Probiotics: A New Treatment for Antibiotic-Associated Diarrhea?

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Antibiotic-associated diarrhea is a frequent side effect of broad-spectrum antibiotics. The clinical presentation of diarrhea reaches from mild to fulminant pseudomembranous *Clostridium difficile* toxin-induced colitis. The frequency of antibiotic-associated diarrhea can affect as many as 25% of patients. In the last decade, there has been an increase of antibiotic-associated diarrhea of 500%. In up to 80%, the cause of diarrhea is not clear [1].

One of the mechanisms for the development of antibiotic-associated side effects seems to be related to an alteration in the intestinal flora. The intestinal flora protects the individual against enteral pathogens by multiple mechanisms: (a) production of bacteriocins; (b) competitive inhibition of binding to the mucosa; (c) enhancing synthesis of mucus, and (d) secretion of secretory IgA [2].

Probiotics (life-viable, non-pathogen microbial organisms) have been shown to have immune modulatory properties and to enhance the mucosal barrier. In fact, probiotics have anti-bacterial, anti-viral and anti-inflammatory properties and restore the intestinal flora balance; they were first used for the treatment or prevention of antibiotic-associated diarrhea. Several probiotics, such as *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus rhamnosus* GG and the yeast *Saccharomyces boulardii* have been evaluated. The clear benefits of probiotics are still debated and the data are conflicting, since many of the trials were small and with an open-label design. D'Souza et al. [3] performed a meta-analysis includ-

ing 9 randomized, double-blind, placebo-controlled trials studying the efficacy of probiotics in this setting. In these trials, 3 different probiotics (*S. boulardii*, *Lactobacillus* spp. and *Enterococcus faecium*) were used. The odds ratio for diarrhea to occur was similar for all species. The combined odds ratio was 0.37 (95% confidence interval 0.26–0.53; $p < 0.01$) in favor of active treatment over placebo. This analysis has been criticized because of its inconsistent definition of diarrhea and that more than half of the studies did not analyze the data on an intention-to-treat basis. The second meta-analysis by Cremonini et al. [4] included only 7 studies with more consistent definitions of outcome. The results were similar. The combined relative risk was 0.39 (95% confidence interval 0.27–0.57). According to these two meta-analyses the results infer that the use of *Lactobacillus* spp. and *S. boulardii* in the prevention of antibiotic-associated diarrhea are beneficial.

In this issue of *Digestion* Hawrelak et al. [5] report in a new systematic review of the effect of a single strain of *L. rhamnosus* GG in preventing the onset of antibiotic-associated diarrhea. This report reflects the inherent problems of this topic. Although 25 clinical trials have been published so far, only 6 placebo-controlled trials could be included. 18 trials included probiotics other than *L. rhamnosus* GG and one trial was not placebo-controlled. Of the 6 trials, 4 used different antibiotics in children ($n = 2$) and adults ($n = 2$). These studies were also different in sample size, duration and doses of the co-

treatment with probiotics. There were only 2 homogeneous studies looking at *Helicobacter pylori* eradication with small numbers of patients included; the same dose and duration of probiotics and the same antibiotics were administered. The reported trials in this systematic review were published in the period ranging from 1990 to 2002 with different methodological qualities (Jadad score between 1 and 5). With these limits in mind, the authors could confirm the findings of the previously reported meta-analysis. In 4 of 6 trials a significant reduction in the risk of antibiotic-associated diarrhea was noted with the co-administration of *L. rhamnosus* GG. Unfortunately, the study with the largest sample size undertaken in hospitalized patients was negative. One potential explanation for these results could be that these patients were sicker than in the other studies, which included only ambulatory patients.

In the evolutionary battle against infectious gastrointestinal disease, probiotics seem to be useful agents to prevent or treat these diseases. Very interesting is the prevention of antibiotic-associated diarrhea. Several other publications (not included in the previous meta-analysis or in the systematic review of Hawrelak et al. [5]) have recently been published. In a double-blind, placebo-controlled study involving 150 elderly patients with an antibiotic regimen, a probiotic mixture of *Lactobacillus* and

Bifidobacterium showed a significant reduction in *C. difficile* toxin in the probiotic group compared to the placebo group (46 vs. 78%) [5]. With respect to diarrhea, the incidence of samples positive for *C. difficile*-associated toxin was 2.9% in the probiotic group compared to 7.25% in the placebo group [6]. Erdevi et al. [7] tested the effect of probiotics in children receiving an antibiotic treatment. 462 children aged 1–5 years receiving sulbactam-ampicillin or azithromycin were randomized to the treatment with *S. boulardii* or antibiotics alone. Antibiotic-associated diarrhea was found in 19% receiving an antibiotic treatment alone and in 6% with the additional probiotic treatment. Finally, a recently published study performed with *Bacillus clausii* reduced the incidence of nausea, diarrhea and epigastric pain associated with a triple anti-*H. pylori* therapy as compared to placebo [8].

One major limitation of all published results is the inhomogeneous and variable definition of diarrhea. In the future, to overcome these problems, it is absolutely mandatory to perform trials with adequate power using the same probiotics with the same doses and duration using a standard and uniform definition of diarrhea. Such trials should demonstrate that a co-treatment with probiotics will definitely reduce antibiotic-associated side effects and reduce health care costs.

References

- 1 Hurley BW, Nguyen CC: The spectrum of pseudomembranous enterocolitis and antibiotic-associated diarrhea. *Arch Intern Med* 2002;162:2177–2184.
- 2 Elmer G W, McFarland LV: Biotherapeutic agents in the treatment of infectious diarrhea. *Gastroenterol Clin North Am* 2001;30:837–854.
- 3 D'Souza AL, Rajkumar C, Cooke J, Bulpitt CJ: Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. *BMJ* 2002;324:1361–1366.
- 4 Cremonini F, Di Caro S, Nista EC, Bartolozzi F, Capelli G, Gasbarrini G, Gasbarrini A: Meta-analysis: the effect of probiotic administration on antibiotic-associated diarrhoea. *Aliment Pharmacol Ther* 2002;16:1461–1467.
- 5 Hawrelak JA, Whitten DL, Myers SP: Is *Lactobacillus rhamnosus* GG effective in preventing the onset of antibiotic-associated diarrhea: A systematic review. *Digestion* 2005;72:51–56.
- 6 Plummer S, Weaver MA, Harris JC, Dee P, Hunter J: *Clostridium difficile* pilot study: effects of probiotic supplementation on the incidence of *C. difficile* diarrhoea. *Int Microbiol* 2004;7:59–62.
- 7 Erdevi O, Tiras U, Dallar Y: The probiotic effect of *Saccharomyces boulardii* in a pediatric age group. *J Trop Pediatr* 2004;50:234–236.
- 8 Nista EC, Candelli M, Cremonini F, Cazzato I A, Zocco M A, Franceschi F, Cammarota G, Gasbarrini G, Gasbarrini A: *Bacillus clausii* therapy to reduce side-effects of anti-*Helicobacter pylori* treatment: randomized, double-blind, placebo controlled trial. *Aliment Pharmacol Ther* 2004;20:1181–1188.