies that used the probiotic combination *Lactobacillus acidophilus* CL1285 and *Lactobacillus casei* LBC80R and a combined analysis of those studies with four studies that used *Saccharomyces boulardii*, showed lower CDI rates in recipients of probiotics compared with recipients of placebo (risk ratio = 0.39; 95% confidence interval 0.19–0.79).

Conclusions: While potential flaws in study design were identified, a review of the available literature suggests that the primary prevention of CDI with specific probiotic agents may be achievable. Additional studies of sufficient size and with rigorous design are needed to confirm these findings.

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1. Introduction

Antibiotics are the major risk factor for a primary episode of *Clostridium difficile* infection (CDI), as well as an important factor for recurrent CDI. The risk associated with antibiotics primarily relates to disruption of the protective host colonic microbiota, but may also involve selection for *C. difficile* strains resistant to the inciting agent.¹ Adjunctive therapy with probiotics has been used widely for patients with CDI, with and without the guidance of physicians. The goal of probiotic therapy is to mitigate the effects of microbiota disruption, and different mechanisms have been

proposed whereby specific probiotics affect the microbiota and interfere with *C. difficile*.²

Most studies of CDI prevention have focused on secondary prevention (i.e., prevention of CDI recurrence), mainly because the risk for CDI is sufficiently high in patients with a recent CDI episode that the effect of intervention is easier to demonstrate; 20–30% after the first episode and ~50% after the second episode.³ The rate of primary episode CDI among antibiotic recipients varies with different antibiotics and populations studied, but is much lower than the rate of recurrent CDI and usually is much less than 10%.⁴ Therefore, a larger study population is needed to demonstrate efficacy in primary CDI prevention.

The efficacy of probiotics in the prevention of CDI has been hotly debated,^{5,6} but many studies and meta-analyses have combined primary and secondary CDI prevention data, which

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among hospitalized patients taking antibiotics.⁴¹ This study was widely criticized for questionable choice and blinding of the placebo drink and the numerous exclusions in the protocol, including high risk antibiotics, making it difficult to understand how these results, if repeatable, would be generalizable.^{47,48} The results, however, were subsequently repeated in a randomized study using another Lactobacillus preparation, *L. casei* and *L. acidophilus* (Bio-K+ CL1285), that did not exclude high risk antibiotics.¹⁰ While there are questions about the design and execution of this study as well, there are reasons to hypothesize that probiotics might be more efficacious in primary CDI prevention than in secondary prevention. We hypothesize that the efficacy of probiotics for the prevention of CDI relates to the extent of disruption of the protective host colonic microbiota.

Appreciation of the extent and diversity of the human colonic microbiota has been enhanced with the development of culture-independent techniques based on amplification of 16s rRNA.⁴⁹ Antibiotics have a profound effect on the richness, evenness, and diversity of the microbiota, even in the absence of overt gastrointestinal symptoms.⁵⁰ Chang et al. used similar techniques to study the microbiota of patients with initial CDI episodes and recurrent CDI episodes compared to controls without CDI infection.⁵¹ The striking finding in that study was the marked redistribution of major bacterial phyla and much lower diversity of the biota among the patients with recurrent CDI. In contrast, the microbiota in patients with an initial CDI episode was more similar to that of the controls than that of the recurrent CDI patients. It is possible that the opportunity for a probiotic effect is greatest at the time of initial exposure to *C. difficile* following antibiotic disruption of the flora but before the more pervasive disruption following established infection with *C. difficile*.

Even though the majority of the randomized probiotic studies of primary prevention for CDI did not show statistically significant differences and were seriously underpowered for this outcome evaluation, the trend was towards protection in nine of the 11 studies. Our meta-analysis provided the opportunity to better understand these trends for the two best-studied probiotic formulations (*L. acidophilus* + *L. casei* and *S. boulardii*). Our findings indicate a consistent and significant effect for the *L. acidophilus* + *L. casei* formulation and a trend towards a beneficial effect for *S. boulardii* preparations; the combined overall effect showed significant protection from CDI (Figure 1).

The recent reports of primary prophylaxis attempts using the Lactobacillus preparation Bio-K+ CL1285^{8–10} are particularly encouraging. The 9-month study conducted in one Montreal area hospital during the 2003–2004 BI/NAP1/027 CDI epidemic came close to showing effectiveness of this product for CDI prevention.⁸ Furthermore, the analysis of the three *L. acidophilus* + *L. casei* studies and the overall combined meta-analysis of the *L. acidophilus* + *L. casei* and *S. boulardii* studies showed significant protection against CDI among antibiotic recipients who took probiotics during their time at risk. While the extraordinary rate of CDI among the placebo recipients in the two studies showing efficacy^{10,41} is still incompletely explained, the possibility of primary CDI prevention using specific probiotics is intriguing and worthy of further study.

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Conflict of interest: SJ, PJM, LVM, WT, CD, BC, DEL, and ECJG have served on the advisory board of Bio-K+. This paper was conceived by the members of the advisory board and was written solely by the advisory board without input from Bio-K+.

References

1. Johnson S, Samore MH, Farrow KA, Killgore GE, Tenover FC, Lyras D, et al. Epidemics of diarrhea caused by a clindamycin-resistant strain of *Clostridium difficile* in four hospitals. *N Engl J Med* 1999;**341**:1645–51.
2. Gorbach SL. Probiotics in gastrointestinal health. *Am J Gastroenterol* 2000;**95**(1 Suppl):S2–4.
3. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent *Clostridium difficile* disease. *Am J Gastroenterol* 2002;**97**:1769–75.
4. Shim JK, Johnson S, Samore MH, Bliss DZ, Gerding DN. Primary symptomless colonization by *Clostridium difficile* and decreased risk of subsequent diarrhea. *Lancet* 1998;**351**:633–6.
5. McFarland LV. Evidence-based review of probiotics for antibiotic-associated diarrhea and *Clostridium difficile* infections. *Anaerobe* 2009;**15**:274–80.
6. Miller M. The fascination with probiotics for *Clostridium difficile* infection: lack of evidence for prophylactic or therapeutic efficacy. *Anaerobe* 2009;**15**:281–4.
7. Castagliuolo I, Riegler MF, Valenick L, LaMont JT, Pothoulakis C. *Saccharomyces boulardii* protease inhibits the effects of *Clostridium difficile* toxins A and B in human colonic mucosa. *Infect Immun* 1999;**67**:302–7.
8. Beausoleil M, Fortier N, Guénette S, L'Ecuyer A, Savoie M, Franco M, et al. Effect of a fermented milk combining *Lactobacillus acidophilus* CL1285 and *Lactobacillus casei* in the prevention of antibiotic-associated diarrhea: a randomized, double-blind, placebo-controlled trial. *Can J Gastroenterol* 2007;**21**:732–6.
9. Psaradellis E, Sampalis J, Rampakakis E. Efficacy of BioK+ CL1285 in the reduction of antibiotic-associated diarrhea—a placebo controlled double-blind randomized, multi-center study. *Arch Med Sci* 2010;**6**:56–64.
10. Gao XW, Mubasher M, Fang CY, Reifer C, Miller LE. Dose–response efficacy of probiotic prophylaxis for antibiotic-associated diarrhea and *Clostridium difficile*-associated diarrhea in adult patients. *Am J Gastroenterol* 2010;**105**:1636–41.
11. Millette M, Luquet F-M, Ruiz MT, Lacroix M. Characterization of probiotic properties of Lactobacillus strains. *Dairy Sci Technol* 2008;**88**:695–705.
12. Goldstein EJ, Citron DM. Bacterial counts from six OTC probiotics: are you getting what you paid for? Presented at the 11th Biennial Congress of the Anaerobe Society of the Americas, San Francisco, California, USA, June 29–July 1, 2012.
13. Elmer GW, McFarland LV, Surawicz CM, Danko L, Greenberg RN. Behaviour of *Saccharomyces boulardii* in recurrent *Clostridium difficile* disease patients. *Aliment Pharmacol Ther* 1999;**13**:1663–8.
14. Wilson KH, Silva J, Fekety FR. Suppression of *Clostridium difficile* by normal hamster cecal flora and prevention of antibiotic-associated colitis. *Infect Immun* 1981;**34**:626–8.
15. Aas J, Gessert CE, Bakken JS. Recurrent *Clostridium difficile* colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube. *Clin Infect Dis* 2003;**36**:580–5.
16. Sambol SP, Merrigan MM, Tang JK, Johnson S, Gerding DN. Colonization for the prevention of *Clostridium difficile* disease in hamsters. *J Infect Dis* 2002;**186**:1781–9.
17. Elmer GW, McFarland LV. Suppression by *Saccharomyces boulardii* of toxigenic *Clostridium difficile* overgrowth after vancomycin treatment in hamsters. *Antimicrob Agents Chemother* 1987;**31**:129–31.
18. Castex F, Corthier G, Jouvart S, Elmer GW, Lucas F, Bastide M. Prevention of *C. difficile* induced PMC by *S. boulardii*. *J Gen Microbiol* 1990;**136**:1085–9.
19. Naaber P, Mikelsaar RH, Salminen S, Mikelsaar M. Bacterial translocation, intestinal microflora and morphological changes of intestinal mucosa in experimental models of *Clostridium difficile* infection. *J Med Microbiol* 1998;**47**:591–8.
20. Kaur S, Vaishnavi C, Ray P, Kochhar R, Prasad KK. Effect of biotherapeutics on cyclosporin-induced *Clostridium difficile* infection in mice. *J Gastroenterol Hepatol* 2010;**25**:832–8.
21. Venugopalan V, Shriner KA, Wong-Beringer A. Regulatory oversight and safety of probiotic use. *Emerg Infect Dis* 2010;**16**:1661–5.
22. Salminen MK, Tynkkynen S, Rautelin H, Saxelin M, Vaara M, Ruutu P, et al. Lactobacillus bacteremia during a rapid increase in probiotic use of *Lactobacillus rhamnosus* GG in Finland. *Clin Infect Dis* 2002;**35**:1155–60.
23. Sullivan A, Nord CE. Probiotic lactobacilli and bacteraemia in Stockholm. *Scand J Infect Dis* 2006;**38**:327–31.
24. Boyle RJ, Robins-Browne RM, Tang ML. Probiotic use in clinical practice: what are the risks? *Am J Clin Nutr* 2006;**83**:1256–64.
25. Snyderman DR. The safety of probiotics. *Clin Infect Dis* 2008;**46**(Suppl 2):S104–11.
26. Ledoux D, Labombardi VJ, Karter D. *Lactobacillus acidophilus* bacteraemia after use of a probiotic in a patient with AIDS and Hodgkin's disease. *Int J STD AIDS* 2006;**17**:280–2.
27. Land MH, Rouster-Stevens K, Woods CR, Cannon ML, Cnota J, Shetty AK. Lactobacillus sepsis associated with probiotic therapy. *Pediatrics* 2005;**115**:178–81.
28. Salminen MK, Rautelin H, Tynkkynen S, Poussa T, Saxelin M, Valtonen V, et al. Lactobacillus bacteremia, clinical significance, and patient outcome, with special focus on probiotic *L. rhamnosus* GG. *Clin Infect Dis* 2004;**38**:62–9.
29. Mackay AD, Taylor MB, Kibbler CC, Hamilton-Miller JM. Lactobacillus endocarditis caused by a probiotic organism. *Clin Microbiol Infect* 1999;**5**:290–2.
30. Simkins J, Kaltsas A, Currie B. Investigation of probiotic use among inpatients at an academic medical center. Presented at the 5th Decennial International Conference on Health Care-Associated Infections, Atlanta, Georgia, USA, March 18–22, 2010.