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Saccharomyces boulardii for the Prevention of Hospital Onset *Clostridium difficile* Infection

Elizabeth A. Flatley[1], Ashley M. Wilde[2], Michael D. Nailor[1,3]

1) University of Connecticut School of Pharmacy, Storrs, CT;
2) Norton Healthcare Department of Pharmacy, Louisville, KY;
3) Hartford Hospital, Hartford, CT, USA

Address for correspondence:
Michael D. Nailor, PharmD, BCPS AQ-ID
80 Seymour Street
Hartford Hospital
Hartford CT 06102
Michael.Nailor@hhchealth.org

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ABSTRACT

Background & Aims: Probiotics, including *Saccharomyces boulardii*, have been advocated for the prevention of *Clostridium difficile* infection. The aim of this project was to evaluate the effects of the removal of *S. boulardii* from an automatic antibiotic order set and hospital formulary on hospital onset *C. difficile* infection rates.
Method. Design: A retrospective chart review was performed on all patients with hospital onset *C. difficile* infection during the 13 months prior (control group) and the 13 months after (study group) removal of an automatic order set linking *S. boulardii* capsules to certain broad spectrum antibiotics. Setting: A large 800+ bed tertiary hospital
Results: Among all hospitalized patients, the rate of hospital onset *C. difficile* infection was 0.99 per 1000 patient days while the *S. boulardii* protocol was active compared with 1.04 per 1000 patient days (p=0.10) after *S. boulardii* was removed from the formulary. No difference in the rate of hospital onset *C. difficile* infection was detected in patients receiving the linked broad spectrum antibiotics during and after the removal of the protocol (1.25% vs. 1.51%, respectively; p=0.70).
Conclusions: Removal of *S. boulardii* administration to patients receiving broad spectrum antibiotics and the hospital formulary did not impact the rate of hospital onset *C. difficile* infection in either the hospital population or patients receiving broad spectrum antibiotics.

Key words: probiotics – *Saccharomyces boulardii* – *Clostridium difficile* infection.

INTRODUCTION

Clostridium difficile infection (CDI) can be a devastating consequence of antimicrobial therapy caused by the overgrowth of *C. difficile* and subsequent production of toxins. Overgrowth is often thought to occur as antimicrobial therapy eliminates normal commensal bacteria while the relatively resistant *C. difficile* persists. The antibiotic classes most commonly associated with CDI have traditionally been cephalosporins and clindamycin: however, in facilities where the North American Pulse field 1 strain is epidemic, fluoroquinolones are commonly associated [1].

Probiotics, including *Saccharomyces boulardii*, are relatively benign live microorganisms that are used to prevent or treat various gastrointestinal complications that arise from diminished commensal bacterial counts including irritable bowel syndrome and non-*C. difficile* antibiotic associated diarrhea [2]. Although there is some data to suggest probiotics may be effective in preventing CDI, randomized control data evaluating *S. boulardii* compared to placebo are sparse [3]. Trials evaluating the utility of *S. boulardii* for the prevention of CDI after it was added to a hospital formulary are unsatisfactory as other measures to control CDI may also have been implemented.

At Hartford Hospital in Hartford, Connecticut, an increase in the incidence of CDI in 2006 prompted the following changes: 1) more stringent cleaning procedures; 2) CDI positive patients were isolated and placed in contact precautions and 3) implementation of a protocol that linked an order to initiate *S. boulardii* therapy to patients receiving antibiotics highly associated with causing CDI. The hospital's electronic medical record automatically generated an order for oral *S. boulardii* 250 mg twice a day for patients receiving any linked antibiotics. At the time the antibiotic was discontinued the

provider was prompted to either continue or discontinue the *S. boulardii* order. The antibiotics linked to order of *S. boulardii* were intravenous formulations of clindamycin, cefepime, ceftazidime, ceftriaxone, cefuroxime, and fluoroquinolones. In 2009, the hospital re-evaluated its CDI prevention strategies. As no new convincing data was published on the administration of *S. boulardii* to prevent CDI, the hospital no longer considered the evidence sufficient to warrant its use. As a result, the protocol was discontinued and *S. boulardii* was removed from the formulary in December, 2009. The purpose of this study was to determine the effect of elimination of *S. boulardii* on hospital onset CDI rates at Hartford Hospital.

METHODS

Study design

To determine the effects of removing *S. boulardii* from the formulary, two types of analysis were performed. The first and primary analysis examined the incidence rate of hospital onset CDI (hCDI) in the general hospital population. The second analysis examined the rate of hCDI among patients receiving linked antibiotics as this group would have been the most likely to benefit from *S. boulardii*. To conduct these two analyses a retrospective review was approved by the Institutional Review Board at Hartford Hospital that examined the time just before removal of *S. boulardii* and the period immediately following it. The control group included all patients admitted from November, 2008 through November, 2009, inclusive, with hCDI. The study group included patients admitted from January 2010, through January, 2011, inclusive, after *S. boulardii* had been removed from the formulary with hCDI. December 2009 was excluded as a washout period during which *S. boulardii* was being transitioned off the formulary.

C. difficile testing

C. difficile testing was initially conducted on clinical samples of unformed stool by enzyme linked assay (ELISA) for toxins A and B. In August 2009, during the control group time period, the procedure for testing was changed to include C. diff Quik Chek Complete (Inverness Medical, Princeton NJ) and a PCR assay of either BD GeneOhm Cdiff Assay (BD Diagnostics, San Diego CA) or GeneXpert *C. difficile* assay (Cepheid, Sunnyville CA). This algorithm is more sensitive than the previous testing method (ELISA) for toxins A and B [5].

Inclusion and exclusion criteria

Patients were included if they had hCDI. For the purpose of this study, the definition of hCDI is a positive *C. difficile* assay at least 48 hour after admission with no record of diarrhea, three or more loose stools per day, or receipt of CDI treatment within the first 48 hours after admission. Patients with a history of CDI were included as long as the recurrence occurred after the first 48 hours of their admission. Patients were included more than once if the CDI episodes were from different admissions. Other exclusion criteria were admission to the inpatient psychiatric ward and the maternity ward. These wards are separated from other areas in the hospital where patients are located, have minimal use of the linked antibiotics and have low CDI rates. Thus, the incidence of CDI in these areas did not reflect that of the general hospital population.

Patients with severe neutropenia, inflammatory bowel disease or bowel ischemia were recommended not to receive this therapy. However, physicians had to manually discontinue the probiotic if they did not want it prescribed. Patients receiving medications through enteral tubes did not receive *S. boulardii* due to infection control risks.

Outcomes

The primary outcome was the incidence rates of hCDI in all hospitalized patients during the control and study group times. Hospital days were tabulated after the removal of psychiatric and maternity ward data. The secondary outcome was the incidence of hCDI among patients who received a linked antibiotic during their hospital course in the control and study groups. A two sided Student's *t*-test and Mann-Whitney U test were calculated for continuous variables for normally and non-normally distributed data, respectively. A Pearson's chi-square test was used to describe differences for categorical variables between two or more groups. An alpha level of 0.05 was established a priori such that all results yielding $p<0.05$ were considered to be statistically significant. SPSS v. 21 (IBM, Armonk, NY 2013) was used for all analyses.

RESULTS

Primary analysis

The demographics of hCDI cases between groups were similar (Table I). There were 167,157 hospital patient days with 167 hCDI cases in the control group and 183,867 hospital patient days with 191 hCDI cases in the study group. No statistically significant difference was detected in the incidence of hCDI between the two groups with 0.99 per 1000 patient days in the control group and 1.04 per 1000 patient days in the study group ($p=0.10$). Additionally, receipt of linked antibiotics was similar in patients acquiring hCDI; 109/167 (65%) patients and 127/191 (66%) patients in the control and study group, respectively. Cefepime, ceftriaxone, and levofloxacin were the most common linked antibiotics in both the control and study groups. Median number of days to acquisition of hCDI also did not differ between the two groups (8 and 7, respectively; $p=0.32$).

Secondary analysis

The allocation of patients receiving *S. boulardii* linked antibiotics during the control time period and study time periods was also similar (Fig. 1). In total, 8708 patients in the control group and 8411 patients in the study group had orders for linked antibiotics. Of the patients who received a linked antibiotic, 109 and 127 patients acquired hCDI in the control and study group, respectively. This equated to a rate of 1.25% and 1.51% among patients who received linked antibiotics in the control and study group, respectively ($p=0.698$).

DISCUSSION

To our knowledge, this is the first study that assessed the impact of eliminating prophylactic *S. boulardii* on rates of

Table I. Baseline demographics and clinical characteristics of patients with hospital onset CDI

Variable (measure)	Control (pre-) group	Study (post-) group	P value
N, % of sample	167, 46.6%	191, 53.4%	-
Age, years (mean ± SD)	65.7 ± 18.4	65.4 ± 18.9	0.87[A]
Race/ethnicity (n, %)			0.37[B]
White	126 (75.4)	142 (74.3)	
Black	19 (11.4)	19 (9.9)	
Hispanic	15 (9.0)	26 (13.6)	
Other	7 (4.2)	4 (2.1)	
Setting pre-admission (n, %)			0.52[B]/0.33*
Home	110 (65.9)	116 (60.7)	
Other hospital	20 (12.0)	20 (10.5)	
Skilled nursing facility	35 (21.0)	53 (27.7)	
Group home	2 (1.2)	2 (1.0)	
Days from admission to first positive *C. difficile* test [median (IQR), min-max]	8 (4-14), 2-141	7 (4-12), 2-95	0.32[C]
Residing in ICU at time of *C. difficile* positive test (n, %)	38 (22.8)	47 (24.6)	0.68
Receipt of any linked antibiotic (n, %)	109 (65.3)	127 (66.5)	0.81[B]
Receipt of ≥2 linked antibiotics (n, %)	40 (24.0)	42 (22.0%)	0.66[B]
Cefepime	63 (37.7)	74 (38.7)	0.84[B]
Ceftazidime	10 (6.0)	5 (2.6)	0.11[B]
Ceftriaxone	45 (26.9)	58 (30.4)	0.48[B]
Cefuroxime	1 (0.6)	0 (0.0)	Not evaluated
Ciprofloxacin	2 (1.2)	6 (3.1)	0.21[B]
Clindamycin	4 (2.4)	3 (1.6)	0.57[B]
Levofloxacin	33 (19.8)	29 (15.2)	0.25[B]

CDI: C. difficile infection; IQR = interquartile range; * if "Group home" (n=4) is excluded; [A] Student's *t*-test; [B] Pearson's chi square test; [C] Mann-Whitney U test

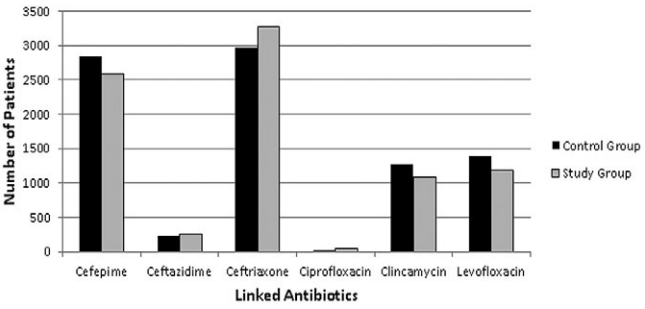

Fig. 1. Number of patients receiving *S. boulardii* linked antibiotics

hCDI in both the overall hospital population and those patients receiving high risk antibiotics. Study times were chosen several years after the implementation of the other infection control measures to minimize bias from these measures may have had on the rate of hCDI. In both the patients receiving linked antibiotics and the overall hospital, a difference in the rate of hCDI was not detected. The findings support our institutions decision to remove *S. boulardii* from the formulary secondary to failure to produce efficacy and to reduce costs and potential adverse effects. At the time of the study, acquisition costs for *S. boulardii* were close to $30 000 a year, resulting in significant cost savings for the institution. Although *S. boulardii* is generally considered to have low pathogenicity and tolerable safety profile, cases of fungemia have been documented from its use as a probiotic [3] and at least one case was associated with its use at our facility. While some experts advocate on behalf of probiotics for antibiotic associated diarrhea [4], guidelines are consistent with our findings and do not support probiotics such as *S. boulardii* for primary prevention of CDI [3].

This study had several limitations including that it is a retrospective review and thus lack of effect cannot be explicitly linked. Also we were unable to specifically measure *S. boulardii* usage in the control group. However, *S. boulardii* orders were automatically ordered with the linked antibiotics and together with our anecdotal observations we believe that almost all patients receiving the linked antibiotics also received the probiotic. As a result of the institution switching to a more sensitive test for CDI [5], a bias may have been introduced that would have favored *S. boulardii* therapy in preventing hCDI since the more sensitive test was used in only 4 months in the control group compared to 13 months in the study group. Within the control group time period, the hCDI rate was 0.83 cases per 1000 patient days during the 9 months before the change in testing compared with 1.1 cases per 1000 patient days for the four months following the testing change (p=0.4).

This study was not powered a priori as the rate of hCDI was not known within the institution. A *post-hoc* power estimate

was done based on a χ^2 test and found that the study had 80% power to detect an absolute difference of 34% in the incidence of hCDI. If the numerical difference that was found between the incidence rate of hCDI in the two groups were true, 20 000 patient days of *S. boulardii* would need to be administered to prevent one additional case of hCDI.

Fecal bacterial species are less diverse in patients with recurrent CDI as compared to patients without CDI or with their first occurrence of the disease [6]. Single species probiotics may not be sufficient to repopulate the colon of patients receiving antibiotics to prevent or help treat CDI. A greater diversity of species repopulation has been trialed for the treatment of recurrent CDI utilizing fecal transplants with great success, but robust single organism trials demonstrating benefit are lacking [7]. Lastly, other modalities might be more advantageous in an effort to prevent CDI. Clinicians are now hypothesizing that antimicrobial stewardship programs may be more effective than probiotic prophylaxis and have other added benefits such as reduced antimicrobial resistance within other species of pathogenic bacteria [8].

CONCLUSION

Administering *S. boulardii* with intravenous broad spectrum antibiotics as prophylaxis was not effective for preventing hospital onset CDI.

Conflicts of interest: none to declare.
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