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Efficacy of Probiotics Lactobacillus Rhamnosus GG and Saccharomyces Boulardii in the Treatment of Antibiotic-Associated Diarrhea and Clostridium Diffiicile-Associated Disease

Estie Klugmann
Touro College

Efficacy of Probiotics *Lactobacillus Rhamnosus GG* and *Saccharomyces Boulardii* in the Treatment of Antibiotic-Associated Diarrhea and *Clostridium Difficile* - Associated Disease

Estie Klugmann

Abstract

Antibiotic therapy may cause serious side effects. Two disturbing effects of antibiotic administration are antibiotic–associated diarrhea and *Clostridium difficile*-associated disorder. Antibiotic-associated diarrhea occurs as a direct result of the normal flora destruction due to the antibiotics – which do not discriminate against pathogens or healthy forms of bacteria. *C. diff* disorder also occurs as an indirect result of antibiotic administration, because the destruction of the normal flora prevents people from having healthy bacteria to prevent disease. There have been studies conducted to determine if replacing the destroyed normal flora with probiotics, or beneficial microorganisms will prevent or treat these conditions. Studies have been conducted to show that the bacterium *Lactobacillus rhamnosus GG* has shown great promise in the treatment of antibiotic-associated diarrhea as there have been positive results achieved in many heterogeneous studies. Treatment of *Clostridium difficile*-associated disorder with the yeast, *Saccharomyces boulardii* remains controversial as different medical researchers struggle to prove or disprove its effectiveness and safety.

Introduction

After being admitted to hospitals, most people expect their health to improve. They believe that the hospitals' sanitary conditions will surely keep them from contracting any illnesses in their weakened states. However, infections can spread rapidly in hospitals and people can also suffer from the side effects of the very treatments intended to help them recover. Both *Clostridium difficile*-associated disease and antibiotic–associated diarrhea are examples of these growing healthcare concerns (Wistrom, 2001). Antibiotic-associated diarrhea involves the onset of diarrhea following the administration of antibiotics. The resulting diarrhea is not linked to a previous disorder or condition (Bartlett, 2002). About 10% to 20% of cases which are attributed to antibiotic-associated diarrhea are also caused by *Clostridium difficile* toxin (Bartlett, 2002). *Clostridium difficile*-associated diarrhea or *Clostridium difficile*-associated disease (CDAD) refers to the diarrhea and other gastrointestinal complaints that result from a *Clostridium difficile* infection (McFee, 2009). It is possible that the percentage of diarrhea cases attributed to *Clostridium difficile* toxin is slightly inaccurate as the *Clostridium difficile* bacteria present in the stools of those diagnosed with antibiotic-associated diarrhea may be benign. Whether the antibiotic-associated diarrhea resulted from the ingestion of antibiotics or from the presence of *Clostridium difficile* toxin, which people who have been immunocompromised are more susceptible to, the results remain the same. People are suffering gastrointestinal distress and hospitals are spending their limited cash resources on dealing with these issues. It is difficult to eliminate the sources of these infections, because the antibiotics used to treat infections in, but not limited to, hospital patients are ineffective against toxin and spore-forming *Clostridium difficile* bacteria. In addition, it is almost impossible to stop the bacterial growth and spread of CDAD within hospitals, as antibacterial cleaning products do not destroy spores from the hands of health care workers and hospital sinks and toilets (McFee, 2009). Medical researchers have been looking for an alternative method to treat AAD and CDAD.

Diarrhea results when the balance of normal intestinal flora is disturbed. In order to restore the normal intestinal flora to its healthy state, medical researchers are turning to probiotics, or live microorganisms which benefit their hosts, (Santosa, 2006) to replace the salutary microorganisms that normally inhabit the gastrointestinal tract (Avadhani, 2011). The intestinal microflora normally play a number of roles in gastrointestinal health. These include: strengthening the layer of epithelial cells in order to prevent the movement of pathobiotics, or microbes that are harmful to their hosts, competing with pathobiotics for positions on the epithelial lining, the production of compounds which will inhibit pathobiotic growth, and the enhancement of the immune response to pathobiotics (Patwary, 2012). Twentieth century Russian scientist Eli Metchnikoff first recognized the health benefits of probiotics when the life span of Bulgarian peasants who consumed fermented milk which contained lactic acid bacteria was longer than expected (Culligan, 2009). The first mechanism he proposed was that the ingested probiotics replace the pathobiotics that have taken up residence in the gut (Surawicz, 2003). As written above, this is still an accepted hypothesis of medical researchers.

Two characteristics that probiotics share with the normal flora that they are intended to replace are their ability to survive the acidic conditions and the enzymatic activity of the human gastrointestinal system (Singhal, 2009). These characteristics allow probiotics to mimic the behavior and functions of normal flora in the gut making it possible for probiotics – microorganisms normally present outside of the gut – to be considered for use as alternative treatments for numerous gastrointestinal problems. Both L*actobacillus rhamnosus GG*, a bacterial microbe, and *Saccharomyces boulardii*, a yeast, have been studied to determine their efficacy and safety in the treatment of antibiotic-associate bacteria and *Clostridium difficile*-associated disorder, respectively. This review will explore the published literature to shed light on

Estie Klugmann graduated in June 2013 with a B.S. degree in Biology. She is currently studying Dentistry at NYU.

these health claims.

Methods

Literature searches were conducted using the health science related databases of the Touro College Online Library: MEDLINE, Proquest Medical Library (Health and Medical Complete), EBSCO multi-search, and PubMed. Both the Touro QuickSearch option and Google Scholar were also utilized. The following keywords were searched: probiotics, probiotics and gastrointestinal health, probiotics and gastrointestinal disorders, probiotics and antibiotic-associated diarrhea, probiotics and *Clostridium difficile*-associated disorder, efficacy of probiotics in the treatment of *a*ntibiotic-associated disorder, efficacy of probiotics in the treatment of *Clostridium difficile*-associated disorder, antibiotic-associated diarrhea and *Clostridium difficile*-associated disorder, probiotic safety, *Lactobacillus rhamnosus GG* and antibiotic-associated diarrhea, *Saccharomyces boulardii* and *Clostridium difficile*-associated disorder, and fungemia and *Saccharomyces boulardii.* Several of the sources listed in the articles found by using these keywords were also used as references where appropriate. Additionally, only articles published in scholarly peer-reviewed journals after the year 1995 were included.

Results and Discussion

Antibiotic-Associated Diarrhea

Although there have been several studies done using different probiotics in the treatment of antibiotic-associated diarrhea, the probiotic which seems to be the most efficacious is *Lactobacillus rhamnosus GG.* It is also a strain which has been well-researched (Hawrelak, 2005). For this reason, Hawrelak and his colleagues conducted a review of six trials which involved the study of the effects of *Lactobacillus rhamnosus GG.* The specific requirements for inclusion were that the studies must concern human clinical trials and investigate the effects of probiotics on antibiotic-associated diarrhea. In addition, the probiotic in question needed to have been *Lactobacillus rhamnosus GG.* He did not discriminate by age, however, and utilized studies which were conducted on both adults and children (Hawrelak, 2005). In addition, Hawrelak included research articles which varied in probiotic dosage. The dosages of colony forming units that were administered for each study ranged from 250 ml LGG yogurt with no CFU count provided to 2 X 1010 CFU capsules twice daily. Despite these inconsistencies, the overall consensus was that the subjects who were receiving *Lactobacillus rhamnosus GG* in any form during each study suffered from diarrhea for a shorter duration (Hawrelak, 2005). Due to the lack of heterogeneity, the results of these studies could not be combined into one and the overall statistical efficacy could not be determined (Hawrelak, 2005). As with Hawrelak's systemic review, the common thread among the studies conducted regarding *Lactobacillus rhamnosus GG* as a potential treatment for antibiotic-associated diarrhea is that *Lactobacillus rhamnosus GG* was used in some form, alone or in conjunction with another probiotic, on a person, of any age, suffering from antibiotic-associated diarrhea.

Hawrelak's review is cited by a study conducted in the University Hospital of North Norway where Wenus and his colleagues studied the possible prevention of antibiotic-associated diarrhea by a fermented probiotic milk drink (Wenus, 2008). The multistrain probiotic milk drink included *Lactobacillus rhamnosus GG* as well as *Lactobacillus acidophilus La-5* and *Bifidobacterium Bb-12* (Wenus, 2008). This study was limited to patients aged 18 years and over and excluded patients with immune deficiency disorders, those who had diarrheal episodes in the past, and those who had taken fermented probiotic drinks as dietary supplements two weeks prior to the study (Wenus, 2008). The final study included 87 adults, 41 of which were included in the placebo group and 46 of which were included in the probiotic group. At the conclusion of the study, 63 patients were available for evaluation. Of those treated with the fermented probiotic milk drink, 5.9% still developed antibiotic-associated diarrhea. However, 27.6% of subjects in the placebo group developed antibiotic-associated diarrhea.

According to Sherwood L. Gorbach, M.D. of Tufts University School of Medicine, the heterogeneity of the studies which include the treatment of antibiotic-associated diarrhea with *Lactobacillus rhamnosus GG*, does not diminish the proof of its effectiveness. In fact, it indicates its versatility. Whether consumed in a fortified milk product or in lyophilized powder form, *Lactobacillus rhamnosus GG* will boost the gastrointestinal tract's defense mechanisms (Gorbach, 2000) .

Although considered technically well-researched by Hawrelak and Gorbach, the effects of *Lactobacillus rhamnosus* on patients affected by antibiotic-associated diarrhea need to be studied further. There needs to be some uniformity in the studies conducted. For example, the elderly should be given yogurt fortified with 2 x 1010 CFUs of *Lactobacillus rhamnsous GG* twice daily and the same study should be conducted on children. Medical researchers are limited if the elderly are given capsules of 1.2 x 1010 CFUs of both *Lactobacillus rhamnosus GG* and *Lactobacillus acidophilus* daily while children are given milk fortified with *Lactobacillus acidophilus La-5* and *Bifidobacterium Bb-12*. It becomes difficult to determine if the bacterial strain, dosage, or medium through which the probiotic is administered caused the patients to improve. A specific ratio of all three may be determined if further research is conducted.

Gorbach's description of the potential health benefits of LGG has led other medical researchers to conduct studies to test the effectiveness of LGG in AAD prevention. Gorbach's conclusions were tested with a study conducted on children. (Vanderhoof, 1999). A group of 202 children with a median age of four years were recruited to participate. These children, who were prescribed oral antibiotics at a primary care pediatric practice, were divided into two groups. One group of children was given inulin placebo pills during the course of antibiotic treatment, while the second group received LGG in capsule form. Children weighing less than 12 kg were given one pill which contained 10 billion colony-forming units of LGG and those who weighed more than 12 kg received a double dosage. Parents were told to document the stool consistencies of their

children. Of the 202 recruits, 188 were evaluated at the end of the study. The subjects who received the LGG capsules were less affected by AAD. Only 7% of those who were administered the LGG capsules suffered from diarrhea and 26% of the children in the placebo group were affected (Vanderhoof, 1999).

Vanderhoof's study shows that LGG minimizes the effects of antibiotics on the gut in children prescribed oral antibiotics. However, the researchers were relying on the cooperation of the children and parents to administer the LGG or placebo capsules and determine if the children's stools were loose enough to be considered diarrhea or not. If this study were conducted under the supervision of the researchers, human error would be minimized. This does not diminish the fact that a significantly smaller percentage of children suffered from AAD after having taken the LGG capsules.

Clostridium Difficile-Associated Disorder

As an alternative treatment of the hospital "superbug" *Clostridium difficile*-associated diarrhea, the yeast *Saccharomyces boulardii* has shown some promise. The Journal of the American Academy of Nurse Practitioners published a meta-analysis of the efficacy of probiotics in the treatment of CDAD. Two of the studies included discussed the efficacy of the nonpathogenic yeast, *Saccharomyces boulardii* (Avadhani, 2011). One of the studies conducted in Gulhane Military Medical Academy, Department of Infectious Diseases and Clinical Microbiology, included 151 patients between the ages of 25 and 50 receiving antibiotic-therapy who were administered *S. boulardii* or a placebo in capsule form twice daily. The stools of those suffering from antibiotic-associated diarrhea were assayed for the presence of *Clostridium difficile* toxin A. In the group receiving the placebo, two patients' stools contained toxin A, while the stool of the one patient in the treatment group suffering from AAD did not (Can, 2006).

The second study included by Avadhani and Miley discussed the lack of therapeutic effect of *S. boulardii* on patients suffering from AAD which resulted from the *Clostridium difficile* infection (Lewis, 1998). This study was limited to elderly patients who had been prescribed antibiotics within the preceding 24 hours. Seventy-two patients were randomly selected for inclusion in either the placebo group or the group that received 113 mg of *S. boulardii* twice daily. In addition, their stool samples were evaluated by the nursing staff to determine whether their stools were loose enough to be considered diarrhea. Whether hard or loose, all stools samples were sent to be tested for *Clostridium difficil*e toxin. Of the 33 people evaluated in the active group, five people were found to have *C. difficil*e toxin present in their stools. In the placebo group, *Clostridium difficile* was found in the stools of 7 people. There was no visible improvement in the group who was administered the S. boulardii. In the discussion section of the study, the researcher, S.J. Lewis, mentions how previous researchers such as G.W. Elmer and L. V. McFarland showed that there was a benefit in taking *S. boulardii*, as opposed to taking a placebo. However, they were unable to repeat these results in later well-designed studies (Lewis, 1998). In response to Lewis' evaluation of previous studies, Elmer and McFarland commented on Lewis' study and claimed that the small trial failed to prove that *Saccharomyces boulardii* is ineffective and that Lewis should have followed up with patients after they had stopped receiving antibiotics. Lewis' study took place over 6 to 11 days. Elmer and McFarland felt that a 6 to 8 week follow up period should have been conducted (Elmer, 1998). Elmer and McFarland also commented on Lewis' point that later studies by McFarland, et. al. (McFarland, et. al., 1995) fail to prove the efficacy of *Saccharomyces boulardii* to treat CDAD. McFarland states that Lewis took the results out of context, because McFarland's study took a follow up period into account and Lewis left those results out of the evaluation of McFarland's work (Elmer, 1998). Lewis replied by pointing out that Elmer and McFarland are biased, because they are associated with Biocodex - the company that manufactures *S. boulardii.* Lewis also explains that he tried to match up the parts of the studies that were comparable in order to present an accurate review of the studies (Lewis, 1998b).

It is clear from this exchange why the use of probiotics to treat disorders is still considered an alternative care method. It is difficult to compare studies that only share a few characteristics in common. The common thread may be that *S. boulardii* was used to treat CDAD, but the dosages, patient-types, and study-length vary. There are researchers who use McFarland's studies and reviews and use them as a basis for their research regarding probiotics and human gastrointestinal health and evidence for the efficacy of *Saccharomyces boulardi*i (Guslandi, 2006) and there are those who remain skeptics (Miller, 2009). In the context of a later meta-analysis conducted by McFarland and published by the American Journal of Gastroenterology, McFarland recognized that the use of probiotics in the treatment of *Clostridium-difficile* disorder remains controversial (McFarland, 2006).

Mark Miller discussed the probiotic movement and described it as a mass hysteria, because people are desperately trying to minimize the after-effects of antibiotic use and cure all gastrointestinal ills. People are placing store in an alternative methods that do not have sufficient evidence to prove their health benefits (Miller, 2009). Miller also notes that McFarland's 2006 meta-analysis states that *Saccharomyces boulardii* is an effective treatment for CDAD when there have been previous meta-analyses to the contrary (Miller, 2009).

In addition to possibly being ineffective in the treatment of CDAD, *S. boulardii* may be harmful to those who ingest it. The use of *Saccharomyces boulardii* may not be appropriate for those who are immunocompromised or immunosuppressed. *Saccharomyces boulardii* was marketed as a dietary supplement that improves gastrointestinal health. However, dietary supplements are not regulated by the FDA's strict regulations and while this yeast may improve the gastrointestinal health of individuals who are not immunocompromised, those who are not in good health may suffer from fungemia, or the presence of fungi in the blood (Venugopalan, 2010). There have been five documented cases of fungemia in patients who were receiving

S. boulardii as treatment for CDAD (Miller, 2009). As with other infections, babies, young children, and the elderly are at a greater risk of contracting CDAD. It appears then that the very people *Saccharomyces boulardii* is intended to treat – those who are immunocompromised due to age, illness, and antibiotic treatment - may not be the people who can benefit from its probiotic properties.

Conclusion

After a review of the available literature discussing efficacy of probiotics *Lactobacillus rhamnosus GG* and *Saccharomyces boulardii* in the treatment of antibiotic-associated diarrhea and Clostridium difficile – associated disorder, respectively, it can be determined that *Lactobacillus rhamnosus GG* has a role in the prevention of AAD. However, it appears that *Saccharomyces boulardii* has not shown itself to be a safe and effective probiotic for those who are ill and should not be used to treat those who suffer from CDAD until more rigorous testing has been done.

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