Prophylaxis and treatment of antibiotic-associated diarrhea: is there evidence for using probiotics?

Natalie Kashefi MD, Kokila Kakarala MD

Case

A 66-year-old woman with a history of liver cirrhosis and alcohol abuse presented with hematemesis and black tarry stools secondary to a variceal bleed. The patient was started on ceftriaxone for prophylaxis of spontaneous bacterial peritonitis and subsequently developed *Clostridium difficile* negative antibiotic-associated diarrhea (AAD). Are probiotics an appropriate adjunct to therapeutic regimens for AAD and could prophylactic use of probiotics have prevented this complication?

Discussion

The use of probiotics in both therapeutic and prophylactic treatment has become increasingly frequent in recent years. Probiotics are defined as live microorganisms which when administered in adequate amounts confer a health benefit on the host.[1] Synbiotics are preparations combining probiotic organisms and prebiotics (nondigestable food ingredients that can benefit the host by selectively stimulating bacteria in the colon).[2] Probiotics have been used in several disorders in populations ranging from infants to the elderly. Studies have shown probiotics are helpful in several diseases, including AAD[2], the induction and maintenance of inflammatory bowel disease remission[3], vaginal health[4], necrotizing enterocolitis[5], and nonalcoholic fatty liver disease.[6] However, a recent systematic review suggests that most probiotic strains may not prevent AAD in elderly patients.[7]

When considering the role of probiotics with AAD, it is essential to have a standard definition for diarrhea. Various definitions currently exist, and this can make it difficult for health care organizations to establish explicit protocols for probiotic use. Diarrhea is objectively defined as passing a stool weight or volume greater than 200 g or 200 mL per 24 hours.[8] For our patient, we will utilize the definition employed in numerous AAD studies, namely a bowel movement consistency on the Stool Consistency Continuum of 1, 2, or 3 for ≥ two consecutive days. The Stool Consistency Continuum is a tool consisting of eight line drawings depicting stools varying from watery to hard.[9]

Antibiotic-associated diarrhea occurs in 5%-39% of patients, depending on patient demographics and the type of antibiotic. AAD is more prevalent in patients over 65 years, due to underlying medical diagnoses, changes in microbiota of the gut, and polypharmacy in addition to the frequent use of broad-spectrum antibiotics. The increased risks for patients with AAD include the development of nosocomial infections, increased hospital stays, increased medical care costs, and the need for diagnostic procedures. Therefore, the evaluation of therapeutic and prophylactic treatment options for AAD becomes important.[10]

Mechanism of action

Probiotics are used to maintain or restore gut metabolism and microflora during and after antibiotic treatment through:

- receptor competition[2]
- competition for nutrients[2]
- inhibition of epithelial/mucosal adherence of pathogens[2]
- decreased colonic pH favoring the growth of nonpathogenic species[2]
- defense against bacteriophages[3]
- reduction of acute immune responses[3]

Corresponding author: **Natalie Kashefi, MD**
Contact Information: Natalie.Kashefi@yahoo.com
DOI: 10.12746/swrccc2015.0311.141

- modulation of intestinal microbiota[5]
- strengthening intestinal wall and decreasing permeability[5]

Furthermore, *Lactobacillus acidophilus* can counteract colitis-induced decreases in DNA, mRNA, and SLC26A3, also known as DRA (downregulated in adenoma). DRA is a membrane protein that mediates chloride and bicarbonate exchange in the intestine, and its decreased expression is associated with various diarrheal disorders. The probiotic's ability to maintain DRA levels contributes to its therapeutic potential in inflammatory disease.[10]

Efficacy of probiotics

The relative risk (RR) has been reported for probiotic administration in the reduction of AAD. In a systematic review involving 63 randomized controlled trials, probiotic use reduced the risk of AAD compared with the control group not using probiotics (pooled RR, 0.58; 95% CI, 0.50 to 0.68; P< .001).[2] The treatment effect equated to a number needed to treat of 13. In a study in which patients were randomized into three study groups, high dose, lose dose, and placebo, a dose response effect on the incidence of AAD was observed. ADD occurred in 12.5%, 19.6%, and 24.6%, respectively, of the patients in this study. The number of daily liquid stools and average duration of diarrhea also decreased with the higher dose.[11]

In rare cases, probiotics have been associated with serious adverse effects, such as fungemia and bacterial sepsis.[12,13] Potential adverse effects of probiotics must be considered and reviewed carefully with efficacy data, since little research has focused on adverse effects of probiotics. Determining which populations benefit the most from adjunct probiotic therapy continues to be a challenge, especially since AAD tends to be self-limiting. Premature, low-birth-weight neonates who are vulnerable to necrotizing enterocolitis might be a high priority group for pro-

Table 1: Comparison of risk ratios for developing AAD between probiotic use and a control in an unspecified populations and patients over the age of 65

Bacteria	**RR in unspecified population[2]**	**95% Confidence Interval**	**RR in patients over 65[7]**	**95% Confidence Interval**
Lactobacillus	0.64	0.47-0.86	*Lactobacillus acidophilus* 0.46	0.16-1.38
			Lactobacillus casei 1.40	0.40-4.87
Saccharomyces	0.48	0.35-0.65	1.53	0.54-4.35
Streptococcus	0.51	0.38-0.68	No Value for *Streptococcus*	
Bacillus licheniformis	No Value for *Bacillus*		0.50	0.29-0.86

RR: Risk Ratio; AAD: antibiotic-associated diarrhea

biotic usage as reduced microbial diversity may be associated with reduced competitive defense against pathogens and less environmental stimulation of the developing the immune and digestive systems.[14] For patients between the ages of 65-103, one randomized open-label trial (n=247) compared the incidence of AAD in a control group to patients using *Bacillus licheniformis* ($1.5x10^9$ cfu/d) for 14 days. As illustrated in Table 1, *Bacillus licheniformis* was effective in preventing AAD, whereas other studies utilizing different strains of probiotics did not have the same efficacy in patients over the age of 65.[7] However, in studies of unspecified populations, numerous strains demonstrated prophylactic value.[2]

Case conclusion

Our 66-year old patient has *Clostridium difficile* negative AAD secondary to ceftriaxone therapy. Due to the patient's age over 65, the most efficacious probiotic for prophylactic use prior to the onset of AAD would have been *Bacillus licheniformis*.[7] Severity of AAD can range from uncomplicated diarrhea to pseudomembranous colitis and dictates the type of therapy initiated.[15] In mild cases fluid and electrolyte replacement is appropriate; more severe cases require the discontinuation or change of antibiotics and diagnostic tests to rule out pseudomembranous colitis or segmental hemorrhagic colitis.[16] Any probiotic strain as an adjunct therapy would also be beneficial in this patient, as studies have reported no significant difference among the different types of probiotics used.[2]

Key points

1. Probiotics are defined as live microorganisms which when administered in adequate amounts confer a health benefit on the host. Synbiotics are preparations combining probiotic organisms and prebiotics (nondigestable food ingredients that can benefit the host by selectively stimulating bacteria in the colon).
2. Probiotics are used to maintain or restore gut metabolism and microflora during and after antibiotic treatment.
3. For individuals over the age of 65, limited evidence suggests that Bacillus licheniformis is the only strain that provides prophylaxis against AAD.

Author Affiliation: Natalie Kashefi and Kokila Kakarala are fourth year medical students at Texas Tech University Health Sciences Center who will graduate in May 2015.
Accepted: 05/03/2015
Reviewers: Richard Winn MD, Kristen Fuhrmann Pharm D
Published electronically: 7/15/2015
Conflict of Interest Disclosures: None

References

1. Shimizu K, Ogura H, Asahara T, et al. Probiotic/synbiotic therapy for treating critically ill patients from a gut microbiota perspective. Digest Dis Sci 2013; 58(1):23-32.
2. Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JN, Shanman R, Johnsen B, Shekelle PG. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. JAMA 2012 May 9; 307(18):1959-69.
3. Wasilewski A, Zielińska M, Storr M, Fichna J. Beneficial effects of probiotics, prebiotics, synbiotics, and psychobiotics in inflammatory bowel disease. Inflamm Bowel Dis 2015 Mar 27.
4. Petrova MI, Lievens E, Malik S, Imholz N, Lebeer S. Lactobacillus species as biomarkers and agents that can promote various aspects of vaginal health. Front Physiol 2015 Mar 25; 6:81.
5. Hsueh W, Caplan MS, Qu XW, Tan XD, De Plaen IG, Gonzalez-Crussi F. Neonatal necrotizing enterocolitis: clinical considerations and pathogenetic concepts. Pediatr Dev Pathol 2003 Jan-Feb; 6(1):6-23.
6. Ma YY, Li L, Yu CH, Shen Z, Chen LH, Li YM. Effects of probiotics on nonalcoholic fatty liver disease: a meta-analysis. World J Gastroenterol 2013 Oct 28; 19(40):6911-8.
7. Xie C, Li J, Wang K, Li Q, Chen D. Probiotics for the prevention of antibiotic-associated diarrhoea in older patients: A systematic review. Travel Med Infect Dis 2015 Mar-Apr; 13(2):128-134.
8. Sweetser S. Evaluating the patient with diarrhea: a case-based approach. Mayo Clin Proc 2012 Jun; 87(6):596-602.
9. Safdar N, Barigala R, Said A, McKinley L. Feasibility and tolerability of probiotics for prevention of antibiotic-associated diarrhoea in hospitalized US military veterans. J Clin Pharm Ther 2008 Dec; 33(6):663-8.
10. Singh V, Kumar A, Raheja G, Anbazhagan AN, Priyamvada S, Saksena S, Jhandier MN, Gill RK, Alrefai WA, Borthakur A, Dudeja PK. Lactobacillus acidophilus attenuates downregulation of DRA function and expression in in-

flammatory models. Am J Physiol Gastrointest Liver Physiol 2014 Sep 15; 307(6):G623-31.
11. Ouwehand AC, DongLian C, Weijian X, Stewart M, Ni J, Stewart T, Miller LE. Probiotics reduce symptoms of antibiotic use in a hospital setting: a randomized dose response study. Vaccine 2014 Jan 16; 32(4):458-63.
12. Lestin F, Pertschy A, Rimek D. Fungemia after oral treatment with Saccharomyces boulardii in a patient with multiple comorbidities. Dtsch Med Wochenshr 2003; 128(48):2531-2533.
13. Land MH, Rouster-Stevens K, Woods CR, Cannon ML, Cnota J, Shetty AK. Lactobacillus sepsis associated with probiotic therapy. Pediatrics 2005; 115(1):178-181.
14. Kitano H, Oda K. Robustness trade-offs and host-microbial symbiosis in the immune system. Mol Syst Biol 2006; 2:2006.0022.
15. McFarland LV. Epidemiology, risk factors and treatments for antibiotic-associated diarrhea. Dig Dis 1998 Sep-Oct; 16(5):292-307.
16. Högenauer C, Hammer HF, Krejs GJ, Reisinger EC. Mechanisms and management of antibiotic-associated diarrhea. Clin Infect Dis 1998 Oct; 27(4):702-10.