Clinical microbiology

Evidence-based review of probiotics for antibiotic-associated diarrhea and *Clostridium difficile* infections

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**Abstract**

Probiotics are living microbes taken to confer a health benefit on the host. Although probiotics have a long history of use in Europe and Asia and have been on the U.S. market for over 14 years, there is still confusion about how to effectively use them. The use of probiotics for the prevention of antibiotic-associated diarrhea (AAD) and the treatment of *Clostridium difficile* infections (CDI) has been tested in randomized controlled clinical trials.

This paper will review the evidence supporting probiotic therapy for these two diseases and also review the advantages and disadvantages of probiotics. The advantages of probiotic therapy include multiple mechanisms of action against pathogens, the ability to interact with the host’s natural defense systems, survival to the target organ and a good risk to benefit ratio. Disadvantages of probiotics include lack of standardization for clinical trial designs, variations in regulatory standards, poor quality control for some products and infrequent serious adverse reactions. Overall, probiotics offer a promising strategy for the prevention and treatment for AAD and CDI.

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1. Introduction

Antibiotic-associated diarrhea (AAD) is a common complication of most types of antibiotics, especially for broad-spectrum antibiotics such as clindamycin, beta-lactams and 3rd generation cephalosporins. Rates of AAD vary from 5 to 39% depending upon the type of antibiotic, age, health status of the host and type of environment (hospitalization, extended care facilities, etc.) [1, 12]. AAD has been reported in a wide variety of populations including outpatients, hospitalized patients and residents of long-term care facilities [1]. The clinical presentation of AAD may be mild (uncomplicated diarrhea) or more severe (colitis), or result in toxic megacolon or death [3]. Consequences of AAD may result in extended hospital stays, increased medical care costs and increased diagnostic procedures [3, 4]. Prevention of AAD has rested on discontinuing the inciting antibiotic or switching to an antibiotic with a narrower spectrum of action, but there are no other current effective preventive measures for AAD.

*Clostridium difficile* infections (CDI) continues to persist as a leading cause of nosocomial gastrointestinal illness [5–7]. The rates of CDI have been increasing globally over the years. In the U.S., CDI rates have doubled from 2001–2005 to 301,200 cases in 2005 [8]. In the U.S., CDI rates are steadily increasing [9] and by 2010, projections estimate 450,000–750,000 cases of CDI per year in the U.S. [9, 10]. Outbreaks of an emergent strain, BI/NAP1/027, caused large outbreaks of severe CDI with high rates of mortality in Canada during 2003–2005 [11]. In one prospective study, the average length of stay for a hospitalization due to a CDI recurrence was 8.8 ± 8.6 days (ranging from 3 to 26 days) [12]. Other studies have documented that CDI extends hospital stays for hospitalized patients from 4 to 36 days [13–16]. In a study of 1034 CDI cases in Massachusetts during 2000, the average cost ranged from $10,212 to $13,675/patient [17], projecting a national cost of CDI of $3.2 billion/year. There are only two standard antibiotic treatments for CDI (vancomycin and metronidazole) and the response rate of metronidazole has been declining [18]. In addition, 20–60% of patients may develop recurrent episodes of CDI despite additional antibiotic treatment. Although other investigational antibiotics are under development, no new antibiotics are superior to the two standard antibiotics.

Probiotics are “live microorganisms, which when administered in adequate amounts, confer a health benefit on the host” [19].

**Keywords:** Probiotics, *Lactobacillus*, *Saccharomyces*, *Yogurt*, Antibiotic-associated diarrhea, *Clostridium difficile*
Probiotics are available as capsules of freeze-dried or lyophilized culture supernatants, dried power of heat-dried culture supernatants, mixed in dairy foods (such as yogurts, cheese, milks, or ice cream) or other foods (kefir, chocolate, wafers) [20–22]. In contrast, a prebiotic is “a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host well being and health” [23]. Synergistic combinations of probiotics and prebiotics are called synbiotics [23].

The interest in probiotics as therapy has increased dramatically since 1999 and the frequency of peer-reviewed randomized clinical trials has kept pace with the global interest in this innovative method of therapy. Most trials have been in the field of acute pediatric diarrhea, but the frequency for antibiotic-associated trials has increased, while the frequency ofC. difficile trials has been limited (Fig. 1).

2. Antibiotic-associated diarrhea

A wide variety of study designs have been used to test probiotics, which makes direct comparison of probiotic trials difficult. One example of a typical study design for prevention of antibiotic-associated diarrhea (AAD) is to enroll a patient population receiving antibiotics for infections and then to randomly assign probiotic or placebo treatment for the duration of the antibiotic. It is important to have sufficiently long follow-up times (usually 4–6 weeks post-antibiotic cessation) to capture delayed-onset AAD. Kotowsha et al. enrolled 269 children who were taking antibiotics for ear or respiratory infections and randomized them to either Saccharomycesboulardii (500 mg/d) or placebo for the duration of the antibiotic treatment [24]. Even though the follow-up time was short (two weeks post-antibiotic), the frequency of diarrhea in the probiotic group was significantly less (3.4%) compared to 17.3% in the placebo group. The yeast probiotic was well tolerated by the children. In contrast, Lewis et al. did not find a significant reduction in AAD in a study of 69 elderly patients randomized toS. boulardii or placebo for 14 days [25]. This failure may have been due to a flawed study design, in that patients were only followed while on antibiotics and no follow-up was done after antibiotics were discontinued. Several studies have shown that AAD may occur while on antibiotics, but AAD may also be delayed for up to two months (in up to 38% of patients) after antibiotics are discontinued [1,26]. In a randomized controlled trial of a probiotic mixture given to prevent AAD, the rate of AAD was similar during antibiotic treatment (6.2% probiotic versus 8.1% control, \( P = 0.74 \)), but cases of delayed-onset AAD post-antibiotic treatment were significantly fewer in the probiotic group (5.7%, \( P = 0.003 \)) compared to the control group (27.5%) [27]. The study by Lewis et al. therefore, may have missed a significant number of AAD cases due to too short a follow-up period.

As the intestinal microflora is composed of many different strains of bacteria and fungal strains, another strategy for probiotic use is to repopulate the disturbed intestine with a mixture of probiotic strains. Unfortunately, the identities of the specific strains of normal microflora responsible for colonization resistance are unknown, so the choice of which strains to include in a probiotic mixture is uncertain. Several types of mixtures have been tested in similar study designs as those described above. One recent trial tested a fermented drink with a mixture ofLactobacillus caseiDN-114001 (2 \( \times \) 1010/d), Streptococcus thermophilus (2 \( \times \) 109/d) andLactobacillusbulgaricus (2 \( \times \) 109/d) against a control milkshake [27]. The study treatment was given randomly to hospitalized adults over 50 years old on antibiotics for the duration of the antibiotic and an additional week. Patients were followed for an additional four weeks for the development of antibiotic-associated diarrhea (AAD). The patients given the probiotic mixture reported significantly less AAD (12.3%, \( P < .05 \)) than those given the control (33.9%). No adverse reactions were reported.

Meta-analysis has been used to pool studies of different probiotic strains to obtain a pooled estimate of the efficacy of probiotics for the prevention of AAD (Fig. 2). A note of caution, however, although most meta-analyses have concluded that probiotics are effective for preventing AAD [28,29], it is inappropriate to conclude that all probiotic strains are effective. The effectiveness of probiotics is strain specific and disease-specific, so that the probiotic strain must be linked to the disease. Most probiotic meta-analyses have focused on one type of disease indication with a variety of probiotic strains (for example, antibiotic-associated diarrhea [28–30]). When there are sufficient numbers of clinical trials, a meta-analysis limited to one disease indication and one type of probiotic strain may reduce the heterogeneity of studies [31]. As an alternative, some meta-analyses have done sensitivity

![Fig. 1. Frequency of published peer-reviewed randomized controlled clinical trials in the scientific literature relating to probiotics over time (1985–2008), either all strains (line) or antibiotic-associated diarrhea (AAD) (hatched bars) or Clostridium difficile infections (CDI) (solid bars).](image-url)
analysis, separating out sub-groups by patient type (for example, just adults or just pediatrics) or by type of probiotic strain [28,32]. A sensitivity analysis found only two probiotic strains had sufficient evidence to show significant efficacy for the prevention of AAD, namely *S. boulardii* and *Lactobacillus rhamnosus* GG [28]. Although many meta-analyses have been done, pooling studies must be performed with these limitations in mind.

### 2.1. C. difficile disease

Probiotics may offer promise as an adjunctive therapy (given along with standard antibiotics vancomycin or metronidazole) for CDI, as several strains produce proteases that directly degrade *C. difficile* toxins or increase the immune response to *C. difficile* toxins A and B [33,34]. A meta-analysis of six randomized controlled trials using probiotics combined with one of the two standard antibiotics to treat CDI found probiotics, in general, significantly reduced the risk of *C. difficile* infections (combined RR = 0.59, 95% CI: 0.41, 0.85, *P* = 0.005) [28]. Although a variety of probiotic strains have been tested, most lack large randomized confirmatory placebo-controlled trials. In most cases, CDI was a secondary outcome for the trial and thus the trial was not powered to enroll sufficient numbers to detect a significant difference in CDI. A limited number of randomized controlled trials have been conducted to test probiotics for the treatment of CDI as their primary outcome (Table 1) [35–39]. In one randomized, controlled trial, patients with CDI were prescribed either one of two doses of vancomycin (2 g/d or 500 mg/d) or metronidazole (1 g/d) then randomized to either *S. boulardii* or placebo (1 g/d for 4 weeks) [36]. Patients treated with the high dose vancomycin and the probiotic had significantly decreased recurrence rates (16.7%) compared to vancomycin and placebo (50%). The probiotic given with the low dose vancomycin or metronidazole was not significantly protective of CDI. This finding was in contrast to a prior trial of the same probiotic strain that showed significant effectiveness of *S. boulardii* as an adjunct to standard vancomycin or metronidazole therapy [35]. Several other trials for CDI were terminated early due to slow enrollment rates and the resulting small study sizes (15–25) precluded any statistical conclusions [37–39]. Although several clinical trials are underway currently testing other strains of probiotics for the treatment of CDI, no further studies have been published.

Some evidence may be inferred in studies that collect data on CDI as one of their secondary outcomes. In a study testing a probiotic mix for the prevention of antibiotic-associated diarrhea, a secondary outcome was the prevention of CDI [27]. Patients were randomized to either a probiotic mix of *L. casei*, *L. bulgaricus* and *Streptococcus thermophilus* (Actimel drink) at a dose of 2.2 × 10⁸ cfu/day or a placebo drink for duration of antibiotic plus

![Forest Plot of 25 randomized controlled trials of probiotics for the prevention of antibiotic-associated diarrhea showing crude and pooled risk ratios. SB — *Saccharomyces boulardii*; LGG — *Lactobacillus rhamnosus* GG; BC — *Bacillus clausii*; BL — *Bifidobacterium longum*; CB — *Clostridium butyricum* MIYAIRI; EF — *Enterococcus faecium* SF68; LA — *Lactobacillus acidophilus*; LAB — *Lactobacillus acidophilus* and *B. clausii*; LABL — *Lactobacillus acidophilus* and *B. longum*; LABLa — *Lactobacillus acidophilus* and *B. lactis*; BLS — *Bifidobacterium lactis* and *S. thermophilus*; BSFO — *Lactobacillus sporogenes* and fructo-oligosaccharide; LABI — *Lactobacillus acidophilus* and *B. infantis*. Adapted from ref. [28].](https://example.com/figure2.png)
children (9, 75%). There are also 24 cases of fungemia in patients with probiotic was $120.00. Although CDI is an important disease, *Tridium butyricum* group (2.9%) compared with the control group (7.2%) [40]. Despite was no significance difference in the rate of CDI in the probiotic biotic mixture of two strains for the prevention of CDI, and there

Table 1

<table>
<thead>
<tr>
<th>Probiotic</th>
<th>Population</th>
<th>Daily dose</th>
<th>Duration (days)</th>
<th>Frequency of CDI relapses in probiotic</th>
<th>Frequency of CDI relapses in controls</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. boulardii</em></td>
<td>124 adult patients on varied doses of vancomycin or metronidazole; recurrent and initial CDAD cases National, 1993–1996, 170 adult patients recurrent CDAD; on vancomycin (500 mg/d, <em>n</em> = 83) or (2 g/d, <em>n</em> = 32) or metro (1 g/d, <em>n</em> = 53)</td>
<td>$3 \times 10^{10}$</td>
<td>28, followed for another 4 weeks</td>
<td>15/57 (26.3%)</td>
<td>30/67 (44.8%)</td>
<td>McFarland 1994 [35]</td>
</tr>
<tr>
<td><em>S. boulardii</em></td>
<td>124 adult patients on varied doses of vancomycin or metronidazole; recurrent and initial CDAD cases National, 1993–1996, 170 adult patients recurrent CDAD; on vancomycin (500 mg/d, <em>n</em> = 83) or (2 g/d, <em>n</em> = 32) or metro (1 g/d, <em>n</em> = 53)</td>
<td>$2 \times 10^{10}$</td>
<td>28, followed for another 4 weeks</td>
<td>Vanco (2g/d) 3 (17%)</td>
<td>7 (50%)</td>
<td>Surawicz 2000 [36]</td>
</tr>
<tr>
<td><em>Lactobacillus</em></td>
<td>25 Adults on vancomycin or metronidazole, recurrent and initial CDAD</td>
<td>Not reported</td>
<td>21</td>
<td>4/11 (36.4%)</td>
<td>5/14</td>
<td>3.7%</td>
</tr>
<tr>
<td><em>rhamnosus GG</em></td>
<td>25 Adults on vancomycin or metronidazole, recurrent and initial CDAD</td>
<td>Not reported</td>
<td>38 days, followed until Day 70</td>
<td>4/11 (36%)</td>
<td>Metro only, 6/9 (67%)</td>
<td>Wullt 2003 [38]</td>
</tr>
<tr>
<td><em>L. plantarum</em></td>
<td>29 Enrolled, 20 adults finished, 9 sites, 1–5 prior episodes, Over 2 years</td>
<td>$5 \times 10^{10}$</td>
<td>28, followed for another 4 weeks</td>
<td>13 (48.1%)</td>
<td>13 (50%)</td>
<td>Surawicz 2000 [36]</td>
</tr>
<tr>
<td><em>L. rhamnosus GG</em></td>
<td>15 Adults on vanco or metro with CDAD, Enrolled over 9 months</td>
<td>$8 \times 10^{10}$</td>
<td>Duration of abx + 21 days</td>
<td>3/8 (37.5%)</td>
<td>1/7 (14.3%)</td>
<td>Lawrence 2005 [39]</td>
</tr>
</tbody>
</table>

* P<0.05 compared to controls, ns=not significant, abx=antibiotics

one week. Of the 113 completing the trial, 0/56 (0%) developed CDI in the probiotic group compared to 9/53 (17%) in the placebo drink group. P < 0.005. The estimated cost of preventing one case of CDI with probiotic was $120.00. Although CDI is an important disease, a limitation of the current probiotic research is a lack of trials of different types of probiotics.

Thusfar, there has only been one published trial using a probiotic mixture of two strains for the prevention of CDI, and there was no significance difference in the rate of CDI in the probiotic group (2.9%) compared with the control group (7.2%) [40]. Despite these limitations, several probiotics are currently under development for CDI including *Lactobacillus acidophilus*, *S. boulardii*, *Clostridium butyricum* and a non-toxigenic strain of *C. difficile*.

3. Safety

The use of a living organism as therapy raises the potential for risk in several areas: transfer of antibiotic-resistance genes, translocation of the living organism from the intestine to other areas of the body, persistence in the intestines or the development of adverse reactions relating to interactions with the host’s microflora. Fortunately, most of these concerns has not been a problem based on the decades of use in Europe and Asia. In Finland, where *L. rhamnosus GG* was been widely used as a probiotic since 1990, there has been no increase in reported adverse reactions or cases of *Lactobacillus* bacteraemia attributable to probiotic strains [41]. In the clinical trials testing probiotics, no reports of bacteraemia or fungemia have been associated with the probiotic *S. boulardii*, mostly in severely ill children and adults [41]. *Bacillus subtilis* probiotic products had rare cases of bacteraemia in 1988–1998, but no current cases have been reported.

Translocation from the intestines to other organs of the body is another potential risk of a living therapeutic. However, most of the probiotics that have been studied in animal models of translocation only show extra-intestinal presence of the probiotic if the animal has been compromised by high antibiotic exposure or is immunocompromised [42]. Only one case of a liver abscess in a 74-year-old severely ill woman was found and the strain isolated from the abscess was identical to the probiotic strain she had been ingesting for 4 months [43]. No cases of translocation have been reported in clinical trials of probiotics for AAD or CDI.

Most clinical trials of AAD and CDI have not reported any serious adverse reactions attributable to the probiotic treatment. The types of mild-moderate adverse reactions typically reported in probiotic trials include nausea, vomiting, abdominal cramps or pain, rash, diarrhea or constipation, but the frequencies are infrequently higher than the control group.

4. Advantages of probiotic therapy

Probiotics offer several advantages and have few disadvantages as a therapeutic mode for AAD and CDI (Table 2).

4.1. Diverse mechanisms of action

A unique advantage of probiotic therapy is these living organisms incorporate a delivery system (most probiotics survive to the target organ) and bring an arsenal of anti-pathogenic strategies into

Table 2

Advantages, disadvantages and recommendations for probiotics for the prevention of antibiotic-associated diarrhea and treatment of *Clostridium difficile* disease.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Future research needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple mechanisms of action possible</td>
<td>Strain specific effects</td>
<td>Standardized protocols</td>
</tr>
<tr>
<td>In situ delivery vehicle</td>
<td>Heterogeneous trials</td>
<td>Confirmatory studies on same strains</td>
</tr>
<tr>
<td>Safe in diverse patient populations</td>
<td>Risks in immunocompromised</td>
<td>Document risks/benefits</td>
</tr>
<tr>
<td>Diversity of potential organisms</td>
<td>Lack of quality control regulations</td>
<td>Cost/benefit analysis</td>
</tr>
<tr>
<td>Aids natural body defenses</td>
<td></td>
<td>Use of adequate dose (10^9-10^10)/day</td>
</tr>
<tr>
<td>Lack of significant drug interactions</td>
<td></td>
<td>Expand types of strains tested</td>
</tr>
<tr>
<td>Inexpensive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
play. Potential mechanisms of action may include: (1) enhancing the natural barrier effect of normal intestinal microflora, (2) modulation of the immune system, (3) direct anti-microbial effects and (4) regulation of intestinal enzymes and interactions with the enteric nervous system [20,44–46]. Newer techniques, including metagenomics and PCR probes have documented that a typical human may carry over 40,000 bacterial species in the collective intestinal microbiome [47]. The normal intestinal flora has many functions, including digestion of food, but the one that is most germane for this discussion is called “colonization resistance” [48]. This involves the interaction of many bacterial microflora and results in a barrier effect against colonization of pathogenic organisms. Normal microflora may act by competitive exclusion of nutrients or attachment sites, produce bacteriocins, or produce enzymes detrimental to pathogenic growth. Factors that disrupt this protective barrier, for example antibiotic use or surgery, results in host susceptibility to pathogen colonization until such time as the normal microflora can become re-established. Probiotics are uniquely qualified to fit into this window of susceptibility and may act as surrogate normal microflora until recovery is achieved. There are several avenues to preserve the barrier effect: probiotics have been shown to protect the integrity of the tight junction between enterocytes [49], or block the attachment sites for pathogens (including C. difficile) or their toxins [33,50]. Some probiotics may directly destroy pathogenic toxins produced by C. difficile toxin A or B [51] or suspected etiologies for some cases of AAD (enterotoxigenic E. coli) [52,53]. Probiotics may also regulate immune responses, either by increasing secretory IgA levels in the intestines [33], by either increasing or deregulating cytokines [34] or inducing higher levels of anti-toxin A/B antibodies [54]. Probiotics may also alter amino acid metabolism, restoring protective levels of short-chain fatty acids in the intestine [55]. Probiotics also affect the regulation of the enteric nervous system [56] and reduce epithelial apoptosis [57]. Not all probiotics have the ability to produce every mechanism of action described above, but many of the strains utilize multiple mechanisms, increasing the probability of probiotic effectiveness against a specific pathogen. The benefit of these multiple mechanisms is the rapid restoration of bacteria disrupted by inciting antibiotics [58].

4.2. Survival to target site

Another advantage of probiotics is that they can act as their own delivery vehicle for anti-pathogenic enzymes or defensive mechanisms. As all of the protective mechanisms described above are an inherent component of the probiotic organism and the enzymes are pre-packaged in a living organism, delivery of the multiple mechanisms of action are carried along when the organism passes through the digestive system. Pharmacokinetic studies in animal models or healthy human volunteers find that probiotic organisms survive passage and are detectable in the stool. Although much of the oral dose is destroyed (usually stool levels are 100 times lower than the oral dose given), the surviving dose is usually effective as a therapy as long as stool levels are over 10^8 organisms/g stool [59]. Few clinical trials using probiotics for AAD or CDI have documented the level of organisms present in the terminal site (colonic lumen). In one trial of patients with recurrent CDI given S. boulardii (2 x 10^10/day) for 28 days, patients who had a subsequent CDI recurrence were found to have significantly lower numbers of S. boulardii (2 x 10^4/gram stool) compared to those who did not recur (1 x 10^9/g stool) [60].

5. Disadvantages/limitations

There are several issues relating to the field of probiotics including the wide diversity in both the types and quality of clinical trials, the limited numbers of trials that have been properly conducted, the quality control of probiotic products on the market and the potential risks associated with probiotic use.

5.1. Dose differences

There is still no consensus on the most effective dose of a probiotic. The range of daily doses in clinical trials has ranged from 10^7/day to 10^11/day [28]. Using an effective daily dose is an important consideration, as several meta-analyses have found efficacy at only the higher doses of probiotic. In 25 RCT trials of probiotics for the prevention of AAD, 8/12 (67%) of trials using a probiotic dose > 10^10/day were significantly protective compared to only 2/12 (17%) if the dose was < 10^9/day [28]. Unfortunately, many probiotics trials still fail to use sufficiently high daily doses of probiotics in their trials. Another issue is that a dose that is found to be effective for one probiotic strain may not be effective for another.

5.2. Quality Control of probiotic products

A disadvantage to the dietary supplement regulations for probiotics is the lack of stringent quality control regulations for foods and dietary supplements. Some probiotic products are manufactured by well-established pharmaceutical companies with existing quality control protocols and batch standards. However, many probiotic products are not regulated and are manufactured in uncontrolled environments. The result is that some probiotic products contain the specific strains and concentrations stated on their labels and some do not. In a recent study where 14 U.S. commercial probiotic products were assayed, only 1/14 (7%) contained the bacteria listed on their label (most had other strains or contaminants) [61]. In another study of 18 commercial probiotic products, 39% had fewer organisms than stated on their label [62], which was similar to a study in the U.K. of 10 Bifidobacterial probiotic yogurts found 10 x 6 fewer organisms than that listed on the labels [63]. In another large study of 58 probiotic products from Europe, U.K., Asia and Canada, they could not detect the probiotic on the label in 30% of the products and 60% had fewer organisms in the product than stated on the label (<10^8/g) [64]. In contrast, probiotic products manufactured by established pharmaceutical companies typically have the stated concentration and bacterial or fungal strain listed on the label.

6. Future research

Future research involves the development of newer technology for delivery mechanisms including nano-encapsulation, water-protected macromolecules; recombinant strains responding to specific triggers in the host, and other microbiologic and biochemical developments [65]. Probiotics offer promise for a wide diversity of diseases and have an excellent safety-benefit ratio. However, the efficacy is disease and probiotic strain specific. Future research on different strains and mixtures, further understanding into the pathogenesis and mechanisms of action and safety are required.

Overall, probiotics are a promising strategy for the prevention of AAD. Although the pre-clinical and indirect clinical evidence is promising for CDI, more research is needed to find more probiotic strains that are effective adjuncts to vancomycin or metronidazole. More research is required using well done randomized controlled trials of sufficient size to detect significant differences.

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References


