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Efficacy of a synbiotic chewable tablet in the prevention of antibiotic-associated diarrhea

Charles Spielholz

Nutraceutical Medical Research, 445 Hamilton Avenue, Suite 1102, White Plains, New York, 10601. USA.
cspielholz@nutraceuticalmedicalresearch.com

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ABSTRACT

Infection by *Clostridium difficile*, a complication of treatment with antibiotics, causes antibiotic-associated diarrhea (AAD) and can lead to colitis and pseudomembranous colitis. Incidence of *C. difficile* infection is increasing among the elderly undergoing antibiotics therapy confined to health care facilities, conditions that are expensive to treat, decrease the quality of life and are life threatening. Use of probiotics has been proposed as a method to decrease the incidence of AAD in health care facilities. To examine the efficacy of using probiotics, 120 nursing home residents undergoing antibiotic therapy were provided with a synbiotic tablet containing two probiotics, *Saccharomyces boulardii* and *Bacillus coagulans*, and a prebiotic, fructooligosaccharide. Residents were evaluated retrospectively for AAD and *C. difficile* infection. It was found that 95% of residents treated with antibiotics and taking the synbiotic tablet were free of AAD. More than 97% of the residents did not become infected with *C. difficile*. No adverse effects were reported. Minor side effects, gastrointestinal upset and nausea, were reported by less than 6% of the residents. The cause of the minor side effects was not known. Only 2.5% of the residents stopped taking the synbiotic tablet because of the gastrointestinal upset. These Results suggest that use of the synbiotic tablet prevents AAD and *C. difficile* infection in nursing home residents undergoing antibiotic therapy. It is concluded that this synbiotic tablet provides an easy to administer and safe approach to controlling AAD and *C. difficile* infection in residents in nursing homes.

Keywords: Synbiotic; *Saccharomyces Boulardii*; *Bacillus Coagulans*; Antibiotic-Associated Diarrhea; *Clostridium Difficile*

1. INTRODUCTION

Antibiotics have significantly decreased mortality resulting from infectious disease and increased the success rates of many medical procedures such as surgery. However, use of antibiotics also causes significant losses to the population of beneficial microbiota residing in the digestive tract. The digestive tract is the front line of defense against infection, representing a significant portion of the total immune system [1]. Loss of native populations of beneficial microbiota exposes the intestinal mucosa and allows non-beneficial and pathological species, including those that are antibiotic-resistant, to populate the intestine [2,3]. This results in a variety of biological changes in the digestive tract including changes in immune function, inflammatory response and normal metabolism [4]. Such changes increase susceptibility to antibiotic-associated diarrhea (AAD) and antibiotic-resistant infectious diseases [2].

Chronic use of broad-spectrum antibiotics in elderly residents in health care facilities, such as nursing homes, long-term care facilities, and hospitals, is leading to a serious increase in the incidence of AAD [5,6]. AAD occurs in 25% to 50% of residents taking antibiotic [7,8]. *Clostridium difficile*, a bacterial, spore-forming, anaerobic species that infects the human digestive tract, is resistant to many commonly used antibiotics and is the cause of *C. difficile*-associated diarrhea (CDAD). CDAD represents 15% to 25% of all AAD occurring in health care facilities [8,9]. *C. difficile* is the cause of approximately half of all cases of antibiotic-associated colitis and almost all cases of pseudomembranous colitis, a life threatening inflammation of the colon [9,11]. There are now over 250,000 *C. difficile* infections requiring hospitalization in the United States each year [10] causing an estimated 15,000 to 30,000 deaths each year. Nationally, the cost of treating *C. difficile* infections is greater than $1 billion per year [4].

Treatment of *C. difficile* infection requires discontinuation of antibiotic therapy, if appropriate, intravenous fluids and administration of either metronidazole or vancomycin [13-16]. Reinfection occurs in up to 30% of those successfully treated [18,19]. Furthermore, use of metronidazole or vancomycin contributes to the increase in antibiotic resistant species [17,19]. Therefore, supplemental and alternate methods using probiotics in the treatment and prevention of *C. difficile* infection have been proposed [20,21]. The idea behind administration of probiotics is to replace the normal population of beneficial microbes that are lost from the digestive tract during antibiotic treatment [21]. Probiotic microbes stimulate the immune system of the gut and suppress the growth of pathological species [2,3].

In this report, the results of a retrospective analysis of residents in nursing homes undergoing treatment with antibiotics and taking a chewable synbiotic tablet as an adjunctive preventative of AAD are presented. The synbiotic tablet contained the nonpathogenic yeast *Saccharomyces boulardii*, the bacteria *Bacillus coagulans*, and a prebiotic, fructooligosaccharide. The purpose of this retrospective study was to analyze and understand the feasibility of administering a synbiotic tablet to residents in a nursing home environment, analyze the potential efficacy with regard to AAD, *C. difficile* infection, and CDAD and to define any safety and tolerability issues.

2. METHODS

Residents in 17 nursing homes receiving antibiotic treatment and taking the synbiotic tablet as part of their standard of care from September 2009 to November 2009 were evaluated retrospectively for the presence of AAD and *C. difficile* infection. The resident population analyzed in this study consisted of 120 people. There were 77 females representing 64.2% of the resident population, and 43 males representing 35.8% of the study population. The residents ranged in age from 40 to 96 years with an average age of 80 ± 10 years (**Table 1**). Twenty six of the residents, representing 20.8% of the study population, had a prior history of infection with *C. difficile*, and 82 of the residents, representing 68.3% of the population, did not have a prior history of *C. difficile* infection. The *C. difficile* history of 15 of the 120 residents, 12.5% of the study population, was not known (**Table 1**).

The synbiotic tablet was in the form of a chewable tablet containing two probiotics and one prebiotic. The two probiotics were 7.5 billion colony forming units (cfu) of the yeast *Saccharomyces boulardii* and 1 billion cfu of the bacteria *Bacillus coagulans*. The prebiotic present in the tablet was 500 mg of fructooligosaccharide. Residents were started on the synbiotic tablet shortly after beginning treatment with an antibiotic. The synbiotic tablet was given twice a day. Administration of the synbiotic tablet continued for two weeks after antibiotic treatment was completed at which time residents were evaluated for the presence of AAD and *C. difficile* infection. Demographic data included the sex and age of each resident and prior medical history with regard to *C. difficile* infection. In addition, all adverse events, side effects, resident compliance, and ease of administration with regard to taking the synbiotic tablet were noted. All data were obtained from resident records through a nurse employed by each nursing home using a questionnaire. Residents were not known by name but were assigned a code to protect their specific identity and privacy.

Table 1. Demographics of the study population.

Study Population n = 120	
Gender	**n (%)**
Female	77 (64.2%)
Male	43 (35.8%)
Age	**years**
Average Age	80 ± 10
Age Range	40-96
Prior *C. difficile* History	**n (%)**
No Prior History	82 (68.3%)
Known Prior History	25 (20.8%)
Prior History Not Known	15 (12.5%)

Statistical analysis of all numerical results was conducted by calculating the average and standard deviation.

3. Results

A total of 128 nursing home residents being administered antibiotics were given a chewable synbiotic tablet twice a day from September, 2009 to November, 2009. Of the 128 residents offered the synbiotic tablet, 120 were evaluated for the purpose of this study and constituted the study population. Eight residents were not evaluated because the data received from the nursing home was incomplete.

Most residents started the synbiotic regimen within 3 to 4 days after beginning antibiotic treatment. The average delay between initial treatment with antibiotics and the start of ingestion of the synbiotic tablet was 2 ± 4 days. Slightly more than one-half of the 120 residents, 64, began taking the synbiotic tablet immediately after beginning antibiotic treatment (that is, beginning at 0 days).

Residents were evaluated for the presence of AAD and *C. difficile* infection 2 weeks after the completion of antibiotic treatment. During this 2-week period, residents were maintained on the synbiotic tablet. The results of the evaluation showed that 95% of the residents in the study population remained free of AAD while taking the synbiotic tablet (**Table 2**). Only 6 of the 120 residents, representing 5% of the study population, suffered from AAD (**Table 2**). More than 98% of the residents did not succumb to a *C. difficile* infection while taking the synbiotic tablet (**Table 2**). Two residents, representing 1.7% of the study population, tested positive for the presence of *C. difficile* (**Table 2**). Only 1 of these 2 residents, which is less than 1% of the study population, suffered from AAD and was classified as having CDAD (**Table 2**).

Clinicians found that the synbiotic tablet was easy to administer (**Table 3**). The tablet was easy to administer to 116 of the 120 residents, 96.7% of the study population.

Resident compliance with taking the synbiotic tablet was very high and is summarized in **Table 3**. Of the 120 residents in the study population, 113, representing 94.2% of the study population, complied with taking the synbiotic tablet for the duration of the study period. There were three reasons that 8 residents did not comply with taking the synbiotic tablet. Two of those residents, 1.7% of the study population, refused the synbiotic tablet. Of those 2 residents, one had been diagnosed with dementia which might explain the refusal. The reason the second resident refused the synbiotic tablet could not be ascertained. Three residents, 2.5% of the study population, stopped taking the tablet because they were discharged from the nursing home: one resident was discharged to another facility, one resident was discharged to a hospital, and one resident was able to return home. There was no relationship of using the synbiotic tablet and being discharged from the nursing home. Finally, 3 residents, 2.5% of the study population, discontinued use of the synbiotic tablet because they experienced gastrointestinal difficulties as presented below.

There were no reports of serious adverse reactions occurring in any of the residents taking the synbiotic tablet (**Table 3**). In addition, 94% of the residents taking the synbiotic tablet did not report any minor side effects of any kind (**Table 3**). Minor side effects, all gastrointestinal in nature, were reported by 7 residents representing only 5.8% of the study population. Three of these residents, 2.5% of the study population, experienced nausea. The nausea had no effect on compliance of resident's taking the synbiotic tablet. Four of the residents, 3.3% of the resident population, experienced gastrointestinal upset while taking the synbiotic tablet, 3 of whom were discontinued taking the synbiotic tablet as described above.

Table 2. Efficacy of the synbiotic tablet.

Study Population n = 120	
Antibiotic-Associated Diarrhea AAD	**n (%)**
Residents Free of AAD	114 (95%)
Residents With AAD	6 (5%)
***C. difficile* Infection**	**n (%)**
Residents Free of *C. difficile* infection	118 (98.3%)
Residents With *C. difficile* infection	2 (1.7%)
CDAD	**n (%)**
Residents Free of CDAD	119 (99.2%)
Residents With CDAD	1 (0.08%)

Table 3. Compliance, adverse reactions and minor side effects of synbiotic table.

Study Population n = 120	
Compliance	**n (%)**
Residents Complying with Tablet Schedule	112 (93.3%)
Residents Unable to Comply with Tablet Schedule	8 (6.6%)
Ease of Administration	**n (%)**
Clinician Indicated Tablet was Easy to Administer	116 (96.7%)
Clinician Indicated Tablet was Not Easy to Administer	4 (3.3%)
Adverse Reactions	**n (%)**
Reports of Adverse Reactions	0 (0%)
Minor Side Effects	**n (%)**
No Minor Side Effects	113 (94.2%)
Reported Minor Side Effects, Continued on Tablet	4 (3.3%)
Reported Minor Side Effects, Discontinued Tablet	3 (2.5%)

Therefore, only 3 residents representing 2.5% of the study population experienced a side effect that suggested they should stop taking the synbiotic tablet, strongly indicating that greater than 97% of the residents had no side effects or adverse reactions that would prevent use of the synbiotic tablet.

4. Discussion

The retrospective data presented in this report suggest that the synbiotic tablet decreased the incidence of AAD, *C. difficile* infection, and CDAD relative to outcomes expected if the population had not taken the tablet. The incidence of AAD in the study population was 5% which was 5-fold lower than the typical literature value of 25% for those not given a synbiotic tablet [5,6]. Less than 2%

of the study population was infected with *C. difficile*, which is 4- to 16-fold lower than the expected 8% to 33% incidence of infection observed in health care facilities [22]. Less than 1% of the study population was afflicted with CDAD, which is as much 15-fold lower than the predicted rates of CDAD for residents in health care facilities.

The low incidence of *C. difficile* infection observed in the study population is also notable because it is at least 60% lower than the incidence expected from recurring infections. Of the residents in the study population, approximately 21% had a prior history of *C. difficile* infection. Based on recurrence rate of 25% [7,17,22], more than 5% of the study population would have been expected to present a *C. difficile* infection; however only 1.7% of the study population presented a *C. difficile* infection, indicating that the synbiotic tablet suppressed *C. difficile* infection by 66%.

The data presented in this report agree well with prior studies using probiotic or synbiotic supplements. In this report, the synbiotic tablet prevented AAD, *C. difficile* infection, and CDAD by an estimated 75% or more relative to expected values. Reported clinical trials have shown that probiotic supplements containing *S. boulardii* or *B. coagulans* decreased levels of AAD by 50% to 85% [23,25] and CDAD by 45% to 85% [26-28]. Meta-analysis of multiple clinical trials has shown that probiotics decrease ADD and CDAD by 40% to 60% [29,30].

The mechanisms by which the components of the synbiotic tablet used in this study, *S. boulardii*, *B. coagulans*, and fructooligosaccharide, function to reduce AAD, *C. difficile* infection, and CDAD have begun to be elucidated. Each of the components of the synbiotic tablet appear to inhibit AAD, *C. difficile* infection, and CDAD through different mechanisms. Studies have shown that *S. boulardii*, can up-regulate IgA expression against *C. difficile* toxin A [31,32]. *S. boulardii* may also inhibit *C. difficile* toxin directly [33-35]. Furthermore, *S. boulardii*, has been shown to inhibit inflammatory signaling pathways which may result in decreased damage to the digestive tract by pathological species [36,37].

In combination with fructooligosaccharide, *B. coagulans* has been shown to have properties that inhibit species that cause AAD [38]. Fructooligosaccharide has been shown to increase the growth of beneficial bacteria such as bifidobacteria [39]. Bifidobacteria cause an increase in short-chain fatty acid concentration and a decrease in the pH in the colon which results in conditions that are not conducive to the growth of certain pathogenic organisms. This may help restore colonization resistance in the digestive tract [40,41]. Use of the synbiotic tablet in this study containing components that function through different mechanisms increases the probability of success.

No serious adverse reactions were reported while any of the residents were taking the synbiotic tablet. Minor side effects involved nausea or gastrointestinal upset. It is not clear that the synbiotic tablet was the actual cause of the nausea or gastrointestinal upset. The synbiotic tablet was easy to administer with clinicians finding that nearly 97% of the residents had no difficulty ingesting the tablet. Resident compliance with taking the synbiotic tablet was very high, with over 93% of residents using the tablet as directed, indicating that the synbiotic tablet was well tolerated by the study population.

There are limitations regarding the interpretation of the results of this retrospective study. The first is that the evaluations for AAD and the presence of *C. difficile* were performed 2 weeks after the completion of antibiotic treatment. Although 80% of AAD cases occur 4 to 5 days after commencing antibiotic treatment, AAD can occur up to 2 months after the initial treatment with antibiotic. Therefore it is possible that some cases of AAD and *C. difficile* infection were missed. Second, this study did not examine a dose response. It is possible that an increased dose of the synbiotic may further inhibit *C. difficile* infections [5,42]. Finally, this study focused solely on adult residents in nursing homes and not patients in hospitals. However, it is believed that the results of this report will be applicable to settings other than nursing homes.

The data presented in this report suggest that the synbiotic tablet can prevent AAD and *C. difficile* infection in residents in a nursing home who receive antibiotics. Development of an approach using synbiotics to replace beneficial microbes lost in the digestive tract during antibiotic treatment could significantly reduce the incidence of antibiotic-resistant infections and the prevalence of AAD in health care facilities. Use of synbiotics could also decrease reliance on antibiotics and thus reduce the rise in antibiotic-resistant pathogens. Furthermore, synbiotics could reduce the treatment costs associated with residents suffering from antibiotic-resistant infections and AAD. For example, it has been shown that decreases in CDAD observed with administration of probiotics are associated with decreases in colitis [26]. The synbiotic tablet used in this study can be incorporated into the health care protocols of health care facilities as an easy to administer, safe, acceptable, and easy to tolerate approach to preventing AAD and *C. difficile* infections.

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