

Probiotics and Antibiotic-Associated Diarrhea

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SUMMARY

Antibiotics are among the most widely prescribed medications. Along with their clearly established benefits in the treatment of infectious disease, antibiotics have many toxicities. These include disruption of the normal gastrointestinal microflora. A common consequence of antibiotic therapy is antibiotic-associated diarrhea, which appears to be related to the suppression or elimination of healthy gut microorganisms. This is associated with a reduction in colonic short-chain fatty acid concentrations and an overgrowth of pathogenic organisms including *Clostridium difficile*. Ingestion of healthful microorganisms known as probiotics is documented to reduce the risk of antibiotic-associated diarrhea and to be an effective treatment for recurrent *Clostridium difficile*-associated diarrhea. Clinical studies have shown that the most effective probiotics for antibiotic-associated diarrhea are *Saccharomyces boulardii*, *Lactobacillus rhamnosus* strains, and combinations of probiotics that usually contain *Lactobacillus* and *Bifidobacterium* species. Research suggests that probiotics may be useful in combating antibiotic resistance among pathogens and may even be safe alternatives to antibiotics for select conditions.

ANTIBIOTICS & BACTERIA – The Good, the Bad, and the Resistant

It should come as no surprise that antibiotics have many adverse effects. The very term “antibiotic” derives from Greek words literally meaning “against life.”¹ Vuillemin, a student of Pasteur, coined the word “antibiosis” in 1889 for a process by which life is used to destroy life.² In the 1940s, Waksman, an agricultural microbiologist, advanced the term antibiotic to mean an antibacterial drug derived from living organisms.¹ Antibiotics kill or inhibit the growth of bacteria. Antibiotics rapidly revolutionized medicine. Infectious diseases that had plagued humankind for millennia from syphilis and tuberculosis to common skin and urinary tract infections became imminently treatable. Throughout the world, antibiotics are among the most commonly and frequently prescribed medications, especially to children and the elderly.³ However, the promises antibiotics held for the control or even elimination of infectious diseases have come up empty due to the rapid emergence of antibiotic resistance and antibiotic toxicities.

Bacterial resistance to antibiotics was recognized almost as soon as they were introduced.^{4,5} As newer and broader spectrum antibiotics are introduced, resistance rapidly and relentlessly follows. The specter of multi-drug resistant pathogens now haunts healthcare institutions. The “anti-life” properties of antibiotics were quickly realized not to be restricted to bacteria. Many antibiotics were distinguished as so toxic that only topical use could be tolerated.⁶ Others were found to have significant adverse effects such as kidney or neurological toxicity.^{7,8} Doctors were slower to recognize that in addition to potential direct toxicity to patients, antibiotics indiscriminately kill normal, healthful bacteria along with pathogens.⁹ Among the normal microflora reduced or eliminated by antibiotics are the essential *Lactobacillus* and *Bifidobacterium* species so crucial for gastrointestinal, genitourinary, and immune system health. The clinical consequences of disrupting

the normal microflora include increased colonization and infection by pathogenic microbes, augmented risk of the emergence and spread of antibiotic resistant bacteria, and enhanced transmission of resistance factors among microorganisms.¹⁰

PROBIOTICS: Microorganisms for Life

Probiotics are living microorganisms that beneficially influence the health of humans when ingested in adequate numbers.¹¹ Probiotic literally means “for life.” The Nobel laureate Metchnikoff is credited with first recognizing the health benefits of probiotics in 1907 suggesting that the consumption of living lactic acid bacteria in fermented foods may promote health and longevity by favorably modulating the gastrointestinal microflora.¹² Over the past century an expanding body of basic and clinical research supports the health benefits of probiotic consumption in a host of disorders including irritable bowel syndrome, inflammatory bowel disease, diarrhea, food allergies, lactose intolerance, urogenital infections, and atopic eczema.¹²⁻¹⁵ The best documented condition that may be prevented or treated with probiotics is antibiotic-associated diarrhea.^{16,17}

ANTIBIOTIC-ASSOCIATED DIARRHEA

Antibiotic-associated diarrhea (AAD) may be the most common adverse clinical effect of antibiotic-mediated disruption of the gastrointestinal microflora.¹⁸ The spectrum of AAD ranges from the nuisance of frequent loose stools to fulminate, life-threatening colitis. The incidence of AAD varies depending upon its definition, antibiotic(s) used, route of antibiotic administration, and the patient population. The medical literature reports that 5 to 39% of adults^{19,20} and 11 to 40% of children²¹⁻²³ will suffer from diarrhea when treated with antibiotics. The more stringent the definition, the lower the reported incidence. The onset of AAD can coincide with initiation of antibiotic therapy or may occur up to 2 months following the conclusion of treatment.¹⁸ Although any antibiotic may be associated with AAD, the highest risk is found with the use of clindamycin, cephalosporins, broad-spectrum penicillins, ampicillin, and amoxicillin.^{10,18} Antibiotics cause diarrhea primarily through two mechanisms: the first is by diminishing or eliminating bacterial species of the normal microflora impairing vital microbial functions such as provision of nutrient short-chain fatty acids to colonocytes and metabolism of bile acids;^{18,24} the second is by creating a niche for the overgrowth of intestinal pathogens including *Clostridium difficile*, *Clostridium perfringens* type A, *Candida albicans*, *Klebsiella oxytoca*, and *Staphylococcus aureus*.^{18,25-27}

CLOSTRIDIUM DIFFICILE-ASSOCIATED DIARRHEA

C. difficile is an anaerobic, gram-positive, spore-forming bacterium that may be found as part of the intestinal microflora, especially in children under the age of two.²⁸ Antibiotic-mediated disruption of the normal intestinal microflora creates a niche allowing the unopposed proliferation of *C. difficile*.¹⁸ It releases potent toxins, enterotoxin A

and cytotoxin B, that markedly inflame the intestinal mucosa causing diarrhea.²⁹ *C. difficile* is responsible for 26 to 50% of AAD and 95% of pseudomembranous colitis, an uncommon, but potentially lethal complication of antibiotics.^{18,19} When associated with pseudomembranous colitis, *C. difficile*-associated diarrhea (CDAD) mortality rates are as high as 38%.¹⁹ Antibiotics are the usual therapy for CDAD often resulting in further disruption of the bowel microbiota. After an initial bout of CDAD, between 20 and 25% of patients will relapse developing recurrent episodes of CDAD.³⁰ Relapses may occur over several years. The incidence of CDAD appears to be increasing, especially among people who have not been recently hospitalized.¹⁹ CDAD also is becoming more severe, less responsive to standard antibiotics, and much more prone to relapse following standard treatment.³¹

PROBIOTICS, ANTIBIOTIC-, & CLOSTRIDIUM DIFFICILE-ASSOCIATED DIARRHEA

Probiotics have been found to reduce the risk of AAD and CDAD. A recent meta-analysis of 25 randomized, controlled trials involving 2,810 patients found that probiotics significantly reduced the relative risk of AAD by 57%.¹⁷ Three types of probiotics were found to be most beneficial: *Saccharomyces boulardii*, *Lactobacillus rhamnosus* GG, and combined probiotics. A meta-analysis of 23 randomized, controlled trials conducted by the United Kingdom West Midlands Health Technology Assessment Group found that probiotics significantly reduced the relative risk of CDAD by 46%.³² *S. boulardii* has been consistently found to reduce the risk of new and recurrent cases of CDAD.³³⁻³⁷ *S. boulardii* has been found to be particularly beneficial for adults who have suffered more than one bout of recurrent CDAD.^{37,38}

Saccharomyces boulardii

S. boulardii is a non-pathogenic probiotic yeast that favorably sustains the normal bowel microecology, defends the gastrointestinal system against the toxic impact of antibiotics, and can prevent or reduce the harmful effects of pathogenic organisms.²⁹ It is a hardy, acid-resistant, temperature tolerant probiotic unaffected by antibiotics or other anti-bacterial agents. Genetically and functionally distinct from brewer's yeast (*S. cerevisiae*) and different from pathogenic *Candida* species, *S. boulardii* will not colonize the human gastrointestinal tract.

Clinical Studies of *S. boulardii* & Antibiotic-Associated Diarrhea

Randomized, placebo-controlled studies have repeatedly confirmed that *S. boulardii* effectively reduces the incidence of AAD. In a study of 180 hospitalized patients, 1 gram daily of *S. boulardii* taken during and up to 2 weeks after antibiotic therapy reduced the incidence of AAD by over 55% (9.5% vs. 21.8%).³⁶ Among the subgroup positive for *C. difficile*, *S. boulardii* reduced the incidence of diarrhea by almost 70% (9.4% vs. 31.0%) although the difference did not attain statistical significance (p=0.07). In a second study of 193 hospitalized patients receiving a β -lactam antibiotic, 1 gram (30 billion CFUs) daily of *S. boulardii* initiated within 72 hours of the onset of antibiotic treatment and continued for 3 days after antibiotic discontinuation reduced the occurrence of AAD by 51% (7.2% vs. 14.6%).³⁹ *S. boulardii* not only decreased the incidence of AAD, but also significantly shortened the duration of diarrhea when AAD occurred. In a third study of 151 non-critically ill, hospitalized adults, 250 mg twice daily (10 billion CFUs/d) of *S. boulardii* cut the incidence of AAD by nearly 85% (1.4% vs. 9%).⁴⁰ In 388 adults receiving antibiotics as outpatients, *S. boulardii* (200 mg or 4 billion CFUs/d) dropped the incidence of AAD by nearly 75% (4.5% vs. 17.5%)⁴¹ and by 80% in 246 antibiotic-treated children (500 mg or 10 billion CFUs/d; 3.4% vs. 17.3%).²³ Only one study involving 72 elderly hospitalized patients failed to find that *S. boulardii*

reduces the incidence of AAD.⁴² This negative finding is compromised by the low amount of *S. boulardii* (113 mg bid) administered to the patients and the short duration of treatment (6 to 7 days). A stratified meta-analysis of 6 high-quality, randomized clinical trials found that *S. boulardii* significantly lowered the risk of AAD by 63%.¹⁷

Saccharomyces boulardii & *Clostridium difficile*

S. boulardii possesses an array of anti-clostridial properties making it highly protective against *C. difficile* overgrowth and toxin-mediated disease.²⁹ It suppresses intestinal populations of pathogenic *Clostridium* species while simultaneously augmenting the numbers of healthful bifidobacteria in the colon. *S. boulardii* secretes an enzyme (54 kDa protease) that inhibits *C. difficile* enterotoxin A and cytotoxin B. This protease inhibits enterotoxin A binding to the intestinal brush border, reduces enterotoxin A-mediated intestinal water, and electrolyte secretion, and decreases intestinal permeability. The protease lyses enterotoxin A and disrupts the intestinal receptors for both *C. difficile* toxin inhibiting their binding. *S. boulardii* stimulates the gut's immune response against *C. difficile* enterotoxin A and inhibits *C. difficile* adherence to intestinal mucosal.

Clinical Studies of *Saccharomyces boulardii* & CDAD

A number of clinical trials have established that *S. boulardii* is effective for recurrent *C. difficile* colitis and diarrhea. In an open label trial involving 13 patients with multiple bouts of *C. difficile* pseudomembranous colitis, 1 gram (20 billion CFUs) per day of *S. boulardii* for 30 days together with vancomycin for 10 days prevented further relapses in 11 patients.⁴³ A multicenter, prospective, placebo-controlled study assessed the efficacy of *S. boulardii* for the prevention of additional relapses in patients with active CDAD treated with either vancomycin or metronidazole.³⁸ In people suffering at least 1 relapse of CDAD, the administration of 1 gram (20 billion CFUs) per day over 4 weeks significantly reduced the incidence of recurrent CDAD by 47% (34.6% vs. 64.7% for placebo). In another placebo-controlled study of 168 patients with intractable, recurrent CDAD, *S. boulardii* (1 g or 20 billion CFUs/d x 4 wks) combined with high dose vancomycin significantly decreased episodes of recurrent CDAD by 67% (16.7% vs. 50%).³⁷ *C. difficile* overgrowth in children and infants can lead to an acute enteritis or a chronic enterocolopathy.²⁹ In an open label trial in 19 children and infants with symptomatic toxigenic *C. difficile* intestinal overgrowth, *S. boulardii* (500-1000 mg or 10-20 billion CFUs/d x 15 days) rapidly resolved symptoms in 18 children and led to the quick disappearance of cytotoxin B from the stool in 16 children.⁴⁴

Lactobacillus rhamnosus

L. rhamnosus is a transient *Lactobacillus* that colonizes the small intestines when regularly consumed.⁴⁵ Possibly the most extensively clinically studied of all probiotics,⁴⁶ *L. rhamnosus* was once classified as *L. casei* and then as a subspecies of *L. acidophilus*, important information to consider when reviewing the medical literature.^{47,48} *Lactobacillus* species antagonize of an array of microbial pathogens, enhance innate and acquired immunity, and inhibit production of inflammatory mediators.^{49,50} Through the production of lactic and acetic acids, hydrogen peroxide, and antimicrobial substances, lactobacilli contribute to the maintenance of colonization resistance to pathogens. Lactobacilli enhance re-establishment of the normal microflora following disruption by antibiotics or other factors, induce production of enzymes that degrade pathogenic toxins, block pathogens from attaching to gastrointestinal mucosal sites, and compete with pathogens for nutrients and microecological niches.⁴⁹ *L. rhamnosus* decreases T cell proliferation, induces CD4⁺ (helper) T cell hyporesponsiveness by regulation of dendritic cell function,⁵¹ increases phagocytic activity in peripheral blood polymorphonuclear

cells and killing activity in natural killer (NK) cells,⁵² and inhibits production of the proinflammatory cytokine TNF- α and interferon- γ .^{51,53} *L. rhamnosus* significantly augments serum and mucosa secreted antibody responses in animal models.^{54,55}

Clinical studies have found that *L. rhamnosus* strains reduce the risk of AAD and improve outcomes in *C. difficile* diarrhea. At least 6 randomized, controlled trials have investigated the administration of *L. rhamnosus* (*L. casei* spp. *rhamnosus* GG) for the prevention of AAD. These studies have involved both adults and children including infants. In a controlled study of 119 children prescribed antibiotics for respiratory infections, *L. rhamnosus* GG was found to reduce the incidence of AAD by 69% (5% vs. 16% for placebo). Another study involving 188 children showed that 10-20 billion CFUs per day of *L. rhamnosus* GG decreased the incidence of diarrhea following oral antibiotics by 72% (7 vs. 25 cases for placebo).⁵⁷ *L. rhamnosus* GG as an adjuvant to triple antibiotic therapy for asymptomatic *Helicobacter pylori* infection was studied in 120 adults.⁵⁸ The relative risk of diarrhea was reduced by 70%. In a study involving 81 hospitalized infants, prophylactic administration of 6 billion CFUs daily of *L. rhamnosus* GG dropped the incidence of nosocomial diarrhea from 33.3% to 6.7%. One study failed to show a benefit for *L. rhamnosus* GG in the reduction of AAD in hospitalized adults receiving antibiotics.⁵⁹ When studies are subjected to meta-analysis, *L. rhamnosus* GG reduced the risk of AAD by 69%.¹⁷

Probiotic Combinations and Antibiotic-Associated Diarrhea
Probiotic microorganisms may interact synergistically with each other to provide benefits that a single strain or species alone may not.⁶⁰ Animal studies consistently demonstrate that combinations of multispecies probiotics offer enhanced protection against such pathogens as *Salmonella enteritidis*,⁶⁰ *Salmonella typhimurium*,⁶¹ and enterohemorrhagic *Escherichia coli* O157:H7⁶² that each individual species in the combination does not. Probiotic combinations that have been shown to reduce the incidence of AAD include *Lactobacillus acidophilus* and *L. bulgaricus*,⁶³ *L. acidophilus* and *Bifidobacterium lactis*,⁶⁴ *L. acidophilus* and *B. infantis*,⁶⁵ *L. acidophilus* and *B. longum*,⁶⁶ and *B. lactis* and *Streptococcus thermophilus*.⁶⁷ A meta-analysis of trials using probiotic combinations in children and adults found a significant reduction in the risk of AAD of 49%.¹⁷

Bifidobacteria and Antibiotic-Associated Diarrhea
Bifidobacterium species are obligate anaerobic lactic acid bacteria normally found in large numbers in the colon especially in infants.^{68,69} Bifidobacteria contribute significantly to the maintenance of gastrointestinal colonization resistance against pathogens through mechanisms such as production of organic acids, hydrogen peroxide and antimicrobial bacteriocins, competition for nutrients and adhesion receptors, inactivation of toxins, and stimulation of innate and acquired immune functions. Among the important physiologic roles of bifidobacteria is the fermentation of polysaccharides and other organic compounds to short-chain fatty acids such as acetate, propionate, and butyrate.^{70,71} Butyrate is not only the preferred energy substrate for colonocytes, it regulates intestinal cellular differentiation, proliferation, and gene expression. Short-chain fatty acids stimulate mineral, salt, and water absorption and modulate colonic luminal and mucosal intracellular pH. Bifidobacteria are exquisitely sensitive to antibiotics and their numbers are rapidly suppressed or eliminated during antimicrobial therapy.⁷² The toxic effects of antibiotics on the normal gastrointestinal microflora not only facilitates the overgrowth of pathogens, but can significantly reduce the production and colonic concentrations of short-chain fatty acids.²⁴ AAD has clearly been associated with reductions in colonic short-chain fatty acids concentrations.²⁴ Most cases of AAD have not

been associated with identifiable pathogens and may well be caused by impaired short-chain fatty acids production. Support and repopulation of colonic bifidobacterial species with *Bifidobacterium* probiotics represent a rational approach to the prevention and treatment of AAD that remains to be more fully evaluated by clinical studies.

PROBIOTICS AND ANTIBACTERIAL RESISTANCE

Although concerns have been raised about the theoretical possibility that probiotic microorganisms could contribute to the spread of antibiotic resistance,⁷³ the more likely scenario is that probiotics will prove to be a useful tool in addressing the problem of resistance. Antibiotic resistance is well-established to be related to overuse or misuse of antibiotics.^{3,74} Research suggests probiotics may have an important therapeutic role as an alternative to antibiotics in the treatment of disorders such as *Helicobacter pylori*⁷⁵ and urogenital infections.⁷⁶ Routine administration of probiotics during antibiotic therapy has the potential to suppress the emergence of antibiotic resistant pathogens. One randomized, double-blind, placebo-controlled study found that compared to patients given antibiotics alone, subjects given probiotics during antibiotic therapy did not develop an increase in antibiotic resistant *Enterococcus* species.⁷⁷ They also had fewer numbers of facultative anaerobes and potentially pathogenic *Enterobacteriaceae*. While further studies are needed to clarify the role of probiotics in addressing the problem of antibiotic resistance, these findings are intriguing.

CONCLUSION

Antibiotics have been a dual edged sword in the therapeutic armamentarium. They have both saved and destroyed lives. Among their most common adverse effects is the disruption of the body's vitally important microflora often leading to disease. Antibiotic-associated diarrhea may be the most common adverse effect of antibiotics. Probiotics offer proven benefits to reduce the risk of AAD and to treat AAD as well as *Clostridium difficile*-associated diarrhea. *S. boulardii*, *L. rhamnosus* strains, and combined probiotic formulations usually incorporating bifidobacterial species have all been proven to have benefit for the prevention of AAD. Probiotics may play an important role in reducing the spread of antibiotic resistance and the emergence of resistant microorganisms. In the future, probiotics may be seen as an alternative to antibiotics for specific conditions.⁷⁸

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