

Carol Rees Parrish, MS, RDN, Series Editor

Clostridioides difficile Infection: Is There a Role for Diet and Probiotics?



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Clostridioides difficile is a spore forming bacterium leading to significant morbidity and mortality amongst hospitalized as well as non-hospitalized patients in the United States. While hospital acquired infections have reduced, in recent years we have seen an increase in community acquired infections. With the focus on antimicrobial therapies and fecal microbiota transplantation, it is important to understand the evidence behind probiotics and nutrition in the management of *C. difficile* infections. There is an abundance of new literature regarding the \$40 billion a year probiotic industry, meanwhile patients require dietary advice following an infection. In this review, we aim to give the non-specialty clinician some clarity regarding these issues.

INTRODUCTION

C*lostridioides difficile* is an anaerobic, gram positive, spore forming bacterium that causes a spectrum of gastrointestinal symptoms ranging from mild diarrhea to colitis, toxic megacolon, intestinal perforation, and death. It is spread via the fecal-oral route and is frequently encountered in hospitals, affecting 1% of US hospital stays¹ and nursing homes where antibiotic use is common. Concerningly, community-acquired infections are common, and recent research suggests other undefined causes

of CDI, as many cases occur without a history of antibiotic use.² There was a significant increase in CDI between 2000-2010, which has been attributed to increased detection with use of nucleic acid amplification testing, more virulent strains, and increased community antibiotic use. Since then, we have seen a reduction in healthcare associated CDI, though there are still almost half a million cases per year within the United States.³ Infection control measures, decreased fluoroquinolone use, and improved antibiotic stewardship have been credited with these results.⁴

In recent years there has been an abundance of new literature on *C. difficile* with regards to management and prevention options. For the non-specialty clinician, it is challenging to determine which data is high quality and what can be applied to their patients. With the spotlight on fecal microbiota

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transplantation (FMT) and other non-antibiotic therapies for CDI, it is understandable that both clinicians and patients are seeking preventative options such as probiotics and nutrition. Here we evaluate the current evidence for these therapies in the prevention of CDI.

Probiotics

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.⁵ The literal translation is “for-life”, which conveys that they are good, natural, and beneficial to biological functions. Proposed mechanisms for beneficial effects include modification of the gut microbiota, competitive adherence to the mucosa and epithelium, strengthening of the gut epithelial barrier, and modulation of the immune system to convey an advantage to the host.⁶ Probiotics are marketed as dietary supplements with colourful labels and vague claims of “friendly bacteria” to “improve gut health.” This 40 billion dollar a year industry,⁷ while extremely appealing to patients and healthcare professionals, operates without the strict oversight by the U.S. Food and Drug Administration that is required of drugs. A quick internet search reveals a plethora of websites recommending various probiotics as a means to improve one’s health for various indications, including after CDI. A 2010 survey of gastroenterologists found that 98% of respondents believed probiotics have a role in treating gastrointestinal illnesses or symptoms, despite the paucity of data to support their use. Sixty percent believed that the literature supported the use of probiotics in the treatment of CDI.⁸ Due to the lack of regulation and freedom to make general health claims on product labels, there is little incentive for manufacturers to conduct clinical trials to support specific indications for their products.⁹

The trouble with many of the available products is that quality control is often sub-optimal with inconsistencies and deviations from the information provided on the product label including misidentified, misclassified or non-viable strains, contaminated products, or diminished functional properties.¹⁰ The belief that probiotics “can’t hurt” has been challenged by case reports of bloodstream infections with probiotic organisms in critically

ill patients leading to the recommendation that they be used with caution in immunocompromised patients and those with structural heart disease or central venous catheters.¹¹ Microbiome analyses have shown that they may actually impede normal recolonization in the gut after a course of antibiotics.¹² Despite this, probiotics are widely recommended by physicians to prevent CDI in patients being treated with antibiotics (primary prevention) or in patients being treated for CDI to prevent recurrences (secondary prevention). Costs range from \$30 to \$100 per month for the most commonly recommended formulations, which are frequently taken for extended courses and typically not covered by insurance. Given these costs, the desire to provide reliable health information to our patients, and the potential for harm, it is important to critically appraise data supporting the use of probiotics in CDI.

Evidence to support probiotics in the management of CDI comes mainly from meta analyses, which pool data from smaller trials of variable probiotic formulations and methodologies. There is a paucity of high-quality clinical trial data of probiotics in CDI, and most studies are underpowered, with CDI as a secondary outcome in studies done to assess prevention of antibiotic associated diarrhea (AAD). A 2016 global review of guidelines, strategies, and recommendations for CDI prevention⁴ labelled probiotics as an area of research, but were unable to recommend their use. There is currently insufficient evidence to recommend any probiotic for the primary or secondary prevention of CDI.

The Literature

The PLACIDE trial is the largest double-blind clinical primary prevention randomized controlled trial (RCT) to date.¹³ This multicenter trial in the United Kingdom enrolled nearly 3000 elderly inpatients who were at high risk of contracting CDI. Patients >65 years old receiving antibiotics were randomized to treatment with a multi-strain preparation composed of bifidobacterium and *Lactobacillus acidophilus* strains or placebo for 21 days. AAD including CDI occurred in 10·8% of the microbial preparation group and 10·4% of those treated with placebo. CDI was an uncommon cause of AAD and occurred in just 0·8% of the microbial

preparation group and 1.2% of the placebo group. The authors concluded that probiotics were of no benefit in prevention of AAD or CDI.

Many nutritional websites and magazines broadly claim “high quality evidence” for probiotics in CDI, most citing the Cochrane Review in 2017 by Golbenberg et al, which looked at probiotics for primary prevention of CDI in adults and children, enrolling 8672 participants.¹⁴ It is important to highlight that 27 of the 31 studies analysed were felt to be of unclear or high risk of bias and more than half had missing data. The incidence of CDI was 1.5% in the treatment group and 4% in the control groups, a 60% risk reduction. They concluded a modest benefit of probiotics (number needed to benefit=42). However, in post-hoc subgroup analysis these benefits only held up in trials enrolling participants with baseline CDI risk >5%, which is higher than the average risk in American hospitals and therefore has questionable clinical application. The conclusions of this Cochrane review have been criticized as misleading, in that only 4/31 trials showed benefits and small, poorly controlled studies had too much influence.⁹ Results were heavily influenced by 5 studies with CDI baseline risk >15%, far above that seen in any hospital setting in the world, raising important questions of the external validity. Major limitations of this meta-analysis were that included studies used many differing probiotic combinations and dosages, multiple trials were small/underpowered, single center, missing data, participants lost to follow up, and in some cases, no fecal samples were obtained.

An earlier Cochrane review of probiotics for treatment of CDI, which included four studies, concluded that there is insufficient evidence to support their use.¹⁵ Published in 2017, the PICO trial randomized 33 patients with an initial mild to moderate CDI to 28 days of a four-strain probiotic or placebo in addition to anti-CDI therapy and showed no difference in rates of CDI recurrence.¹⁶

In light of all this evidence and despite what product labels and websites will claim, probiotic prophylaxis for CDI prevention is not recommended by the American College of Gastroenterology,¹⁷ the Association for Professionals in Infection Control and Epidemiology,¹⁸ or the European Society of Clinical Microbiology and Infectious Diseases.¹⁹

***Saccharomyces Boulardii* Hope for Recurrent CDI?**

There were several publications in the 1990s involving *Saccharomyces boulardii* that showed promise regarding CDI secondary prevention.²⁰ *S. boulardii* is a yeast that grows on lychee fruit. It was discovered by a French pharmacist who observed South-East Asian natives chewing the skins of the fruit to lessen the symptoms of cholera. It produces a protease that inactivates the receptor site for *C. difficile* toxin A, lending biologic plausibility to its use in CDI.²¹

A 1994 multicenter RCT showed decreased CDI recurrence in patients treated with *S. boulardii* in addition to either metronidazole or vancomycin in those who had already suffered a recurrence (34.6% with *S. boulardii* vs 64.7% with placebo).²² There was no benefit over placebo in patients with primary infection. A follow up study published in 2000 enrolled 168 recurrent CDI patients who were treated with a 28 day course of *S. boulardii* or placebo in addition to anti-CDI therapy.²³ The benefits in this study were limited to the subgroup who were treated with high-dose vancomycin and *S. boulardii* (16.7% recurrence vs. 50% with placebo). Those who received low dose vancomycin or metronidazole had similar rates of recurrence whether they were treated with the probiotic or placebo. The study was small, with n=32 in the high-dose vancomycin group, hence, no firm conclusions can be drawn. Unfortunately, a larger planned trial was never conducted and the benefits of *S. boulardii* for secondary prevention remain unknown.

Dietary Probiotics

Following a CDI, many patients seek dietary advice to prevent recurrence. This is another area without robust evidence to guide us. Dietary sources of probiotics include fermented milk products (such as yogurt, kefir, and buttermilk), fermented vegetables (such as kimchi and sauerkraut), and fermented soy products (such as miso and tempeh). There have been several studies looking into the use of yogurt in prevention of AAD, but not CDI. In 2003, one center randomized 202 elderly hospitalized patients receiving antibiotics to receive 16 ounces of yogurt per day for a week. The control group

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received no yogurt. The yogurt group reported less antibiotic associated diarrhea (12% vs 24%, $p=0.04$) and less diarrhea days (23 vs 60 days). The role of dietary probiotics in CDI is unclear and it

is important to note that following CDI patients may have lactose intolerance and post-infectious irritable bowel syndrome,²⁴ so consumption of yogurt for that purpose may lead to worsening gastrointestinal (GI) upset.²⁵

Table 1. Summary of the Evidence for Probiotics and Diet in *C. difficile* Infection

Probiotics

- There is currently insufficient evidence to recommend any probiotic for the primary or secondary prevention of CDI

Food-based Probiotics

Without robust evidence

- Fermented milk products (such as yogurt, kefir, and buttermilk)
- Fermented vegetables (such as kimchi and sauerkraut)

Foods to Avoid after CDI

Clinical practice without clear evidence

- Dairy: Lactose intolerance can accompany post-infectious IBS
- Spicy Foods
- Greasy foods
- Caffeine

Microbiome and Select Diets

Paucity of data: None have been proven to reduce incidence of CDI

- Western Diet: decreased microbiome diversity, theoretically increased CDI
- Gluten free diet: decreased microbiome diversity, theoretically increased CDI
- Plant based diet: increased diversity, theoretically protective against CDI

Food Additives

Clinical practice without clear evidence

- Fiber - animal models show quicker elimination of CDI.
 - We recommend psyllium for all patients after CDI
- Sugar alcohols - animal models suggestive, but no proven link with increase CDI
- Artificial Sweeteners - alters the microbiome, but no proven link with CDI
- Trehalose (sugar additive listed on food labels as “a natural flavor”) - linked with increased hypervirulent CDI
 - Found naturally in: mushrooms, shrimp, and algae contain small amounts of trehalose, followed by certain seeds, honey
 - A common food additive in: dried and frozen food, instant food (noodles, rice, soups), sugar coatings and fillings, baked goods, seafood

Nutritional Tips Following CDI

In the immediate recovery period from CDI, patients are at increased risk for postinfectious irritable bowel syndrome (IBS) and ongoing diarrhea and therefore should consider following general advice that is given to other patients with IBS. There is however a lack of evidence for any of the following nutritional recommendations in the setting of CDI and further studies are required. Patients with post infectious IBS may have associated lactose intolerance; therefore, we advise avoiding high lactose containing foods, in particular milk and other high lactose containing milk products for 2-4 weeks.²⁴ Additionally, greasy foods, spicy foods,²⁶ and excessive caffeine intake²⁷ are often reported to cause GI distress and should be avoided at least in the short-term following CDI.

Microbiome

In recent years there has also been rapidly growing interest in the human gut microbiome in facilitating health benefits and its role in many diseases.²⁸ No longer the “forgotten organ”²⁹, the function of the microbiome is now being extensively investigated. Encompassing 10¹⁴ microorganisms, including bacteria, viruses, fungi, and protozoa,³⁰ both human and animal models have shown the importance of the microbiome in resistance against CDI.³¹ Disruption of the microbiome is at the core of the pathogenesis,³² though we have yet to identify which specific microbes are responsible. Given the importance of the microbiome in the development of CDI, there are select diets that may improve or diversify the microbiome and alter one’s chance of developing an infection.

Select Diets

Several studies have shown the consumption of a Western diet, consisting of high animal protein and fat with low fiber has resulted in reduced diversity overall and specifically lower amounts of *Bifidobacterium* and *Eubacterium*.³³⁻³⁴ Consumption of a gluten free diet may lead to reduced diversity and increased pathogenic bacteria.³⁵⁻³⁶ A vegan or plant-based diet appears to promote microbiome diversity.³⁷⁻³⁸ From this it might be inferred that a Western or gluten free diet may be associated with increased CDI, meanwhile vegan or plant-based diets may be protective against the development

of CDI. Further studies are needed before making recommendations on this.

Fiber

Dietary fiber is found in beans, grains, vegetables, and fruits. Most fiber is not absorbed, remaining in the gut where it improves the consistency of the stool.³⁹ There are no human studies relating fiber intake to CDI, however animal studies have shown that a diet high in soluble fiber can help eliminate CDI quicker than diets high in insoluble fiber.⁴⁰⁻⁴² The recommended amount of dietary fiber is 25g per day for moderately active Americans.⁴³ Most individuals are unable to obtain this goal with diet alone. Fiber supplements may be recommended to meet this goal and there is evidence to support benefits in various GI conditions, including IBS,³⁹ constipation,⁴⁴ and post infectious GI symptoms,⁴⁵ such as after CDI. We recommend products containing psyllium, a plant-based fiber, which absorbs liquid and provides bulk to the stool for our CDI patients. We suggest starting with 1 sachet in the evening to avoid side effects such as daytime gassiness that may occur when taken in the morning. Dose can be titrated to effect.

Sugar Alcohols

Sugar alcohols or polyols such as mannitol and sorbitol are found naturally in many foods such as pineapples, sweet potatoes, and carrots, but are also found in many processed foods and liquid medications. While some mouse studies have suggested that an increase in gut polyols is associated with increased susceptibility to CDI,⁴⁶ there is no evidence in humans that increased dietary sugar alcohol intake is associated with CDI.

Food Additives

Research is well underway regarding artificial sweeteners and their alteration of the gut microbiome. Saccharin and sucralose have been shown to shift populations of microbiota.⁴⁷ One study in *Nature* by Collins et al found that the hypervirulent strain ribotype 027 is able to grow on low concentrations of trehalose, a naturally occurring sugar that the food industry began using to improve texture and stability of products in the early 21st century, around the time that CDI rates skyrocketed.⁴⁸ Trehalose is found naturally

in small amounts in mushrooms and shrimp, however significantly higher amounts are added by the food industry to dried and frozen foods including ice cream and frozen vegetables as well as instant noodles, soups, and many baked goods. People who do not tolerate mushrooms may lack the enzyme trehalase and suffer GI symptoms with other trehalose containing foods.⁴⁹ Any possible link between this and CDI is unclear. See Table 1 for summary of the evidence for probiotics or diet.

CONCLUSIONS

The treatment and recovery from CDI is multifaceted. There is currently no evidence that probiotics reduce the incidence or recurrence of CDI. They are an enormously lucrative market with little regulation or incentive for drug companies to perform the trials that could potentially lead to progress in this area. Disruption of the microbiome is at the core of the pathogenesis of this disease. Increasing the diversity of one's microbiome can be achieved through consuming a plant-based diet with increased dietary fiber, however the link between these interventions and a reduction in CDI is yet to be made. There is much hope that altering the microbiome, through diet and/or use of probiotics will become frontline in the treatment and recovery from *Clostridioides difficile* infection, however further research is required. ■

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Answers to this month's crossword puzzle:

1	C	O	M	O	R	B	I	D	5	I	T	7	I	E	8		9	W
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42	S	E	D	A	T	E			43	Y	E	S		S				Y