C. diff Prevention and Adjunctive Therapy with Prebiotics & Probiotics

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Let's picture for a moment a common scenario that occurs in the long term care (LTC) setting. A resident develops a symptomatic urinary tract infection (UTI) and is treated with a course of antibiotic therapy. Although this is necessary to destroy the pathogenic microorganisms which are causing pain and discomfort to the resident, it will also destroy their beneficial intestinal microorganisms that act as a front-line defense, protecting the body against numerous invaders and pathogens. After the devastating effects of antibiotics on the resident’s intestinal microbiota (microflora), it can take up to three months to restore the beneficial microorganisms to “normal” levels. During this time the resident is highly vulnerable and susceptible to infection and disease.

As adults age, the risk for developing infections increases. Beneficial intestinal microorganisms decrease and harmful ones increase, the intestinal mucous membrane thins increasing the ability of bacteria to adhere, and immunosenescence progresses. Furthermore, the environment in a health care setting harbors many opportunistic, pathogenic microorganisms that lie in wait for a disturbed microbiota they can invade and thrive in. Now the resident who took antibiotics to treat their UTI has disturbed their protective barrier allowing a bacterium such as clostridium difficile (C. diff) to proliferate. By treating one condition, another problem is created resulting in a vicious cycle.

Between 50% and 75% of residents in LTC are exposed to 1 or more courses of antibiotics over a 12-month period (1-5).

**C. difficile:**

- Spore-forming bacteria
- Most common cause of acute diarrheal illness & nosocomial infections of the gastrointestinal tract in the US
- Up to 33% of LTC residents treated with an antibiotic acquire C. diff
- In the last decade, there has been an increase in antibiotic-associated diarrhea (AAD) of 500% (6)
- C. diff accounts for 15% to 25% of all episodes of AAD (7).
- Prevalence of colonization in LTC ranges up to 20%, compared with <3% in healthy adults (8-10)
- Releases toxins in the intestine causing
  - mucosal inflammation
  - intestinal damage
  - problems ranging from mild diarrhea to severe pseudomembranous colitis, toxic mega colon, & bowel perforation
- LTC residents are at high risk due to:
  - extended lengths of stay
  - advanced age
  - frequent hospitalizations
  - widespread use of antibiotics and proton pump inhibitors (11)
- Symptoms can develop within the first week of antibiotic therapy and up to 10 weeks after its discontinuation (12, 13) and include:
  - loose, watery, foul-smelling stools, cramping, abdominal pain, loss of appetite, fever
  - can lead to dehydration, electrolyte imbalance, protein-energy malnutrition and significant
  - weight loss
- C. diff associated disease (CDAD) has a 25% mortality rate in frail elderly residents (13).
Recall the resident with a UTI, who was treated with antibiotics, allowing C. diff to multiply and cause harmful effects (Table 1). The resident was placed on antibiotics once again, for 10-14 days, to treat the C. diff. Now just imagine how compromised their intestinal microbiota must be after repeated antibiotic therapy, the depletion caused by profuse diarrhea, and the destruction caused by C. diff toxins. This explains why as many as 45% of affected residents will experience a recurrence of symptoms within 1-2 months (14, 15). Furthermore, up to 65% of residents who have suffered two or more episodes will have another recurrence (15). In order to stop the vicious cycle corrective measures should be taken to replenish microbial balance strengthening residents' defenses against further infection.

C. diff infections have increased in incidence and have surpassed Methicillin resistant Staphylococcus Aureus (MRSA) infections in number of cases according to the Centers for Disease Control (CDC). Epidemic outbreaks, particularly those associated with newer, hypervirulent mutated strains, are becoming a widespread problem. These epidemic strains are far more deadly than the organisms of 30 years ago, possibly due to over utilization of antibiotics. In order for C. diff to cause illness the intestinal microbiota must be disturbed (as with antimicrobial therapy) and C. diff must be ingested. Once both of the above occur, a person can become colonized and/or develop C. diff Associated Disease (CDAD). Therefore, C. diff can be prevented by keeping the intestinal microbiota of residents in balance. Effective treatment of CDAD must: 1) Reduce the burden of C. diff and its toxins on the intestine, 2) Assist the host’s immune system, and 3) Restore the normal colonic microbiota. We know that antibiotics do not restore the normal colonic microbiota, so what is being done in LTC to counteract and restore the destructive effects of antibiotics on intestinal microbiota and protect residents from Antibiotic Associated Diarrhea (ADD)/C. diff? When given in adequate doses and with the appropriate strains, prebiotics and probiotics have been shown to effectively prevent and provide adjunctive therapy for CDAD. In the next section, common questions on prebiotics and probiotics for preventing and treating AAD/C. diff are reviewed.

### Treatment includes:

- Discontinuation of antibiotics that led to the C. diff if possible
- A course of metronidazole (250 mg 4X/day or 500 mg TID/day) for 10-14 days or
- Vancomycin (125 mg QID) for 10-14 days

1. **What are prebiotics & probiotics and where can they be found?**

   Prebiotics are live microorganisms which, when administered in adequate amounts, confer a health benefit to the host. Probiotics are available in foods and dietary supplements in the form of capsules, chewable tablets, freeze-dried powders, gum, chews, wafers, and liquids. On their own, foods do not provide sufficient quantities of the probiotics needed to restore the gut microbiota of older adults on antibiotic therapy or with C. diff infection. Probiotics in supplement form are required in order to provide the levels necessary to restore a favorable microbial balance after the devastating effects of antibiotics.
Unlike probiotics, which are live bacteria or yeast, prebiotics are non-digestible food ingredients that positively affect the host by selectively stimulating the growth and/or activity of one or a limited number of beneficial bacteria in the colon (19). In effect, prebiotics act as food for gut bacteria. A number of food ingredients have been shown to act as prebiotics. These include fructooligosaccharides (FOS), inulin, galactooligosaccharides (GOS), lactulose, polydextrose, and digestive resistant maltodextrin (19). FOS is the most clinically researched prebiotic to date with positive results. It is found naturally in bananas, onions, garlic, and Jerusalem artichokes. Prebiotics have been added to yogurt, kefir and other dairy drinks, functional waters, nutrition bars, soymilk, medical foods, and dietary supplements.

2. What is the rationale for using probiotics & prebiotics for prevention and adjunctive therapy for AAD/C. diff?

The gut of a healthy adult contains an estimated 100 trillion bacteria of various species, known as the gut microbiota. Incidentally, this is 10 times as many cells as are contained in the entire body itself. These organisms are extremely active and interact continuously with each other and with the cells lining the gut, as well as with the immune, endocrine and central nervous systems. Amazingly, taken together, their level of metabolic activity matches that of the liver (20). This 2-3 pound mass of microbiota could really be considered as a separate organ due to the multitude of indispensable functions it performs. Contained in this mix of 400-odd bacterial species are both beneficial and harmful micro-organisms. It is crucial to keep one’s microbiota balanced since it is the body’s front line defense against pathogens and plays a major role in our immune system. As we age all of our immune defense are weakened. Probiotics can help increase intestinal beneficial bacteria, can reinforce the intestinal lining’s function as a “barrier,” preventing bacteria associated with the intestine from passing into the bloodstream, and improve overall immunity. The tremendous number of bacteria growing in our intestine must compete to survive, often by destroying other organisms and their toxins. Since about 70% of the immune system is based in the intestinal tract, keeping sufficient populations of beneficial bacteria there may play a role in preventing some diseases.

Prebiotics like FOS may help in the prevention and treatment of C. diff infections by aiding in the restoration of microbiota and the strengthening of intestinal barrier integrity. FOS resist degradation by digestive enzymes and pass intact through the stomach and small intestine. Once FOS reach the colon, anaerobic bacteria ferment them to obtain energy and carbon for their own growth. During this process, these bacteria also generate short-chain fatty acids (SCFAs), which reduce pH in the gut creating a less favorable environment for harmful bacteria. As a result of the fermentation, there is an increase in the concentration of beneficial bacteria (bifidobacteria) in the large intestine, an increase in calcium absorption, an increase in fecal weight, and a shortening of gastrointestinal transit time, all of which help normalize bowel function (21). FOS are also used to help to manage diarrhea and constipation. The production of SCFAs, like butyric acid, serves as the primary fuel for the cells of the large intestine and helps maintain their health and integrity, which can become damaged by C. diff toxins. Bifidobacteria are beneficial because they stimulate the immune system, increase resistance to infection and diarrheal disease, and enhance overall gut health (22). The number of intestinal bifidobacteria decrease as we age.

3. How do I know which probiotic to recommend?

Probiotics are not a one size fits all. Just as one wouldn’t prescribe some random antibiotics to treat an infection, the same holds true for probiotics. The probiotic chosen should be based on the condition that is being prevented or treated. It is important to understand that not all probiotics work on all conditions and therefore appropriate selection should be based on those clinically proven for specific disease states. For the condition of AAD/C. diff, the clinically proven probiotics include: Saccharomyces Boulardii, Saccharomyces Boulardii in combination with Bacillus Coagulans and FOS, Lactobacillus Rhamnosus GG (effective in children), Lactobacillus Reuteri ATCC 55730, Lactobacillus Casei DN-114 001, Lactobacillus Acidophilus CL1285 in combination with Lactobacillus Casei LBC80R (Table 2). It is also important to note the population in which the probiotic was tested. For example, Lactobacillus Rhamnosus GG capsules have been shown to be effective in children, but a large trial (n = 302) on adult inpatients found the same probiotic had no effect on AAD rates (23).

The addition of these probiotics to the diet of residents undergoing antibiotic therapy replaces natural bacteria that would normally counteract C. diff by competing for resources in the colon. Probiotics have been associated with diminished rates of C. diff and reduced costs associated with treatment of these infections (24). It has also been suggested that probiotic administration may reduce hospital costs associated with CDAD by 50% vs. standard therapies (25). For AAD and C. diff, Saccharomyces Boulardii (S. Boulardii) has been shown to be the most effective probiotic, with over 50 years of clinical research and use (26-33). Doses of S. Boulardii in these studies ranged from 500 mg to 1 g administered daily either during antibiotic therapy, or continued for up to 2 weeks after completion of antibiotic regimens. S. Boulardii grows well at body temperature, is not systemically absorbed into the circulation, reaches a high steady-state level of 107 to 108 colony forming units (cfu) within the colon in a matter of days, yet is rapidly eliminated within 2–5 days of discontinuing use. S. Boulardii produces an enzyme that destroys the C. diff toxins and their receptor sites in the intestine helping to prevent recurrence. S. Boulardii also stimulates host immune defenses and intestinal enzymes that enhance nutrient digestion and absorption. It produces acids that combat disease-causing microorganisms, assist in mineral absorption, and nourish the colon. This unique probiotic organism also stimulates chloride absorption, reduces symptoms of CDAD, and permits normal bacterial gut microbiota to be reestablished.
(29). It was previously mentioned that effective treatment of CDAD needs to do three things: 1) Reduce the burden of C. diff and its toxins in the intestine, 2) Assist the host’s immune system, 3) Restore the normal colonic microbiota. S. Boulardii does all three and should be recommended for use with antibiotic therapy.

Yogurt can be considered probiotic if there is scientific evidence that indicates the yogurt product in question has high amounts of the strains and has demonstrated health benefits. When recommending yogurts or dairy drinks for AAD and C. diff only products that have been clinically proven for that condition should be used. For example, the dairy drink containing L. casei DN-114 001 (100 million cfu/ml), S. thermophilus (100 million cfu/ml), and L. bulgaricus (10 million cfu/ml) has been shown to be effective in lowering incidence of AAD (12% vs. 34 %) and CDAD (0% vs. 17 %) (30). On the other hand, two yogurts were found to be ineffective at preventing AAD (34). One was a bio yogurt containing S. thermophilus (8X108 cfu/g), L. acidophilus (3X106 cfu/g), and B. anamalis lactus (5X106cfu/g) and the other a commercial yogurt containing S. thermophilus (8X108 cfu/g), with L. delbrueckii bulgaris (3X106cfu/g). These demonstrate the importance in product selection instead of a ‘one size fits all approach’.

4. How are probiotics classified?
Probiotics are frequently recommended in health care settings for the prevention of AAD. Since the universally recognized probiotic is Lactobacillus Acidophilus (also called acidophilus), this is the typically recommended probiotic. There are many issues concerning this recommendation. First, probiotics are classified by their genus, species, and most importantly their strain. There are hundreds of strains of Lactobacillus Acidophilus and the genetic difference is far greater. Lactobacillus is the genus, acidophilus is the species, but which strain is being used? Has it been clinically tested and shown to prevent or treat the condition it is being used for? And if the strain is unknown, then how can the proper dosing be determined? For example, Lactobacillus Acidophilus CL1285 in combination with Lactobacillus Casei Lbc80r at a dose of 50 billion cfu per day, has been clinically shown to reduce the occurrence of AAD and C. diff (35). However, if a generic Lactobacillus Acidophilus with an unidentified strain is being used, the chances of the microorganisms being viable and effective against AAD are low. It is important to distinguish between the different types of probiotics, since each strain determines the specific role a probiotic can play rather than just its genus (Lactobacillus). Thus assigning the term Lactobacillus or Acidophilus to a probiotic, for example, is an imprecise way of identifying it.

Most often, probiotics come from two groups (genera) of bacteria, Lactobacilli and Bifidobacterium. However, there are also yeast based probiotics such as S. Boulardii. Lactobacilli are a major part of the lactic acid bacteria group, named as such because most of its members convert lactose and other sugars to lactic acid. In humans they are present in the vaginal and gastrointestinal tract. To date, 56 species of lactobacilli have been identified. Bifidobacterium are also classified as lactic acid bacteria, as they produce lactic acids as well as acetic acids. Bifidobacteria are normal inhabitants of the human colon. Newborns, especially those that are breastfed, are colonized with Bifidobacteria within days of birth. To date, 30 species of Bifidobacteria have been isolated. The misclassification and misuse of probiotics may be one of the reasons that they often receive mixed reviews.

5. What dose should I use and for how long?
Some probiotic products are effective at levels of 50 million cfu per day to more than 1 trillion cfu per day. It is not possible to provide one “minimum dose” that applies to all probiotics because different probiotics are effective at different levels. Product doses should be based on levels that were tested in human studies and shown to be effective. For prevention of AAD, probiotics should be taken for the duration of antibiotic therapy and continued up to 2 weeks after completion of antibiotics. Bacteria based probiotics, such as L. acidophilus CL1285 + L. casei Lbc80r, should be taken at least 2 hours apart from taking antibiotics since antibiotics destroy bacteria. Yeast based probiotics such as S. boulardii, on the other hand, can be taken at the same time antibiotics are taken. For residents diagnosed with C. diff, probiotics should also be taken along with antibiotic therapy and then continued at least 2 weeks after. Certain products containing probiotics can be taken daily to maintain gastrointestinal health. This may be appropriate for residents frequently on antibiotics or with recurrent C. diff or who are on low dose prophylaxis antibiotics for UTIs.

6. How do I select stable probiotics?
Since probiotics are living microorganisms, they must be handled with great care. In order to confer a health benefit, a significant number of probiotic cells must reach the intestines intact. If properly prepared and stored, probiotics can remain viable and reach the intestine alive when consumed. The issues with many probiotics on the market today are their inability to survive high heat and pressure inherent in the manufacturing process, short shelf lives, and lack of resistance to stomach acids, bile, and various enzymes in the gut. Some probiotic products require refrigeration while others do not. It is important that the temperature requirements for storage on the label are read and followed closely. Certain probiotic strains are more viable than others and if using the products that have been clinically studied there is some evidence of their viability. Probiotics must be able to survive the aerobic condition of the product in which they are contained, as well as exposure to the acidic condition of the stomach, bile acid, and pancreatic secretions in the small intestine. It is therefore important to ensure the probiotics used are protected either by freeze drying, microencapsulation, a bio-film, or found naturally in a spore form. For example, the probiotic Bacillus Coagulans is naturally encapsulated in a spore shell that does not dissolve until it reaches the intestine,
where it multiplies rapidly, increasing the beneficial bacteria in the colon and producing lactic acid to lower the pH. The previously mentioned nonpathogenic yeast, S. Boulardii, is another example of a stable probiotic. It is acid and heat stable and antibiotic resistant, unlike probiotic bacteria which can be destroyed by antibiotics.

A prebiotic can be combined with a probiotic to make a synbiotic, which improves the survival rate and proliferation of the probiotic in the gastrointestinal tract and helps ensure that it reaches the colon in numbers adequate to confer a health benefit. The benefits of probiotics are dependent on their viability, growth, and metabolic activity, which can be maximized with the addition of prebiotics. Probiotics must also compete with resident bacteria in the gastrointestinal tract. With the addition of a prebiotic food substrate, the probiotic cells are better equipped to survive and proliferate. This greater stability, which a synbiotic combination facilitates, also translates into longer shelf-life. In a randomized, double blind, placebo controlled clinical study, a supplement containing Bacillus Coagulans and FOS significantly reduced the number of days and duration of AAD (36). Providing foods and supplements that contain synbiotics to residents with C. diff, AAD, or those at risk, will help ensure optimal delivery to the gut, strengthening their front-line defense and improving quality of life.

7. Are probiotics safe?
Experts estimate that the risk of developing an infection from ingested probiotics is “negligible,” occurring in less than 1 per million users of probiotic supplements (37). When probiotic-related bacteremia or fungemia has been reported, patients often had a prior history of underlying immune compromise or chronic disease or debilitation (38). Probiotics should be used cautiously in immunocompromised individuals, including those in a debilitated state or with malignancies (38). A review of 143 human clinical trials of probiotics conducted over a 39-year period concluded that there were no adverse events reported with probiotic use in the 7,526 people who had participated in the studies (39).

8. What should I expect?
In residents on antibiotic therapy probiotics may help prevent the occurrence of AAD, C. diff, & diarrhea. In residents positive with AAD/C. diff, probiotics may help reduce duration of the diarrhea and may help prevent recurrence of AAD & C. diff.
• Fewer outbreaks & transmissions of infection within the facility
• A reduction in dehydration & malabsorption associated with AAD
• A reduction in the inappropriate use of antibiotics
• A reduction in the number of patients with infections who are transferred to acute-care settings
• A reduction in direct & indirect patient care costs as a result of more appropriate resource utilization

9. How can Dietitians be proactive?
The intestinal microbiota is essential to health, with effects on nutrition, metabolism, pathogen resistance, and other vital processes. Recurring antibiotic use causes a devastating effect on internal microbial ecosystems with potentially debilitating consequences. Given the rising economic and social burden of infections, the prevention and treatment of CDAD in LTC requires a multi-component approach including use of pre- and probiotics. Since pre- and probiotics can play an integral role in preventing C.diff colonization among residents taking antibiotics, and improve intestinal barrier integrity in residents with CDAD, dietitians should recommend their use when appropriate. In order for dietitians to be proactive, they should be routinely notified when a resident has a UTI and is on antibiotics, or when a resident has C. diff. As scientific knowledge on pre- and probiotics continues to evolve, it is important that dietitians stay current, monitoring emerging findings and translating them into practical recommendations.
Jennifer Sallit RD, PhD, served as a Scientific Director for Nutricia North America at the time of publishing, where she conducted clinical and market research in gerontological nutrition for medical food product development. Dr. Sallit was an Adjunct Professor at Florida International University, where she taught courses in Nutrition and has been involved in nutritional research for the last 12 years. She holds a Doctorate in Dietetics and Nutrition from Florida International University and a B.S. in Food Science and Nutrition from Drexel University. Dr. Sallit presents CPEs on nutrition for wound healing, bowel regularity, urinary tract infections, and clostridium difficile. Her current research focus is on improving the nutritional status of older adults. For the past several years she has specialized in the area of prebiotics and probiotics and their role in the treatment and prevention of antibiotic associated diarrhea and Clostridium difficile infection.

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