Residency Review

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The Evidence is Out: Case Open on Probiotics

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The body's microbiome, a community of organisms in the gut that naturally balances itself with "good" and "bad" bacteria, can be disturbed with antibiotic use. Antibiotics, although intended for infection treatment, can cause an imbalance in the microbiome as pathogen overgrowth can occur. This unintended imbalance can last for several months and can paradoxically lead to infections.[1] With microbiome disruption, there is an increased risk of infection caused by Candida fungi, such as diaper rash, vaginal yeast infections, and thrush in the mouth and throat. Patients with serious conditions or those with weakened immune systems are at an increased risk of severe infections and death as a result of Candida fungi.

Furthermore, in comparison to those who have not recently taken antibiotics, people who have taken antibiotics in the past month are more at risk of bacteria-induced foodborne illnesses and diarrhea. Antibiotic-associated diarrhea (AAD), which is associated with several pathogens including *Clostridium difficile (C.diff)*, *Clostridium perfringens*, *Klebsiella oxytoca*, and *Staphylococcus aureus*, occurs in 5-35% of patients taking antibiotics. The extent of the AAD varies depending on the specific type of antibiotic prescribed, the health of the patient, and the exposure to pathogens.[2]

People are 7-10 times more likely to develop a bacterial infection caused by *C.diff* after taking antibiotics than those who have not recently taken antibiotics. *C.diff* infections cause nearly half a million illnesses and more than 15,000 deaths across the globe annually; *C.diff* infections inflict a massive $6.3 billion cost to the U.S. healthcare system annually.[3] With an increased risk of infections and an associated increase in healthcare costs with antibiotic use, recent research has focused on preventative measures. One potentially promising lead is with probiotics.

Probiotics are living microorganisms that may prevent and treat AAD through normalization of the unbalanced gastrointestinal flora.[4] These living microorganisms may enhance intestinal flora via various proposed mechanisms including immunity stimulation, nutrient competition, pathogen adherence to epithelium and mucosa inhibition, epithelial invasion inhibition, and antimicrobial substances production.[5] Numerous probiotic species have been studied, commonly including the *Lactobacillus* genus, *Bifidobacterium* genus, and *Saccharomyces* genus.

Recently, new 2017 *C.diff* guidelines put forth from the Infectious Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) addressed the role of probiotics in primary prevention of *C.diff* infections. Due to insufficient data, the administration of probiotics is not recommended for primary prevention at this time.[6] The *C.diff* guidelines did not issue a concrete recommendation for probiotics as prevention due to varied results in probiotic research in terms of probiotic effectiveness and the strength of those studies.

Blaabjerg et al conducted a systematic review to assess the benefits and harms of probiotics as prevention of AAD in an outpatient setting.[4] Seventeen randomized controlled trials with 3631 participants were included in this systematic review. The strains of probiotics studied were *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, and *Saccharomyces boulardii*. AAD was present in 8.0% of the probiotic group compared to 17.7% in the control group. Interestingly, the use of more than one probiotic strain was not more efficacious than one strain alone in the prevention of AAD. The results from this systematic review suggest that probiotic use may be beneficial in the prevention of AAD in an outpatient setting. However, despite the significant results, the overall quality of the included studies was poor.

There is data to suggest that probiotic use may decrease the duration and frequency of loose stools in children with persistent diarrhea in addition to reducing the length of hospital stay in this patient population.[7] Each year, 10.2 million children under the age of five die each year globally; about 20% of these deaths are a result of persistent diarrhea lasting longer than two weeks. As part of a Cochrane review, Hitzeman and colleagues analyzed four randomized controlled trials comparing probiotic agents to placebo in children with persistent diarrhea that was thought to be infectious.[8] Of these four trials, one was considered to be of high quality. This particular trial demonstrated that the duration of diarrheal illness in hospitalized children was reduced by four days in the probiotic group treated with *Lactobacillus rhamnosus* and the average hospital stay was reduced by eight days. Of the 235 children included in the trial, not one child reported adverse effects.[9]

Probiotic use in people with irritable bowel syndrome (IBS) also seems promising, both as prevention and treatment of symptoms. IBS often presents with intermittent abdominal pain accompanied by diarrhea, constipation, or alternating episodes of both.[10] Evidence suggests that bacterial imbalances in the body's microbiome may lead to IBS diagnosis and subsequent, recurrent exacerbations. There have been several studies, with varying reliability, that have demonstrated potential benefit with probiotics for this patient population.[11,12,13] *Bifidobacterium infantis* was shown to be superior when compared to placebo in relieving abdominal discomfort, constipation, distension, and bloating.[14]

As with any product on the market for consumer use, the safety of probiotic products is a major consideration. In the meta-analysis conducted by Blaabjerg et al, the researchers further analyzed ten trials reporting adverse events with probiotic use.[4] The review demonstrated that there was no statistically significant difference in the incidence of adverse events between the intervention and control group, suggesting that the use of probiotics is safe for patients without compromised immune systems. In a review conducted by Hempel et al, researchers analyzed eighty-two studies to evaluate relative risk of AAD among patients taking antibiotics and probiotics compared to those who were taking antibiotics alone; twenty-three of the probiotic studies discussed adverse outcomes and none was found.[15]

However, probiotics must be used with caution. Due to their bacterial nature, probiotics may not be appropriate for patients with compromised immune systems.[16] In addition to immunocompromised patients, other patient populations might be at risk by taking probiotics. In 2008, a study published in *The Lancet* demonstrated that adult patients with acute pancreatitis who received probiotics had an increased mortality over those who did not.[17]

Furthermore, a study based in Germany showed an increase in wheezing bronchitis in infants born to women who were treated with *Lactobacillus* during the perinatal period of their pregnancies with the intention of preventing atopic dermatitis in infants.[18]

Additionally, there are concerns over probiotic product quality. According to the National Center for Complementary and Integrative Health (NCCIH), a branch of the National Institute of Health (NIH), some probiotic products have been found to contain fewer numbers of live microorganisms or different bacterial strains than those labeled on the product. The U.S. Food and Drug Administration (FDA) has not approved any probiotics for preventing or treating any health problem, including AAD.[19]

The use of probiotics for diarrhea treatment and prevention in adults and children has not been thoroughly studied to date. While there is evidence to suggest benefits from probiotics usage, further research is needed to ascertain more specifically their potential benefits and drawbacks. Limited evidence demonstrates a benefit in patients with IBS.

Clinical Guide to Select Probiotic Products Available in the U.S. – Adult Health[20]
Adapted from AEProbio 2018 edition

Brand Name	Probiotic Strain	Dosage Form	CFU/Dose	Number of doses/day	Indication (Level of Evidence)
Activia®	B. (animalis) lactis	Ferm. Milk lq	1b/serving	1-3 servings	C - (I) IBS (I)
Align®	B. longum	Capsules Chewables	1b/capsule	1 capsule	IBS (I)
Bio-K+®	L. acidophilus CL L. casei L. rhamnosus	Ferm, soy lq Capsule Ferm. milk lq. Ferm. rice lq. Capsule	50b/tub 25b/capsule 50b/tub 30b/capsule 50b/tub 12.5b/capsule 50b/capsule	½ -1 tub 1-2 capsules ½ -1 tub 1-2 capsules ½ -1 tub 1-2 capsules 1-2 capsules	AAD (I) CDAD (I)
BioGaia® ProTectis®	L. reuteri	Drops Chew. tabs	100m/5drops 100m/tab	5 drops 1 tab	AAD (II) C (I) ID (II)
Culturelle®	L. rhamnosus GG	Capsule Chew. tab	10b/capsule 20b/capsule 10b/tab	1 capsule 1 capsule 1 tab	AAD (I)
DanActive / Actimel®	L. casei sp. Paracasei	Ferm. milk lq.	10b/serving	1-2 servings	AAD (I) ID (II)
Florastor®	Saccharomyces boulardii lyo	Sachet Capsule	5b/sachet 5b/capsule	1-2 sachets 1-2 capsules	AAD (I) CDAD (I) IBD-UC (III) TD (I)
GoodBelly®	L. plantarum	Capsule	10b/capsule	1-2 capsule	AAD (III) CDAD (III) IBS (I)
Ideal Bowel Support®	L. plantarum	Capsule	10b/cap	1-2 capsules	AAD (III) CDAD (III) IBS (I)
Mutaflor®	Echerichia coli Nissle	Capsule	2.5-25b/capsule	1-2 capsules	IBD-UC (I)
NatureMade® Digestive Probiotic Daily Balance	L. plantarum	Capsule	10b/capsule	1-2 capsule	AAD (III) CDAD (III) IBS (I)
Ultra Probiotic Complex by GNC	L. acidophilus L. acidophilus B. bifidum B. lactis	Capsule Packet	25b/ 50b/ 75b per capsule 25b/packet	1-2 capsule 1-2 packets	CDAD (II) IBS (II)
UltraFlora® Intensive Care	L. plantarum	Capsule	10b/capsule	1-2 capsules	AAD (III) CDAD (III) IBS (I)
Visbiome™	L. acidophilus L. paracasei L. delbrueckii subsp. bulgaricus L. plantarum B. longum B. infantis B. breve S. thermophilus	Capsule Sachet	112.5b/capsule 450b/sachet	1-4 capsule 1-2 sachets	C (II) IBD-P (I) IBD-UC (I)

AAD: Antibiotic-associated diarrhea; B.: Bifidobacterium; b: Billion; C: Constipation; CDAD: Clostridium difficile associated diarrhea; Chew: Chewable; Ferm: Fermented; IBD-UC – Irritable bowel disease ulcerative colitis; IBD-P - Inflammatory bowel disease – Pouchitis; IBS: Irritable bowel syndrome; ID: Infectious diarrhea; L.: Lactobacillus; lq: Liquid; m: Million; Oz: Ounce; Subsp.: Subspecies; Tabs: Tablets; TD: Traveler's diarrhea

(I): Evidence obtained from at least one properly designed randomized trial

(II): Evidence obtained from well-designed controlled trials without randomization Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group. Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence

(III) Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

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Gut-wrenching bacteria: The good, the bad, and C. diff

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Clostridiodides difficile, previously termed *Clostridium difficile*, is a common cause of infectious diarrhea and one of the most prevalent causes of health-care-associated infections in the United States.[1] In February 2018, the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) released updated guidelines for *C. difficile* infections (CDI). Though some recommendations remain consistent with the 2010 IDSA/SHEA CDI guideline, there were many significant changes addressed in the update.[2]

Key changes include the following:

Removal of metronidazole as first-line therapy in adults

One of the most significant changes includes the removal of metronidazole as a first-line treatment for CDI. Metronidazole was previously described as "the drug of choice for the initial episode of mild-to-moderate CDI." The recent update suggests a 10-day course of either oral vancomycin (125 mg four times a day) or fidaxomicin (200 mg twice daily) should be used over metronidazole (in non-resource poor environments) for an initial episode. This new recommendation is based on several clinical trials that demonstrate superior cure rates and less frequent recurrences following vancomycin therapy compared with metronidazole.

The first study, a prospective, randomized, double-blind, placebo-controlled trial, clinical cure rates were assessed in 150 patients. Patients were stratified to two groups, mild *C. difficile*–associated diarrhea (CDAD) and severe CDAD, and then randomly assigned to receive oral vancomycin (125 mg four times a day) or metronidazole (250 mg four times a day) for 10 days. When stratified by disease severity, there was no significant difference in cure rates among patients with mild CDAD (vancomycin 98%; metronidazole 90%; P=0.36). However, among the patients with severe disease, treatment resulted in clinical cure in 76% of metronidazole treated patients and in 97% of vancomycin treated patients (P =0.02). The overall cure rate was superior for patients given oral vancomycin (97%) compared to metronidazole (84%; P <0.006).[3] The second study was a pooled analysis of two multinational randomized trials conducted to compare the efficacy of tolevamer, a nonantibiotic toxin-binding polymer, with vancomycin and metronidazole. A total of 1118 patients were randomly assigned, in a 2:1:1 ratio, to oral tolevamer for 14 days, oral vancomycin (125 mg every 6 hours) for 10 days, or oral metronidazole (375 mg every 6 hours) for 10 days. Tolevamer was inferior to both metronidazole and vancomycin (P <0.001), and metronidazole was inferior to vancomycin (P =0.02; 44.2%, 72.7%, and 81.1%, respectively). Vancomycin was not found to be superior to metronidazole in patients with severe CDI (78.5% vs. 66.3%, respectively; P =0.059).[4] Combined, these two studies demonstrated that metronidazole was inferior to oral vancomycin for clinical cure in patients with CDI (P =0.002) and for resolution of diarrhea at end of treatment without CDI recurrence 21-30 days after treatment (P =0.002).[3, 4]

Fidaxomicin was FDA-approved in 2011, making it a newly-recommended agent in the 2018 update. Clinical trials have shown fidaxomicin may be associated with even fewer CDI recurrences, likely due to its narrow spectrum of activity. Two randomized, controlled trials compared oral vancomycin to oral fidaxomicin for the treatment of CDI. The primary endpoint, resolution of diarrhea, was similar between groups (fidaxomicin 88%; vancomycin 86%; RR 1.0; 95% CI 0.98–1.1). Sustained clinical response, defined as resolution of diarrhea at end of treatment without recurrence 25 days after treatment, was superior for fidaxomicin compared to vancomycin (71% vs. 57%, respectively; RR 1.2; 95% CI 1.1-1.4).[5, 6] Further, a post hoc analysis investigated the composite endpoint of persistent diarrhea, CDI recurrence, or death over 40 days. Fidaxomicin reduced the incidence of the composite endpoint by 40% compared to vancomycin (95% CI, 26-51%; P <0.001), primarily due to decreased recurrence in the fidaxomicin arm.[7] Within the new update, fidaxomicin is recommended as a first-line option similar to oral vancomycin. The decision to choose one over another should be based on patient specific factors.

Finally, in the previous guideline, CDI cases associated with hypotension or shock, ileus, or megacolon were described as severe, complicated. In the update, they are termed fulminant CDI. Intravenous metronidazole remains an adjunctive agent in these cases, particularly in the presence of an ileus.

Revised treatment strategies for recurrent CDI

The 2018 update also includes new recommendations for the treatment of recurrent CDI, which occurs in approximately 25% of patients. Recommendations are dependent on the treatment strategy used in the initial episode. If metronidazole was used, a 10-day vancomycin course can be initiated for the first recurrence. However, if a 10-day course of vancomycin was initially used, the recurrence should be treated with either oral vancomycin as a tapered and pulsed regimen or with a 10-day course of fidaxomicin. If a 10-day fidaxomicin course was initially used, the first-recurrence should be treated with a tapered and pulsed regimen of oral vancomycin.

Second and subsequent recurrences can be treated with oral vancomycin as a tapered and pulsed regimen, vancomycin followed by rifaximin, or fidaxomicin. The recommendations for antimicrobials in recurrences are weaker due to the limited data available. However, the panel now recommends fecal microbiota transplantation (FMT) for patients with multiple recurrences who have failed appropriate antibiotic treatments. This is considered a strong recommendation based on a moderate quality of evidence, as several clinical trials that have shown efficacy and favorable short-term safety of FMT. Specifically, a prospective, randomized clinical trial directly compared FMT and vancomycin in 43 patients with ≥2 recurrent episodes of CDI. Patients who underwent a fecal microbiota transplant were significantly more likely to achieve a sustained resolution of diarrhea after the first fecal infusion compared to patients treated with vancomycin (81% vs. 27%, respectively; P <0.001).[8]

Consideration of prophylaxis against CDI

Previous guidelines do not address prophylaxis against CDI. The 2018 guideline acknowledges that patients who need to receive other antibiotics during or shortly after the end of CDI therapy are at higher risk for recurrence. While guidelines do not currently give a recommendation due to lack of data, they do state the following: "if the decision is to institute CDI prevention agents, it may be prudent to administer low doses of vancomycin or fidaxomicin (eg, 125 mg or 200 mg, respectively, once daily) while systemic antibiotics are administered." The updated guideline also recognizes that probiotics have shown potential in preventing CDI recurrence. A variety of probiotics have been evaluated, though *Saccharomyces boulardii* and *Lactobacillus spp*. have been most commonly used in clinical trials. One systematic review and meta-analysis analyzed data from 19 randomized clinical trials of hospitalized patients receiving antibiotics in addition probiotics to prevent CDI. Authors suggested that probiotics were significantly more effective when given closer to the first dose of antibiotics.[9] However, due to the lack of significant and reproducible efficacy in clinical trials, the use of probiotics is not recommended by IDSA guidelines at this time.

Recommendations for pediatric patients

Previous guidelines do not address CDI in the pediatric population. Briefly, the update recommends either metronidazole or vancomycin is recommended for the treatment of children with an initial episode or first recurrence of nonsevere CDI. Vancomycin is preferred over metronidazole for both severe cases and in subsequent recurrences.

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