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Brief Report

Probiotic use as prophylaxis for *Clostridium difficile*-associated diarrhea in a community hospital

Shelby L. Hudson PharmD, MS^a, Gretchen Arnoczy MD^b, Heather Gibson PharmD, BCPS^{c,*}, Christina Thurber PharmD, BCPS^a, Jayne Lee RN, MPH, CIC^d, Andrew Kessell PharmD, MBA, MS^e

^a Pharmacy, FirstHealth of the Carolinas Moore Regional Hospital, Pinehurst, NC

^b Infectious Disease, FirstHealth of the Carolinas Moore Regional Hospital, Pinehurst, NC

^c Antimicrobial Stewardship/Infection Control, FirstHealth of the Carolinas Moore Regional Hospital, Pinehurst, NC

^d Infection Control, FirstHealth of the Carolinas Moore Regional Hospital, Pinehurst, NC

^e Antimicrobial Stewardship/Pharmacy, FirstHealth of the Carolinas Moore Regional Hospital, Pinehurst, NC

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A B S T R A C T

This study was a retrospective chart review from January 1, 2015 through June 30, 2017, comparing the incidence of *Clostridium difficile*-associated diarrhea (CDAD) in patients taking select broad spectrum antibiotics with probiotics versus without probiotics. The purpose was to determine if probiotic use was associated with a reduction in the incidence of CDAD. A total of 5,574 hospital encounters were reviewed, showing a 0.96% incidence of CDAD in patients receiving a probiotic compared to a 2.19% incidence of CDAD in patients with no probiotic (risk ratio = 0.442; $P = .00743$). These findings show probiotic use was associated with a statistically significant lower incidence of positive *C. difficile* test results compared to no probiotic use.

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Clostridium difficile-associated diarrhea (CDAD) can result from a disruption of normal gastrointestinal (GI) tract flora, which allows the proliferation of the *C. difficile* organism. One primary cause of disruption of GI flora is the use of broad spectrum antibiotics.¹ Probiotics can promote normal GI flora and offset the negative microbiota effects of antibiotics to potentially prevent the development of CDAD.^{2,3} This has both clinical and financial implications for the health care system. There are close to half a million *C. difficile* infections (CDI) in the United States each year, with a total cost of \$3.2 billion or \$2,454 per case.^{4,5} This compares to an average cost of \$24 per course of probiotic treatment for CDAD prophylaxis.⁶ The purpose of this study was to determine if probiotic use during broad spectrum antibiotic therapy was associated with reduced incidence of CDAD within a single community hospital.

METHODS

This study was conducted at a 402-bed, acute care, not-for-profit community hospital. The institutional review board deemed this

* Address correspondence to Heather Gibson, PharmD, BCPS, FirstHealth of the Carolinas Moore Regional Hospital, c/o Infection Control, 155 Memorial Dr, Pinehurst, NC 28374.

E-mail address: hdgibson11@gmail.com (H. Gibson).

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study exempt from human studies review. Data collection involved a retrospective chart review for the period January 1, 2015 through June 30, 2017, comparing the incidence of positive *C. difficile* test results in patients taking select broad spectrum antibiotics with probiotics versus without probiotics during the same encounter. The single inclusion criterion was a minimum of 3 days of intravenous ciprofloxacin, levofloxacin, cefepime, ceftriaxone, imipenem/cilastatin, meropenem, sulfamethoxazole/trimethoprim, piperacillin/tazobactam, and/or clindamycin. The single exclusion criterion was age <18 years old. Concurrent use was defined as evidence of a probiotic ordered at least 2 days prior to *C. difficile* testing. The 2 probiotics used at this institution during this time period were *Saccharomyces boulardii* and *Lactobacillus acidophilus*. The χ^2 test (P value) and relative risk ratios were used to compare rates of positive *C. difficile* test results between groups.

RESULTS

A total of 5,574 unique hospital encounters were identified that involved a minimum of 3 days of study antibiotic. Two thousand sixty-three of these encounters involved the initiation of probiotics at least 2 days prior to *C. difficile* testing with 20 encounters having

positive *C. difficile* test results (0.96%). Three thousand five hundred eleven of the 5,574 encounters did not involve probiotic use initiated at least 2 days prior to *C. difficile* testing, of which 77 encounters had positive *C. difficile* test results (2.19%). The difference in incidence of positive *C. difficile* test results was significant at 0.96% with concurrent probiotic use and 2.19% without probiotic use (risk ratio = 0.442; $P = .00743$; number needed to treat = 88). The average time of probiotic use per encounter was 7 days. Of the patients receiving probiotics, 58.2% received *L. acidophilus*, 38.1% received *S. boulardii*, and 3.7% received both *L. acidophilus* and *S. boulardii*.

DISCUSSION

Several recent studies have investigated probiotics for the reduction of CDAD with conflicting results. The lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in older inpatients (PLACIDE) trial found no evidence of probiotic effectiveness in preventing antibiotic-associated diarrhea including CDAD.⁷ Alternatively, 1 study showed a delayed decrease in CDI incidence after prophylactic probiotic administration,⁸ and a 2017 Cochrane review found moderate evidence suggesting that probiotics are effective at preventing CDAD.⁹ Several limitations exist within these studies including differences in probiotic formulation, duration of probiotic therapy, higher than normal rates of CDI, and inclusion of patients not at high risk for CDI. Because of these issues, the recent Infectious Diseases Society of America/Society for Healthcare Epidemiology of America Clinical Practice Guideline for *C. difficile* Infection states there is insufficient evidence to recommend routine probiotic use for the prevention of CDI.⁴

The exclusion and inclusion criteria for this study were purposefully simplified to allow for a larger sample size and to increase the likelihood of detecting any underlying differences between groups. Demographic data were not analyzed owing to the large sample size and is a limitation of our study. It should be noted that this creates potential for confounding factors that could have influenced these study results.

The initiation of probiotics was analyzed in relation to positive *C. difficile* testing as opposed to the initiation of antibiotics that differs from previous studies. This method was chosen to ensure patients who received broad spectrum antibiotics and a probiotic after a positive *C. difficile* test were not included in the data set, thus guaranteeing patients received the probiotic as prophylaxis. This is a potential limitation in our study.

Although some providers at the hospital regularly choose to add probiotics for the purpose of CDAD prophylaxis, there is currently no institution-provided guidance regarding this practice and is completely at the discretion of the provider and patient. It is possible that providers and patients who chose to do so may also be more proactive in other methods of preventing *C. difficile* spread including effective hand hygiene or minimizing antibiotic therapy. Probiotic use did show a slight increase during the 30 month study time frame ($R^2 = 0.6$).

Probiotic use is not risk free. Individuals who are immunocompromised owing to HIV, chemotherapy, or other immune-modulating

conditions are more likely to develop complications of probiotics. Treatment in this setting must always consider risk versus potential benefit.¹⁰

There are currently several methods available for *C. difficile* testing. At the initiation of this study, primary polymerase chain reaction testing was used. Within the time frame of data collection, this method was transitioned to enzyme immunoassay for *C. difficile* toxins A and B, and glutamate dehydrogenase antigen with reflex to polymerase chain reaction in the event of discordant glutamate dehydrogenase and toxin results. Although this change would be expected to influence the overall number of positive *C. difficile* test results, this should impact both study groups equally.

CONCLUSIONS

This study found that probiotic use initiated at least 2 days prior to *C. difficile* testing in patients receiving broad spectrum antibiotics was associated with a statistically significant reduction in CDAD incidence. Although a retrospective analysis cannot prove causation, the results of this analysis provide evidence of an association with probiotic use and a decline in CDAD. Select providers at our institution are already choosing to add probiotics to patient regimens containing broad spectrum antibiotics. This presents an opportunity for additional research and facility-wide guidance regarding probiotic use in our community hospital.

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