The Role of Probiotics in the Prevention and Treatment of Antibiotic-Associated Diarrhea and Clostridium Difficile Colitis

Gerald Friedman, MD, PhD, MS, MACG, AGAF

INTRODUCTION

Diarrhea is one of the most frequent side effects of antibiotic use. The incidence of antibiotic-associated diarrhea (AAD) varies between 5% and 39% of patients, with a higher percentage seen in hospitalized patients.¹

AAD is defined as otherwise unexplained diarrhea that occurs in association with the administration of antibiotics. It is characterized by a change in the normal stool frequency with at least 3 loose or watery stools daily for 3 days. Early onset of diarrhea

Department of Medicine, The Mount Sinai School of Medicine, 1 Gustave L. Levy Place, New York City, NY 10029, USA
E-mail address: gfmd379@gmail.com

http://dx.doi.org/10.1016/j.gtc.2012.08.002 gastro.theclinics.com
0889-8553/12/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
occurs within 2 to 7 days, being earlier with children than outpatient adults. Delayed onset of diarrhea may occur within 2 to 8 weeks after the antibiotic has been discontinued.

Special attention should be accorded to at-risk hospitalized patients who may develop Clostridium difficile infection (CDI) complicating AAD. Prompt stool analysis for toxins A and B is essential for these patients. At-risk patients for CDI include patients aged greater than 65 years, patients with multiple comorbidities, immunosuppression, exposure to radiation and chemotherapy, inflammatory bowel disease (IBD), hepatic cirrhosis, prolonged hospitalization, and treatment with proton pump inhibitors (PPIs) (Box 1). Pharmacologically, the use of broad spectrum antibiotics and the duration of antibiotic therapy increase risk of AAD.

CAUSES OF AAD

Antibiotics cause diarrhea by several mechanisms. First, suppression of anaerobic bacteria results in reduced metabolism of carbohydrates inducing an osmotic diarrhea. Secondly, antibiotics disrupt the protective effect of commensal bacteria. The disruption of microbial diversity reduces colonic mucosal resistance to pathogenic opportunistic bacteria, particularly CDI.3 Following discontinuation of the antibiotic, restoration of the normal commensal bacteria may take several weeks, months, or longer to occur, thus placing the patient at longer term risk for disease-causing pathogenic agents. Finally, antibiotics with prokinetic activity, such as erythromycin and clavulanate, promote diarrhea.

PREVENTING AAD WITH PROBIOTICS

Multiple studies support the use of probiotics for preventing AAD. AAD presents a fertile area to study the efficacy of probiotics. The study design is simplified because diarrhea is a predictable side effect; the impact of the antibiotic usually occurs early in the course of administration; the duration of therapy is usually limited (eg, 10–14 days), and, in most instances, the side effects of added probiotics are

<table>
<thead>
<tr>
<th>Box 1</th>
<th>Risk factors for CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td></td>
</tr>
<tr>
<td>Age greater than 65 years</td>
<td></td>
</tr>
<tr>
<td>Multiple comorbidities</td>
<td></td>
</tr>
<tr>
<td>Immunosuppression</td>
<td></td>
</tr>
<tr>
<td>Exposure to radiation</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Prolonged hospitalization</td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td></td>
</tr>
<tr>
<td>Hepatic cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Antibiotic therapy</td>
<td></td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td></td>
</tr>
<tr>
<td>Prior history of CDI</td>
<td></td>
</tr>
<tr>
<td>Use of fluoroquinolones</td>
<td></td>
</tr>
</tbody>
</table>
minimal. In addition, given the spectrum of AAD, possibly eventuating to the more serious CDI, an effective probiotic represents a major step in reducing more serious illness. Most studies, both in children and adults, have been reported with positive results. Interpretation of studies is difficult partly because of the varied populations, age of the patients, comorbidities, drug interactions, duration of probiotic administration, numbers of patients involved, the nature and dose of the offending antibiotic agent, and the lack of randomized, placebo-controlled trials (Box 2). Clinically acceptable probiotics must be species specific; of human origin; survive passage from the oral cavity through the gastric acid barrier, digestive enzymes, and bile acids; travel down the small bowel into the colon; nidate; and proliferate therein. Probiotics should be of adequate dose, preferably greater than 10 billion cfu/gm in adults, maintain their viability and concentration, and have a dependably measurable shelf life at the time of purchase and administration (Box 3). When these qualities have been met, targeted illnesses require randomized, placebo-controlled, double-blinded trials on appropriate populations.

**MECHANISMS OF ACTION OF PROBIOTICS**

Probiotics offer protection from potential pathogens by enhancing mucosal barrier function by secreting mucins, providing colonization resistance, producing bacteriocins, increasing production of secretory immunoglobulin A (IgA), producing a balanced T-helper cell response, and increasing production of interleukin 10 (IL-10) and transforming growth factor beta, both of which play a role in the development of immunologic tolerance to antigens (Box 4).^5

**SINGLE STRAIN PROBIOTICS USED FOR TREATING AAD**

*Lactobacillus GG*

Gorbach^6^ began a search for the “ideal” lactobacillus by listing the biologic characteristics of a probiotic that would benefit human health. He collected strains of lactobacilli from stool specimens of healthy human volunteers. Each strain needed to survive the impact of gastric acid, bile acids, and pancreatic proteolytic enzymes; transit the small bowel to the colon where it would adhere to intestinal cells; colonize; and proliferate. The strain has to be safe, have good growth characteristics, and produce an antibacterial substance. The strain having the fastest growth and possessing the other characteristics was identified in 1985 and was named Lactobacillus GG (LGG) after its discoverers. LGG produces an inhibitory substance with activity against a variety of bacterial species, including anaerobic bacteria. LGG can be cultured in stool for 7 days after administration and from intestinal biopsy specimens for 28 days.

---

**Box 2**

**Problems assessing probiotic publications**

- Insufficient number of trial patients
- Variable ages of patients
- Multiple comorbidities
- Varied nature and dose of offending antibiotic
- Different durations of probiotic administration
- Lack of randomized, placebo-controlled trials
Saccharomyces Boulardii

Saccharomyces boulardii, a probiotic yeast, was discovered in 1920 by the microbiologist Henri Boulard when he was in Indochina. He noted that during an epidemic of cholera, the natives who ingested a special tea did not develop this diarrheal illness. The tea was made by cooking the outer skin of lychee and mangosteens. Boulard succeeded in isolating the responsible agent, a special strain of yeast, which he named Saccharomyces boulardii.

In 1947, the patent for the yeast was purchased by Laboratories Biocodex, which initiated research and manufacturing protocols. The lyophilized product, in capsule form, is stable at room temperature for more than 1 year. This preparation survives the actions of acid, bile acids, and proteolytic enzymes in its passage to the colon. Steady state concentrations are achieved in a mean of 3 days, and the cells are cleared from the stools from 2 to 5 days after discontinuation.

The mechanisms of action of S. boulardii include antitoxin effects by blocking pathogen toxin receptor sites or direct destruction of the toxin as exemplified by the degradation of toxins A and B of C. difficile and by reducing the effect of cholera toxin. S. boulardii interferes with the growth of several pathogens including Candida albicans, Salmonella typhimurium, Yersinia enterocolitica, and Alpha hemolysin. The yeast may also protect the integrity of epithelial tight junctions, reducing permeability to potential pathogens. In addition, S. boulardii has been demonstrated to increase the recovery rate of bacterial flora following the impact of antibiotics on the commensal flora.

S. boulardii is resistant to antibacterial agents. The yeast may cause an increase in secretory IgA levels and may act as an immune stimulant by reducing proinflammatory responses.

Box 3
Characteristics of clinically acceptable probiotics

| Species specific |
| Human Origin |
| Survive passage gastric, small bowel to colon, nidate/proliferate |
| Adequate dosage; preferably greater than 10 billion CFU/g |
| Maintain viability and concentration from time of purchase |
| Dependably measurable shelf life |
| Requires randomized, double-blind, placebo-controlled trials |

Box 4
Mechanisms of action of probiotics

- Enhancing mucosal barrier function by secreting mucins
- Increasing tight junctions
- Providing colonization resistance
- Producing bacteriocins
- Increasing production of secretory IgA
- Producing a balanced T-helper cell response
- Increase production of IL-10 and transforming growth factor beta
MULTISTRAIN PROBIOTICS FOR TREATING AAD  
*L. Casei, S. Thermophilus, and L. Bulgaricus*

S. thermophilus and L. bulgaricus are used to produce yogurt by the fermentation of lactic acid.8 More recently, 2 combined lactobacillus strains, *L. casei* and *L. acidophilus*, have been shown to be effective in a dose response manner to dramatically reduce AAD.9 A smaller study of this agent was also used during a 2003 to 2004 endemic of CDI in Quebec Canada with beneficial results.10

PREVENTION OF PEDIATRIC AAD

Six placebo-controlled, RCTs comprising 766 children were included in a meta-analysis of probiotics preventing AAD that was published in 2006.11 Treatment with probiotics compared with placebo reduced the risk of AAD from 28.5% to 11.9%. Pre-planned subgroup analysis showed that reduction of the risk of AAD was associated with the use of LGG, *S. boulardii*, or *B. lactis*, and *Streptococcus thermophilus*. Probiotics reduced the risk of AAD in children; of every 7 patients who would develop diarrhea while being treated with antibiotics, one fewer will develop AAD if also receiving probiotics.

No adverse effects were observed in any of the included trials. However, the investigators cautioned regarding the use of probiotics in immune-compromised patients. They recommended identification of populations at high risk of AAD who would benefit most from use of probiotic therapy, assessment of additional probiotic strains, designing an effective dosing regimen, and addressing the cost effectiveness of using probiotics to prevent AAD in children.

A Cochrane Database review of the data on probiotics in preventing pediatric AAD was published in 2011.12 Sixteen studies were reviewed and provided the best available evidence. The studies tested 3432 children (2 weeks to 17 years of age) who were receiving probiotics coadministered with antibiotics to prevent AAD. These short-term studies showed probiotics to be effective for preventing AAD. Probiotics were generally well tolerated (no significant side effects between probiotics and control groups). Both *L. rhamnosus* and *S. boulardii* at dosages of 5 to 40 billion CFU/d may prevent the onset of ADD, with no serious side effects in otherwise healthy children. This benefit for high-dose probiotics needs to be confirmed by a large randomized study. No conclusions regarding other probiotic agents could be drawn.

PREVENTING ADULT AAD

Compiling data referable to the efficacy of probiotics suppressing AAD in adults is complicated by numerous factors. Variations in the clinical setting (hospitalized or community), numbers and ages of patients, nature of the population, type of antibiotic, duration of therapy, use of different probiotics, failure to designate the strain, variable dosages, and duration of therapy are some of the major factors making statistical judgment difficult. Three meta-analyses have been published in an effort to obtain useful clinical data. In 2002, D’Souza and colleagues13 and Cremonini and colleagues14 combined 9 and 7 trials, respectively.

In the D’Souza study, 2 of the 9 studies investigated the effects of probiotics in children. Four trials used *S. boulardii*, 4 used lactobacilli, and one used a strain of enterococcus that produced lactic acid. Three trials used a combination of probiotic strains of bacteria. The probiotics were given in combination with antibiotics, whereas the control groups received placebo and antibiotics. The odds ratio (OR) in favor of active treatment over placebo was 0.39 (95% confidence interval [CI], 0.25–0.62, *P*<.001) for
the yeast and 0.34 (0.19–0.61, \( P < .01 \)) for lactobacilli. The combined OR was 0.37 (0.26–0.53; \( P < .001 \)) in favor of active treatment over placebo.

The investigators concluded that biotherapeutic agents may be useful in preventing AAD. Cremonini and colleagues (vide supra) limited their meta-analysis to 7 trials, which used the 2 most widely used probiotics Lactobacillus spp. and S. boulardii. Two studies involved children; 3 assessed the decrease in the occurrence of AAD during the administration of S. boulardii, and 4 during the administration of Lactobacillus spp. The search was limited to randomized studies. The inclusion criteria included a placebo design, with diarrhea as a primary end-point and a minimum of 2 weeks of follow-up. A total number of 881 patients were studied. The combined relative risk (RR) was 0.3966 (95% CI, 0.27–0.57). The results suggested a strong benefit of probiotic administration on AAD.

META-ANALYTIC POOLING

A large and comprehensive meta-analysis pooling trials of probiotics in the prevention of pediatric and adult AAD was accomplished by McFarland\(^\text{15}\) in 2006. Study selection included trials in which specific probiotics were given to either prevent or treat the diseases of interest.

Trials were required to be randomized, blinded, controlled in humans, and published in peer-reviewed journals. Thirty one of 180 screened studies, totaling 3164 subjects, met the inclusion and exclusion criteria. From 25 RCTs (2810 patients), probiotics significantly reduced the RR of AAD (RR = 0.43, 95% CI, 0.31–0.58, \( P < .001 \)).

Six of the trials, which included 1119 patients, used S. boulardii as the probiotic. One of the trials involved the use of triple antibiotics with concomitant S. boulardii for the eradication of Helicobacter pylori (43 patients). The same probiotic was used in a 246 pediatric patient trial. Six trials used LGG as the single probiotic; 388 pediatric patients in 3 trials, 267 adult patients in one trial, and 262 patients involved in 3 triple antibiotic/LLG trials for the eradication of H. pylori.

Overall, of 16 RCTs of adult AAD, 7 (44%) showed efficacy, whereas 9 RCTs (67%) showed significant efficacy in children. Of note, optimal results occurred with dosages of probiotics greater than \( 10^{10} \) cfu/g. Sixteen of 31 (84%) trials reported on adverse effects. In 24 trials, there were no adverse episodes. Nine percent of patients on S. boulardii reported increased thirst and 14% reported increased constipation. Thirty seven percent of patients on LGG reported mild gaseousness and 25% noted bloating.

AAD AND HELICOBACTER PYLORI THERAPY

A recent review of S. boulardii\(^\text{16}\) included 3 trials conducted in patients with H. pylori infection. These patients were treated with triple therapy, which includes 2 antibiotics and a PPI for 2 weeks.

Duman and colleagues\(^\text{17}\) treated 204 patients with 1 g of S. boulardii (\( 2 \times 10^{10} / \text{d} \) for 2 weeks) and triple therapy compared with 185 patients who received only triple therapy. Of the 389 patients, 376 completed the treatment phase and the 4-week follow-up. Fewer patients given S. boulardii (6.9%) developed AAD compared with the control group (15.6%, \( P = .007 \)).

Two other RCTs were conducted in adult patients receiving triple therapy for H. pylori infections and both showed a significant reduction in AAD for those treated with S. boulardii.\(^\text{18,19}\) In summary, the use of concomitant probiotic therapy in association with multiple antibiotics and PPIs is helpful in reducing the antibiotic-induced gastrointestinal side effects.
META-_ANALYTIC CONFIRMATION OF RESULTS SUPPORTING USE OF PROBIOTICS FOR AAD

A statistically sophisticated meta-analysis adding confirmation for the use of probiotics for treatment of AAD was published in April, 2012 by Videlock and Cremonini. They used a meta-analysis of randomized, double-blinded, placebo-controlled trials including patients treated with antibiotics and administered a probiotic for at least the duration of the antibiotic treatment.

They used a meta-analysis of randomized, double-blinded, placebo-controlled trials including patients treated with antibiotics and administered a probiotic for at least the duration of the antibiotic treatment. Meta-analysis and meta-regression methods were used to synthesize data and to assess influence of mean age, duration of antibiotics, risk of bias, and incidence of diarrhea in the placebo group on outcomes. Subgroup analyses explored effects of different probiotic species, patient populations, and treatment indications.

Thirty four studies were included with 4138 patients. Pooled RR for AAD in the probiotic group versus placebo was 0.53 (95% CI, 0.44–0.63), corresponding to a number needed to treat (NNT) of 8 (95% CI, 7–11). Pooled RR for AAD during treatment of H. pylori was 0.37 (95% CI, 0.20–0.69), with an NNT of 5 (95% CI, 4–10). This updated meta-analysis confirmed the results enumerated, supporting the effects of probiotics in AAD. Studies on the effect of probiotics in preventing the occurrence or reoccurrence of Clostridium difficile colitis were not included and will be discussed later in this article.

AAD–THE PATHWAY TO CLOSTRIDIUM DIFFICILE COLITIS

The spectrum of AAD ranges from self-limited diarrheal episodes without complications to antibiotic-associated colitis. Ten percent to 25% of all cases of AAD are due to overgrowth of C. difficile.

C. difficile is an anaerobic, gram-positive spore-forming rod that colonizes the intestinal tract after alteration of the normal gastrointestinal flora. Disruption of the protective colonic flora by broad spectrum antibiotics is the commonest predisposing factor to CDI by altering “colonization resistance.”

The extent of this disruption varies among individuals with restoration of normal flora usually taking 1 month after discontinuation of the antibiotic. However, in some instances it may take 6 months or longer. It is now well established that antibiotic treatment increases susceptibility to enteric infections.

C. difficile is the most common infectious disease affecting the gastrointestinal tract. It occurs in 8% to 10% of hospitalized patients and is responsible for 20% to 30% of cases of hospital-acquired diarrhea. The infection is mediated by 2 exotoxins, A and B, causing diarrhea and colonic mucosal inflammation. The spectrum of the disease varies from mild diarrhea to severe fulminant watery diarrhea associated with fever, leukocytosis, abdominal pain, distention, and hypoalbuminemia.

The rate and severity of C. difficile has increased nationally and worldwide in part related to a new hyper virulent strain, initially described in early 2000 in Quebec, Canada and the University of Pittsburgh Medical Center, USA. Molecular analysis was characterized as group B1 by restriction endonuclease analysis, as North American pulse-field type NAP1, as pulse-field electrophoresis, and as ribotype 027. The new strain is characterized by greater toxicity, a significant increase in toxins A and B, a higher rate of recurrent disease, and reduced response to metronidazole.

THE SPECTRUM OF CDI INFECTION

The spectrum of disease varies from an asymptomatic carrier state to mild diarrhea or life-threatening fulminant diarrhea and colitis. The carrier state affects approximately 20% of hospitalized patients. Although asymptomatic, they serve as a reservoir for
environmental contamination. An even greater number of carrier patients are seen among nursing homes and long-term health facilities.27

Typical inhospital presentation is an elderly (>65 years of age) patient with an exposure to an antibiotic within the past 2 months presenting with frequent watery diarrhea for 2 to 3 days in association with crampy abdominal pain, nausea, and anorexia. Laboratories reveal leukocytosis, elevated C-reactive protein (CRP) level, and hypoalbuminemia. Stool examination result is positive for toxins A and B. The patient is placed in an isolation room and immediately treated with vancomycin 125 mg orally 4 times daily and carefully assessed on a daily basis.

Risk factors for inhospital patients include age greater than 65 years, male gender, immunodeficiency, multiple comorbidities, increased length of hospital stay, prolonged antibiotic use, antineoplastic medications, use of PPIs, use of fluoroquinolones, and the presence of IBD.

Community risk factors include pregnant and peripartum women, diminished immune status, nursing home patients, and IBD. A typical community patient would be a 26-year-old woman with a history of quiescent ulcerative colitis with no antibiotic exposure who experiences an acute flare with sudden onset of bloody diarrhea, fever, and leukocytosis. Stool analysis result is positive for toxins A and B. The patient is placed on metronidazole, 500 mg, 3 times daily, fluid, and electrolyte replacement and observed carefully for early signs of improvement; if no improvement occurs within 48 to 72 hours, the patient should receive 250 mg of vancomycin 4 times daily.

CLASSIFICATION OF DISEASE SEVERITY

Milder cases include low-grade diarrhea and less-systemic symptoms, including low-grade temperature, fewer cramps, and minimal leukocytosis. Colonic mucosal biopsies reveal inflammatory changes confined to the superficial epithelium and lamina propria with few crypt abscesses.

More advanced cases are exemplified by increased diarrheal episodes (>10–15 stools/d), greater abdominal pain, fever, and leukocytosis averaging 15,000. Mucosal biopsies are characterized by severe glandular disruption, crypt abscesses, and increased mucus secretion.

Fulminant colitis is characterized by severe lower abdominal pain and distention. Marked diarrhea is present followed by hypovolemia, lactic acidosis, hypoalbuminemia, and toxic mega colon, which may lead to perforation. Leukocytosis greater than 30,000 is a poor prognostic sign. Histopathology reveals intense necrosis involving full thickness of the mucosa with confluent pseudomembranes.

DIAGNOSIS OF CDI

Diagnosis should be suspected in any patient (especially elderly) developing clinically significant acute diarrhea within 2 months of antibiotic use or within 3 days of hospital admission. Clinically significant diarrhea is defined as 3 or more loose stools daily for at least 2 days. Additional important features of the patient’s history include use of current medication, particularly immunosuppressives, PPIs, or steroid therapy.

A review of comorbidities is necessary with special attention to IBD and recent pregnancy. An allergic history and a prior history of C. difficile infection are important. A nutrition history, including weight loss and food and water intake, is essential. The differential diagnosis includes other enteric pathogens that can cause diarrhea, which includes salmonella, C. perfringens type A, Staphylococcus aureus, C. albicans, Campylobacter, and Shigella.
Travelers’ diarrhea should be considered in patients with a recent history of foreign travel. Noninfectious diseases including irritable bowel syndrome, celiac disease, drug-induced diarrhea, and so on should be ruled out.

Major findings on physical examination include direct lower abdominal tenderness in association with fever and dehydration. Bedside sigmoidoscopic examination in an isolation room may reveal findings from mild patchy erythema and friability to marked edema, plaque formation, and severe pseudomembranous colitis. Stool guaiac test results are generally positive. Leukocytosis and hypoalbuminemia may be notable.

LABORATORY DIAGNOSIS

A complete blood count may reveal anemia (microcytic, hypochromic) and leukocytosis (elevated neutrophils) secondary to inflammation, hypovolemia (secondary to protein loss/diarrhea), and possible electrolyte imbalance. CRP level may be elevated. Stool examination may reveal stool leukocytes. Testing for toxins A and B (performed only on diarrheal stools) include enzyme immunoassay (EIA), which is rapid, but less sensitive than cell cytotoxin assay and polymerase chain reaction testing, which is rapid, sensitive, and specific.

Repeat testing during the same episode of diarrhea is usually of limited value. Imaging: plain films may be helpful to determine toxic mega colon or perforation. Abdominal computed tomography scan in patients with pseudomembranous colitis reveals thickening of the abdominal wall.

TREATMENT OF CDI

The primary goal for treatment of clostridium difficile colitis is to commence therapy, preferably as soon as the diagnosis is confirmed.24,28

- If diagnostic tests are unavailable, when severe or complicated CDI is suspected, empirical therapy should be initiated.
- If the result of stool toxin assay is negative, the decision to start therapy must be individualized. Discontinue therapy with the inciting antibiotic agent as soon as possible.
- Institute supportive care including hydration and electrolyte replacement. Avoid use of antiperistaltic medication (narcotics and anticholinergics).
- For mild to moderate initial episode of CDI, metronidazole is the drug of choice. The recommended dosage is 500 mg 3 times daily for 10 to 14 days.
- The exception is the presence of the virulent strain NAP1/BI/027, which may be resistant to metronidazole. Vancomycin orally in a dosage of 125 mg 4 times daily for 10 to 14 days should be substituted.
- Vancomycin is the drug of choice for initial episode of severe CDI. The dosage is 125 to 250 mg orally 4 times daily for 10 to 14 days. Vancomycin is given orally (and per rectum, if ileus is present), with or without intravenously administered metronidazole, is the regimen of choice for severe, complicated CDI.
- The vancomycin dosage is 500 mg orally 4 times daily and 500 mg in 100 mL normal saline rectally every 6 hours as a retention enema.
- The metronidazole dosage is 500 mg intravenously every 8 hours.
- Surgical consultation should be obtained early in the course of severe, complicated CDI.29
- Colectomy should be considered for severely ill patients. The patient’s overall condition, an elevated serum lactate rising to 5 mmol/L and a white blood cell count (WBC) rising to 50 thousand cells/µL have been associated with increased
perioperative mortality. If surgical intervention is indicated, a subtotal colectomy with rectal preservation is recommended.

**OTHER THERAPEUTIC CONSIDERATIONS**

The search for new antimicrobial agents against C. difficile is driven by a desire to find an alternative to metronidazole and vancomycin, both as treatment of the acute inflammatory process, and to prevent recurrent episodes of colitis.

A recent Cochrane Review\(^3\) investigated the efficacy of antibiotic therapy for C. difficile-associated diarrhea. Only RCTs assessing antibiotic treatment of CDI were included in the review. Fifteen studies with a total of 1152 participants with CDI were included. Nine different antibiotics were investigated: vancomycin, metronidazole, fusidic acid, nitazoxanide, teicoplanin, rifampin, rifaximin, bacitracin, and fidaxomicin. Most of these studies were active comparator studies comparing vancomycin with other antibiotics.

Vancomycin was found to be superior to placebo for improvement of symptoms of CDI including resolution of diarrhea. Most of the studies found no statistically significant difference in efficacy between vancomycin and other antibiotics. Many of these studies had small numbers of patients and suffered from methodological quality.

Teicoplanin, however, was found to be superior to vancomycin for curing the CDI. Teicoplanin is expensive and not readily available in the United States.\(^3\)

The Food and Drug Administration has recently approved a new macrocyclic antibiotic with minimal systemic absorption, high fecal concentrations, and limited activity in vitro and in vivo against components of normal gut flora. The drug, fidaxomicin, has a narrow antimicrobial spectrum against gram-negative organisms and fungi. The dosage is 200 mg orally every 12 hours. The rates of cure with fidaxomicin were non-inferior to vancomycin in the treatment of CDI. A multicenter trial with 629 patients also revealed a lower rate of recurrence of the infection.\(^3\)

Tolevamer is a nonantibiotic, toxin-binding polymer, which noncovalently binds C. difficile toxins. This agent effectively treats mild to moderate C. difficile inflammation but does not alter commensal diversity.\(^3\)

**RECURRENT CLOSTRIDIUM DIFFICILE COLITIS**

Recurrent C. difficile colitis occurs in 20% to 35% of patients with CDI, reflecting possible relapse of the original strain or reinfection with a new strain. Recurrence can occur within days to within 4 weeks following therapy with either metronidazole or vancomycin. The risk of recurrence is increased in patients who have already had one recurrence, rising from about 20% after an initial episode to about 40% after a first recurrence and to more than 60% after 2 or more recurrences.\(^3\)

There are several suggested mechanisms explaining C. difficile relapses:

1. Reinfection may occur after initial clearance if there is repeat exposure in a contaminated environment because clostridial spores can persist in the environment allowing for exogenous reinfection.
2. Resistant spores may not have been destroyed during the initial antibiotic eradication of vegetative forms of C. difficile.\(^3\)
3. The antibiotic triggering the acute infection may have dramatically altered the commensal bacteria to an extent that delayed homeostasis of the diverse protective bacteria, thus allowing the C. difficile vegetative form to proliferate.
4. Increased frequency of recurrences following metronidazole therapy.
5. Increased frequency of recurrences in patients older than 65 years of age.
6. Patients with a defective immune response to toxin A (Box 5).36

**TREATMENT OF RECURRENT CDI**

Vancomycin is recommended for the first recurrence in patients with a WBC of 15,000 cells/μL or higher or a rising serum creatinine level. A significant number of patients with a second recurrence will be cured with a tapering or pulsed regimen of oral vancomycin. After the initial dosage of 125 mg 4 times daily for 10 to 14 days, followed by 125 mg twice daily for 1 week, and then 125 mg every 3 days for 2 to 8 weeks.

Other potential options include other antimicrobial agents such as fidaxomicin, nitazoxanide, monoclonal antibody, intravenous IgG, the use of C. difficile toxoid vaccine, or fecal transplantation.

Fecal biotherapy involves infusion of bacterial flora obtained from the feces of a healthy donor to reverse the bacterial imbalance responsible for the recurring nature of the infection. Donor stool is collected from a family member who has been tested for bacterial, viral, or parasitic pathogens. The stool is mixed with sterile saline and delivered through a nasogastric tube, colonoscopically or by retention enema. Published results of patients who have failed prior therapy report dramatic responses to this approach.40

**INFECTION CONTROL AND PREVENTION MEASURES**

The most important infection control and prevention measures include measures for patients, visitors, and health care workers; environmental cleaning; restrictions on antimicrobial agents; and the use of selected probiotics.

Infection spreads via the fecal-oral route. A patient-isolation room with a dedicated toilet is necessary; lid-down flushing is recommended. Hand washing with warm water and soap is indicated for patients, visitors, and health care providers. The latter should be gloved and gowned appropriately.

Contact precautions should be maintained for the duration of diarrhea. Disposable medical equipment, including disposable rectal thermometers should be used. Chlorinated agents (with at least 1000 ppm available chlorine) should be used for effective room cleaning and disinfection. PPIs and antiperistaltic medications should be discontinued.

**MONITORING ANTIMICROBIAL AGENTS**

Antibiotic use is widely accepted as an important modifiable risk factor for C. difficile-associated diarrhea. The antibiotics most frequently implicated in the predisposition to

---

**Box 5**

**Mechanisms contributing to recurrent CDI**

- Previous CDI infection
- Repeat exposure to a contaminated environment
- Resistant spores not destroyed during initial antibiotic eradication
- Extreme and prolonged alteration of commensal bacterial flora with delayed restoration of flora
- Age greater than 65 years
- Patients with defective immune response to toxin A
CDI include fluoroquinolones, clindamycin, and broad spectrum penicillins and cephalosporins. Any antibiotic can disrupt the diversity of commensal bacteria and allow colonization by C. difficile.

The use of broad-spectrum antimicrobials, using multiple antibiotics, as well as prolonged duration of antibiotic agents contribute to the increased incidence of CDI.\textsuperscript{42} It is important to minimize the frequency and duration of antimicrobial agents in an effort to reduce the incidence of CDI. An antimicrobial stewardship program including pharmacy stop dates may be helpful.\textsuperscript{43}

\textbf{USING PROBIOTICS TO PREVENT CDI}

The ideal probiotic preventing CDI is an agent that rapidly reduces AAD, prevents disruption of commensal bacteria, replaces previously depleted microflora, and returns microfloral functionality to the patient. The agent should be nontoxic, reasonably priced, and readily available, with an acceptable shelf life and RCTs confirming its efficacy.

As noted previously, multiple clinical trials have confirmed the efficacy of various probiotics in the treatment of AAD. Thus, blocking the pathway from AAD to CDI reduces the ability of the vegetative form of the C. difficile organism break through the protective barrier of the intact protective commensal bacteria.

There are several recent randomized placebo-controlled studies that support this concept.\textsuperscript{8} One thousand seven hundred and sixty patients were assessed for eligibility, of which 1625 were excluded. Total allocation included 135 patients, 69 in the probiotic group and 66 in the placebo group; including follow-up, the final analysis allowed for 57 patients in the probiotic group and 56 patients in the placebo group. The treatment group received a probiotic yogurt drink containing L. casei DN-114001 (L. casei Immunitas) (\(1.0 \times 10^8\) cfu/mL), S. thermophilus (\(1.0 \times 10^8\) cfu/mL), and L. bulgaricus (\(1 \times 10^7\) cfu/mL). The placebo group received a long-life, sterile milkshake (Yazoo, Campina, Netherlands). Lactobacillus counts of the probiotic drinks were performed to ensure activity.

L. casei Immunitas had previously been shown to survive passage to the colon. Participants ingested the drinks within 48 hours of starting the antibiotic, continuing for 1 week after stopping the antibiotic. The participants drank 100 gm (97 mL) twice daily before or 1 to 2 hours after meals.

There were no reported adverse events related to the study drink. Most patients received an antibiotic, but about 40% received 2. The most common reasons for antibiotic use were respiratory infections (49%) or prophylaxis before or after surgery (25%). Primary analysis was intention to treat.

There was a significant reduction in both the incidence of AAD (\(P = .007\)) and C. difficile-associated diarrhea (\(P = .001\)) in the probiotic group. The investigators concluded that consumption of a probiotic drink containing L. casei, L. bulgaricus, and S. thermophilus can reduce the incidence of AAD and C. difficile-associated diarrhea, with the potential of decreasing morbidity, health care costs, and mortality if used routinely in patients aged more than 50 years. Three trials using another L. casei strain have been reported.

Two Canadian population studies were conducted with the primary objective of studying AAD and a secondary objective of determining the impact of the probiotic on CDI. The third study was a single center study performed on an Asian population (Shanghai).

A prospective, randomized, double-blind, placebo-controlled study was conducted at Maisonneuve-Rosemont Hospital, Montreal, Quebec.\textsuperscript{10} Among 89 randomized,
hospitalized patients, AAD occurred in 7 of 44 patients (15.9%) in the lactobacilli group and in 16 of 45 patients (35.6%) in the placebo group (OR 0.34, 95% CI, 0.125–0.944; \( P = .05 \)). The median hospitalization duration was 8 days in the lactobacilli group compared with 10 days in the placebo group (\( P = .09 \)). Lactobacilli fermented milk was well tolerated. Among all study patients, one patient in the lactobacilli group (2.3%) and 7 patients in the placebo group (15.6%) developed CDI (OR 0.126, 95% CI, 0.020–1.109; \( P = .06 \)).

This study was followed by a Canadian centre study involving 216 patients randomized to L. acidophilus CL1285 and L. casei to placebo. The mean number of days with diarrhea was 1.19 (3.20) days for the placebo and 0.67 (2.05) days for the lactobacilli group (\( P = .040 \)). Adjusted multivariate linear regression results showed that the duration of diarrhea for the lactobacillus group versus placebo was reduced by 51.5% (bSE = 0.515 (0.0256), \( P = .045 \)). The incidence of diarrhea was 21.8% for the lactobacilli group and 29.4% for the placebo group (OR = 0.667, \( P = .067 \)). One patient in the Lactobacilli group was positive for C. difficile toxin as compared with 4 in the placebo group (OR = 0.433, \( P = .645 \)).

Another randomized, double-blind, placebo-controlled, dose-ranging study added impetus to the Hickson study.9 This single-center study randomized 255 adults in patients, aged 60 to 70 years, to 1 of 3 groups: 2 probiotic capsules consisting of 100 billion CFU/ml of the probiotic mixture L. acidophilus CL1285 and L. casei LBC8OR and one probiotic capsule containing 50 billion CFU/ml and one placebo capsule against group 3 that includes 2 placebo capsules daily. Probiotic prophylaxis began within 36 hours of initial antibiotic administration and continued for 5 days after the last antibiotic dose. Patients took their daily dose 2 hours after breakfast and antibiotic administration each day. Patients were then observed for an additional 21 days.

Higher dose probiotic use had a lower AAD incidence compared with the lower dose probiotic (15.5% vs 28.2%, \( P = .02 \)). Each probiotic group had a lower AAD incidence than placebo (44.1%, ‘< .001 for higher dose probiotic and \( P = .02 \) for lower dose probiotic). Patients on the probiotic had a shorter duration of symptoms. There was also a reduction in CDI incidence from 23.8% in the placebo group to 1.2% in the higher dose probiotic group (\( P = .002 \) vs placebo) and 9.4% in the lower dose probiotic group (\( P = .03 \) vs placebo). This report proved to be a classic dose-response result.

Despite the strain differences, L. casei was present in both studies. Further randomized studies would add to the value of both of these studies. The results of these studies compare favorably with a similar trial.44 That study reported that patients taking a probiotic containing Lactobacillus and Bifidobacterium had a 2.9% CDI incidence versus 7.3% in a placebo group. The dose-response relationship implies that higher probiotic dosages may be associated with better outcomes. These studies also emphasize the value of prophylactic probiotic therapy in selected at-risk populations, particularly the elderly.

**ADJUNCTIVE PROBIOTIC THERAPY TO PREVENT RECURRENT CDI**

There is evidence suggesting that the yeast S. boulardii may reduce the incidence of recurrent CDI when adjunctively with high-dose vancomycin.45

**SAFETY OF PROBIOTICS**

The safety of probiotics is expertly reviewed in a separate article of this issue. Probiotics have an excellent overall safety record.46 Major risk factors include immune compromise, premature infants. Minor risk factors include central venous catheter,
altered epithelial barrier, jejunostomy feedings, and cardiac valvular disease or valvular replacement.

**THE ECONOMIC IMPACT OF CLOSTRIDIUM DIFFICILE INFECTION**

The incidence of CDI is increasing worldwide. This infectious illness has resulted in increased morbidity, mortality, and financial cost to the health care system. In fact, a large CDI economic evaluation confirmed that health care-associated cases of CDI are associated with significantly higher mean cost and longer length of stay than those of matched controls, with the greatest effect on costs at the lowest level of severity of illness. This evaluation is further exacerbated by the increased recognition of the impact of CDI on patients, both children and adults with IBD.

**SUMMARY**

Clearly, current evidence favors the use of probiotics in the prevention of symptoms of AAD. Lactobacilli, S. boulardii, and selected multistrain combinations, in appropriate dosages, are all clinically useful. The safety profile, with the exceptions noted earlier, is acceptable particularly in view of the short-term use of an antibiotic when accompanied by a probiotic. Recent statistical analysis substantiates this view. Of greater importance is the compelling evidence that high-risk patients (especially the elderly) can prevent the morbidity and mortality related to CDI by using selected probiotics to block the pathway from AAD to CDI.

**REFERENCES**


