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THE ROLE OF PROBIOTICS IN THE PREVENTION OF ANTIBIOTIC-ASSOCIATED DIARRHEA

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Diarrhea is a common complication of antibiotic therapy occurring within several days of starting therapy to weeks after the antibiotic has been discontinued. Any antibiotic can induce diarrhea but broad spectrum antibiotics such as ampicillin, amoxicillin, cephalosporins, and clindamycin are the major culprits.[1] Several mechanisms have been proposed for antibiotic-associated diarrhea (AAD). With the reduction in anaerobe concentration after antibiotic administration, carbohydrate metabolism is decreased resulting in an osmotic diarrhea. Additionally, some antibiotics such as erythromycin and clavulanate have prokinetic effects. Lastly, antibiotics create an environment in the GI tract that allows pathogenic bacteria to overpopulate.[1] *Clostridium difficile* (*C. difficile*), a gram positive, spore-forming anaerobe is the most predominant infectious agent isolated accounting for 15% to 25% of all cases of antibiotic-associated diarrhea.[2] Symptoms of *Clostridium difficile*-associated diarrhea (CDAD) range from nuisance diarrhea to life threatening pseudomembranous colitis or toxic megacolon.

Antibiotics are the key predisposing players in the pathogenesis of CDAD. The normal GI flora is eradicated by antibiotics leading to an imbalance in the enteric ecosystem and loss of protection by the normal microflora. This unstable environment allows colonization of pathogenic microbes such as *C. difficile*. *C. difficile* exerts its injurious actions with the production of two toxins, enterotoxin A and cytotoxin B. Enterotoxin A is responsible for activating and recruiting inflammatory mediators, while cytotoxin B is responsible for cytotoxic effects.[3]

Over the past several years, the incidence of CDAD has risen dramatically.[4] Both the number of CDAD hospitalizations and CDAD-related age-adjusted case-fatality have doubled in the US as reported by the National Inpatient Sample data from 2000 to 2005 (Table 1). The number of deaths associated with CDAD exceeds that of all other intestinal infections combined.[5] Health care expenditures for CDAD have escalated to over 1 billion dollars/year in the US.[2] With the emergence of the hypervirulent strain, NAP1/BI/027, CDAD is increasingly displaying a more complex clinical course and higher mortality rate.[6] The NAP1/BI/027 strain accounts for a binary toxin that produces 16 times more enterotoxin A and 23 times more cytotoxin B than control strains.[7]

Current treatment options for CDAD include metronidazole for mild to moderate cases and vancomycin for more severe cases. Unfortunately, there have been reports of decreased response rates and increased recurrence rates with metronidazole treatment.[8]Approximately 20% of patients will have re-

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Table 1. Adult hospitalizations with *C. difficile*, by age group, in the United States, 2000-2005[5]

Hospitalizations	2000	2001	2002	2003	2004	2005
18-44 y	14,738	15,001	18,747	19,393	22,168	25,662
45-64 y	28,280	29,527	39,421	43,290	50,898	61,757
65-84 y	69,018	74,010	98,148	105,404	122,875	147,675
≥ 85 y	22,325	25,194	31,899	35,363	43,341	56,209
All adults	134,361	143,732	188,215	203,450	239,282	291,303

Adapted from Zilberberg[5]

currence of CDAD despite initial treatment.[9] These patients are more prone to have repeated episodes of CDAD that can last up to 4 years. There is a growing interest in the potential benefits of alternative therapies, such as probiotics, to prevent further spread of this clinical problem.

Probiotics are live microorganisms that bestow a health benefit to the host when provided in adequate amounts.[10] The word probiotic translates as "for life."[11] The rationale for using probiotics in AAD and CDAD is to restore normal GI microflora. Probiotics can be classified into three main groups: *Lactobacilli*, *Bifidobacteria*, and miscellaneous as shown in Table 2. *Saccharomyces boulardii* and the *Lactobacilli* species have been the most extensively studied in AAD and CDAD.[2]

MECHANISM OF ACTION

The precise mechanisms of action of probiotics remain unclear. Current evidence indicates that each probiotic strain is unique and the effects vary from one strain to another. Even if the strain belongs to the same species, the beneficial effect characterized by one strain cannot be applied to another strain.[12] Probiotics, in general, exert antimicrobial actions by decreasing luminal pH (*Lactobacilli* and *bifidobacteria* belong to a group of bacteria that produces lactic acid), secreting antimicrobial peptides, inhibiting bacterial invasion, and blocking bacterial adhesion to epithelial cells. They also augment barrier integrity by increasing mucus production.[13] In addition to these mechanisms, probiotics are also theorized to boost immune function by stimulating local macrophages to amplify antigen presentation to B lymphocytes and enhancing secretory IgA production both locally and systemically.[2] Probiotics may also play a role in modifying cytokine profiles.[2]

Sacchromyces boulardii

Not all probiotics are bacteria. *S. boulardii* is a non-pathogenic yeast derived from lychee and mangosteen fruits. It was first discovered in 1939 by a French scientist named Henri Boulard who noticed the natives of Southeast Asia chewing on the skins of these fruits to control cholera-induced diarrhea.[14] *S. boulardii* is commercially available in the US under

Table 2. Microorganisms that are considered to be probiotics[11]

***Lactobacillus* spp.**	***Bifidobacterium* spp.**	**Others**
L. acidophilus	*B. bifidum*	*Saccharomyces boulardii*
L. plantarum	*B. breve*	*Escherichia coli Nissle*
L. rhamnosus	*B. infantis*	*Streptococcus thermophilusa*
L. gasseri	*B. longum*	*Enterococcus faeciumb*
L. fermentum	*B. adolescentis*	
L. casei	*B. lactis*	
L. crispatus		
L. delbrueckii		
L. johnsonii		
L. paracasei		
L. reuteri		

Table 3. Summary of six randomized placebo-controlled trials of probiotics for prevention of RCDAD[4]

Source	N	Patient population	Probiotic	Antibiotic	Results	Comments
McFarland et al[16]	124	Initial CDAD Recurrent CDAD	*S. boulardii* 1 g daily	Vancomycin or metronidazole	26% in the probiotic group had RCDD compared to 44.8% in the placebo group	p = 0.04 Dose, duration, and choice of antibiotic were not controlled
Surawicz et al[17]	168	Recurrent CDAD	*S. boulardii* 1 g daily	High dose vancomycin or low dose vancomycin or metronidazole	16.7% in the probiotic group had RCDD compared to 50% in the placebo group	p = 0.05 Decreased recurrence in high dose vancomycin treated patients only (n=32)
Pochapin et al[20]	25	Initial CDAD Recurrent CDAD	*L. rhamnosus* GG	Vancomycin or metronidazole	36.4% in the probiotic group had RCDD compared to 35.7% in the placebo group	No significant difference
Wullt et al[21]	20	Recurrent CDAD	*L. plantarum* 299v 5×10^{10} CFU	Metronidazole	36% in the probiotic group had RCDD compared to 67% in the placebo group	Not clinically significant; Study underpowered
Lawrence et al[22]	15	Recurrent CDAD	*L. rhamnosus* GG	Varied (chosen by primary clinician)	37.5% in the probiotic group had RCDD compared to 14.3% in the placebo group	Not clinically significant; Study underpowered
Plummer et al[19]	138	Inpatient elderly receiving antibiotics for any cause	*L. acidophilus* and *Bifidobacterium Bifidum*	Varied (chosen by primary clinician)	CDD developed in 2.9% in the probiotic group compared with 7.25% in the placebo group	Study underpowered to detect a clinically significant difference

CDAD = *Clostridium difficile*-associated diarrhea; RCDAD = Recurrent *Clostridium difficile*-associated diarrhea.

the trade name, Florastor®. Clinical trials have shown *S. boulardii* to be advantageous in AAD. *S. boulardii* was significantly better than placebo in preventing AAD in several clinical trials. Recommendations regarding *S. boulardii* use were developed based on evidence presented at the Advances in Clinical Use of Probiotics Workshop held at Yale University. *S. boulardii* received a grade "A" recommendation in prevention of AAD in outpatient and inpatient adults. An ''A'' recommendation is based on strong, positive, well-conducted, controlled studies in the primary literature.[15]

There is currently no evidence to support prophylactic probiotic use for prevention of an initial episode of CDAD. Many of the clinical trials for AAD do not identify the cause of diarrhea so it is very difficult to determine how much diarrhea is attributable to *C. difficile* and how effectively probiotics reduce the occurrence of CDAD. Most of the clinical trials failed to draw cultures, *C. difficile* toxin assays, and viral identification studies.[14] Some trials have analyzed CDAD as a secondary outcome but the differences were insignificant due to the small amount of individuals who had *C. difficile* infection.

However, there is some evidence to support *S. boulardii* in decreasing the incidence of recurrent CDAD (RCDAD). The beneficial effects of *S. boulardii* in RCDAD may be attributed to its ability to

Table 4. Selected Commercially Available Probiotic Products[15]

Product	Probiotic Species	Dose	Cost
Culturelle®	*Lactobacillus rhamnosus* GG	1-2 capsules per day (35 billion microorganisms per capsule)	$20.99 for 30 capsules. Price obtained from Walgreens.
VSL#3®	*Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*,*Lactobacillus casei*, *Lactobacillus bulgaricus*, *Streptococcus thermophilu*	0.5-8 packets per day (450 billion live lactic acid bacteria per packet)	$79.50 for 30 packets. Price obtained from naturespharmaceuticals.com
Activia yogurt	*Bifidus regularis*	# of bacteria not stated	$3.50 for a pack of 4. Price obtained from Publix.
Florastor®	*Saccharomyces boulardii*	1 capsule BID (5 billion live cells per 250 mg capsule)	$37.50 for 50 capsules. Price obtained from newtimrx.com
Acidophilus Pearls®	*Lactobacillus acidophilus*	# of bacteria not stated	$12.99 for 30 pearls. Price obtained from GNC.com
GI48®	*Lactobacillus fermentum*	1 capsule every other day (up to 2 billion CFU per 100 mg capsule)	$32.00 for 30 capsules. Price obtained from evitamins.com

secrete a protease that neutralizes *C. difficile* toxins A and B. McFarland et al. conducted a multi-center, double-blind, randomized, placebo-controlled study in 124 adult patients with active or recurrent *C. difficile* disease.[16] The study included 64 patients with an initial episode of CDAD and 60 patients with at least 1 previous episode of CDAD. All patients received metronidazole, oral vancomycin, or both antibiotics along with a 1 month supply of *S. boulardii* (1gm/day) or placebo. Patients were followed-up in 1 month. Patients who were given *S. boulardii* had a significantly lower relative risk of *C. difficile* diarrhea when compared with those given placebo (RR, 0.43; 95% CI 0.20–0.97) as concluded by multivariate analysis. *S. boulardii* was not shown to be effective in patients with an initial episode of CDAD but was effective in patients with a prior history of CDAD. Patients with a prior history of CDAD who were started on *S. boulardii* had a significantly decreased recurrence of CDAD, from 64.7% to 34.6% (P=0.04).

A follow-up study was conducted to substantiate the results produced in the Mcfarland study. Surawicz et al. analyzed the efficacy of *S. boulardii* in combination with antibiotics for the prevention of recurrent CDAD in a double blind, placebo-controlled trial.[17] Patients were randomized to receive 10 days of high dose vancomycin, low dose vancomycin or metronidazole along with placebo or *S. boulardii* at a dose of 1 g/day (two 250-mg capsules b.i.d.) for 4 weeks. Standardized culture methods were used to test for presence of *C. difficile* and ELISA kits were used to detect toxin A. Standard cytopathic cell cultures were used to detect toxin B. Results showed that the frequency of recurrence of CDAD was significantly reduced when *S. boulardii was* combined with high-dose vancomycin, but had no effect in combination with low-dose vancomycin or metronidazole. In the high dose vancomycin and *S. boulardii* group, 16.7% of patients had a recurrence of CDAD compared to 50% of patients in the group receiving high-dose vancomycin and placebo (P = 0.5). In preventing further recurrences of

CDAD, *S. boulardii* and vancomycin was 67% more effective than treatment with vancomycin alone.

Lactobacillus rhamnosus GG (LGG)

LGG, marketed as Culturelle®, comes from the normal human microflora. LGG has been extensively studied for the prevention of AAD. Most studies have shown efficacy in children for the prevention and treatment of AAD. However, in adults, LGG has not demonstrated any beneficial effects. Some authors criticize that the LGG dose used in the clinical trials were too low. Thomas et al. conducted a randomized, placebo controlled study with LGG at a dose of 20 x 10^9CFU daily in 302 hospitalized adults and concluded that LGG was no more effective than placebo in preventing AAD.[18] There is insufficient data to support using LGG for prevention of CDAD. Almost all of the data on LGG and CDAD are derived from case reports.

However, there has been a study conducted on the combination of *Lactobacillus* and *Bifidobacterium*. In a double-blind, placebo controlled study, Plummer and colleagues analyzed the effect of probiotics on the incidence of CDAD in hospitalized elderly patients placed on antibiotic therapy.[19] One-hundred and fifty patients receiving antibiotic therapy were randomized to receive either *Lactobacillus* and *Bifidobacterium* or placebo for 20 days. Only 138 completed the study, 69 with the combination of antibiotics and probiotics and 69 with only antibiotics. In the probiotic group, the incidence of samples positive for *C. difficile*-associated toxins was 2.9% compared with 7.25% in the placebo group. There was not enough power in the study to detect a clinically significant difference.

Dosing

Table 4 indicates the recommended dosing on the package label for maintenance of normal GI health. There are no established dosing recommendations for probiotics in AAD and CDAD but Katz et al. has provided dosing guidelines for LGG and *S. boulardii* based on clinical trial data (Table 5).

Quality Control of Probiotics

Probiotics are considered dietary supplements and therefore not strictly regulated by the FDA. The manufacturer determines much of the efficacy and safety of probiotics. Some probiotic products are inactivated or nonviable after being manufactured. The number of viable bacteria at the time of use determines the effectiveness of the probiotic.[5] Many of the products contain less bacteria than stated on the label. Some contain unknown organisms or other types of contaminates.[19] Universal standard testing procedures must be implemented to guarantee the quality and safety of the probiotic.

Safety

Probiotics are generally considered safe and are well tolerated. Side effects include flatulence or changes in bowel habit.[23] Cases of bacteremia and fungemia have been documented but are rare and seen most often in the severely ill or immunocom-

Table 5. Guidelines for Probiotic use in Antibiotic-associated Diarrhea and *C. difficile* Diarrhea[9]

Prevention of antibiotic-associated diarrhea
Adults: *S. boulardii* 1 g daily
Strength of evidence: good
Children: LGG 1-2 x 10^{10} CFU daily
Strength of evidence: good
Avoid in immunocompromised patients
Prevention of *C. difficile* diarrhea
No evidence to support efficacy in primary prevention of *C. difficile*
Recurrent *C. difficile* diarrhea
Adults: *S. boulardii* 1 g daily
Strenth of evidence: moderate
Children: not enough data to make a recommendation
Avoid in immunocompromised patients

Adapted from Katz[9]

promised. There have been reports of LGG–associated bacteremia in children with short gut syndrome and in children who have central venous catheters. Endocarditis in an elderly patient with mitral regurgitation after a dental extraction and liver abscess in an elderly diabetic patient have also been reported with LGG.[24] In addition, there have been reports of isolated candidemia with *S. boulardii*.[25]

SUMMARY

Lactobacillus GG and *S. boulardii* have shown positive results in preventing AAD. As for other probiotics, little evidence exists to conclude whether they are efficacious in preventing AAD. With the increasing outbreaks of CDAD, more clinical trials are needed to evaluate probiotics for the primary prevention of CDAD. There is scarce evidence to support routine clinical use of probiotics for RCDAD. *S. boulardii* may have a positive impact in RCDAD; however, better designed, well executed clinical trials need to be conducted to validate proof of efficacy.

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