The Role of Probiotics in Clostridioides difficile Disease Severity and Time to Disease Resolution

Stephanie Dym¹, Meredith Akerman², Nicole Fenner³, Burke A Cunha⁴, Sharon Blum¹,*

¹Department of Pharmacy, NYU-Winthrop Hospital, Mineola, New York, USA
²Department of Biostatistics, NYU-Winthrop Hospital, Mineola, New York, USA
³Long Island University Arnold and Marie Schwartz College of Pharmacy, Mineola, New York, USA
⁴Department of infectious Disease NYU-Winthrop Hospital, Mineola, New York, USA

*Corresponding author: Sharon Blum, Department of Pharmacy, NYU-Winthrop Hospital, Mineola, New York, USA. Email: Sharon.Blum@nyulangone.org

Received: September 02, 2021Published: September 24, 2021

Abstract

Background: Clostridioides Difficile Infection (CDI) is the leading cause of hospital-related diarrhea. It accounts for 15,000-30,000 deaths per year in the US and costs approximately $5 billion annually. The Infectious Disease Society of America guidelines have no recommendations regarding probiotic therapy. There is conflicting data regarding its efficacy and research on the role of probiotics in disease severity is lacking. Our primary objectives are to assess the impact of probiotics on CDI severity and disease resolution.

Methods: This was an IRB approved, single-centered, retrospective cohort analysis. Electronic medical records identifying patients diagnosed with CDI in NYU-Winthrop Hospital between 8/1/15-2/28/17 were reviewed. Clostridioides difficile positive patients were allocated into four groups depending on probiotic administration and time of initiation. Patients with a +tcdB gene were included. Patients with missing severity values or time to formed stool data were excluded. The primary outcomes were incidence of severe CDI and time to disease resolution. Chi-square or Fisher’s exact tests were used to compare groups for categorical variables; the Mann-Whitney or Kruskal-Wallis tests were used for continuous data. Time to CDI resolution was analyzed using standard methods of survival analysis. The groups were compared using the log-rank test.

Results: 210 CDI cases were analyzed, 65% of which were severe. 56% of patients were female and median age was 75 years (18.6-97.5). There was no difference in disease severity between the probiotics and no probiotics arms (p=0.32). Median time to disease resolution was 4 days. No difference in time to disease resolution was observed between patients never on probiotics and patients on established probiotic regimens (p=0.64). There was a significant increase in time to resolution in patients starting probiotics >24 hours after CDI diagnosis (p=0.03).

Conclusion: Probiotics increase pill burden as well as cost to patients and healthcare systems, without ameliorating disease severity or time to disease resolution.

Initial episode of C. difficile infection (CDI) is classified by the Infectious Disease Society of America (IDSA) Guidelines as non-severe, severe, or fulminant based on specified clinical data. Severe CDI is diagnosed based on a white blood cell count ≥ 15 000 cells/mL or a serum creatinine level > 1.5 mg/dL [1]. Although the most updated IDSA guidelines on the management of C. difficile recommend similar treatment courses for non-severe and severe CDI, studies have shown a significant difference in outcomes, prognosis, and burden on the healthcare system based on disease severity stratification. Patients with severe CDI have prolonged hospitalizations, increased need of intensive care management, increased risk of colectomy, and increased risk of mortality [3-5].
There is currently no consensus on the role of probiotics in CDI therapy, and specifically, in severe CDI [1,6,7]. While multiple beneficial roles of probiotics have been proposed [8], the data from clinical studies are conflicting [9-12]. In-vitro and pre-clinical studies have shown that probiotics can replenish the normal gut flora in patients who received antibiotics, provide intestinal barrier protection, modulate the innate and adaptive immune system and increase phagocytosis, and provide inherent antimicrobial activity [8,11]. Multiple studies have looked at the effects on incidence of first CDI occurrences [9,13] and recurrent CDI [14,15], with varying results between studies, yet these authors have been unable to find any studies that examined the effects of probiotics on incidence of severe CDI versus non-severe CDI, nor studies examining the effects of probiotics on time to disease resolution (soft or formed stool).

The purpose of this study is to explore a new place in therapy for probiotics in the setting of CDI. We aim to compare the incidence of severe CDI in patients taking probiotics versus no probiotics and to establish any differences in time to CDI resolution.

**Methods**

**CDI case obtainment**

This was a retrospective, single-center, cohort study of CDI positive cases at NYU-Winthrop Hospital from August 2015 through February 2017. This study was granted exempt status by the NYU-Winthrop’s institutional review board. A list of CDI-positive cases during our study timeframe was collected from the hospital’s microbiology lab. Patients were included if they were at least 18 years of age and had a positive C. difficile toxin B (tcdB) gene detected by PCR. Patients were excluded if they were missing CDI severity lab markers, when the available markers indicated non-severe CDI, and if the time to soft or formed stool was not documented. The electronic medical record (EMR) was used to collect the following data points: age, gender, use of antibiotics, use of probiotics, probiotic strains used, markers of CDI severity, number of loose stools at time 0 and 72 hours, time to soft or formed stool, and CDI course of treatment.

**CDI diagnosis**

Stools samples were sent to the microbiology lab for C. difficile testing in patients who presented with watery stools. CDI diagnosis was made via rapid detection of tcdB by real-time PCR.

**Defining study outcomes**

CDI severity was defined based on IDSA guidelines. Patients were determined to have severe CDI if they had any one of the following: white blood cell count > 15,000 cells/µL, serum creatinine > 1.5 mg/dL, or hypotension [1]. Hypotension was not clearly defined by the IDSA guidelines, so we used the criteria provided by the National Heart, Lung, and Blood Institute of systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg [19]. Albumin levels were collected, as well. Although albumin is not included in the IDSA’s CDI severity criteria, historically, many papers have used hypoalbuminemia as a marker of severe CDI [3,5,20].

Time to CDI resolution was defined as time to non-watery stools. The EMR progress notes were searched for stools described as “soft,” “formed,” or “non-watery.” We also determined CDI to be resolved if a patient had no stools in a 24-hour period.

**Probiotic strains**

At NYU-Winthrop Hospital, providers have the option of two probiotics. Lactobacillus acidophilus is on formulary. A serving size of 2 caplets provides 50 million colony forming units. Saccharomyces boulardii is available as a non-formulary alternative.

**Distinguishing probiotic use groups**

We had two probiotic use groups in our incidence of severe CDI analysis—no probiotics and probiotics. However, at the onset of data collection, we found that those two groups did not accurately represent the probiotic treatment course of our patients when analyzing time to disease resolution. To better portray the effects of probiotics on time to CDI resolution, we divided our patients into four probiotic use groups as follows (Table 1): never on probiotics (group 1), probiotics started at least 24 hours prior to CDI diagnosis (group 2), probiotics started within 24 hours of CDI diagnosis (group 3), and probiotics started at least 24 hours after CDI diagnosis (group 4).

**Statistical Analysis**

Descriptive statistics (mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum values for continuous variables; frequencies and percentages for categorical variables) were calculated separately by group. The chi-square test or Fisher’s exact test, as deemed appropriate, was used to compare the groups for categorical variables. For the two-group comparisons, the two-sample t-test or Mann-Whitney test was used for continuous data. For four group comparisons, analysis of variance (ANOVA) or the Kruskal-Wallis test was used.

The analysis of “Time to Disease Resolution” was accomplished by applying standard methods of survival analysis, i.e., computing the Kaplan-Meier product limit curves, where the data was stratified by group. In cases where the endpoint event had not yet occurred, the time until last follow-up was used and considered ‘censored’. The groups were compared using the log-rank test.

A result was considered statistically significant at the p<0.05 level of significance. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

**Results**

Two hundred and ten cases of tcdB gene were detected from August 2015 through February 2017.

**Disease Severity**

All 210 cases were included in the CDI disease severity analysis (Figure 1). There were 169 patients in the no probiotics arm and 41 patients in the probiotics arm. There were no significant baseline characteristic differences between the two groups (Table 2). The median age was 75 years (range 18.6-97.5 years) and 57% of patients were female. Over 80% of patients were on antibiotics, and presumably more had taken antibiotics within 12 weeks of their diagnosis. Of the patients who were taking probiotics, over 97% were taking L. acidophilus and 2.4% were taking S. boulardii.

Citation: Stefanie Dym1, Meredith Akerman1, Nicole Fenner1, Burke A Cunha1, Sharon Blum1*, The Role of Probiotics in Clostridioides difficile Disease Severity and Time to Disease Resolution  IJCMCR. 2021; 13(3): 001

DOI: 10.46998/IJCMCR.2021.13.000311
Table 1. Probiotic Use Group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CDI Severity</th>
<th>Time to CDI Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group Designation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never on probiotics</td>
<td>Group 1: Never on Probiotics</td>
<td></td>
</tr>
<tr>
<td>Probiotics</td>
<td>Group 2: On probiotics &gt; 24 hours before CDI diagnosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 3: On probiotics within 24 hours of CDI diagnosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 4: On probiotics &gt; 24 hours after CDI diagnosis</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Study Flowchart.

Figure 2: Rates of Severe and Non-severe CDI in Patients on No Probiotics versus Probiotics.
Figure 3: Kaplan-Meier Curves Representing Time to CDI Resolution and Comparing Probiotic-use Groups in Multiple Analyses.
Sixty-six percent of patients never on probiotics presented with severe CDI compared to 58% of patients in the probiotics group (p=0.32) (Figure 2). We found no significant differences between the groups in any one of the markers for severe CDI, including white blood cell count, serum creatinine, blood pressure, and albumin.

### Time to Disease Resolution

One hundred and ninety cases were included in the time to CDI resolution analysis. Cases were distributed in the following way: 86 patients in group 1, 39 patients in group 2, 41 patients in group 3, and 24 in group 4 (Figure 1). There were no significant differences in baseline characteristics among the 4 groups (Table 3). Median age was 74.4 years (range 18.6-97.5 years) and 55.3% of patients were female. Eighty-one percent of patients were on antibiotics and, similar to the disease severity group, presumably more had taken antibiotics within 12 weeks of their diagnosis. Of the patients taking antibiotics, 96% were taking L. acidophilus. We also looked for differences in CDI treatment regimens as this could have been a confounding factor in the time to CDI resolution analysis. There was no significant difference among the groups in the use of oral vancomycin, metronidazole, and tigecycline.

The median time to soft or formed stool was 4 days (range 1-18 days). In group 1 (patients who were never on probiotics), group 2 (patients who were on probiotics at least 24 hours prior to CDI diagnosis), group 3 (patients who were started on probiotics within 24 hours of CDI diagnosis), and group 4 (patients who were started on probiotics greater than 24 hours after CDI diagnosis), the median time to soft or formed stools was 4 days, 3 days, 4 days, and 6 days, respectively. There was a significant difference in time to CDI resolution among the four groups (p < 0.034) (Figure 3a). In group 4, the group that was started on antibiotics at least 24 hours after diagnosis, the median time when patients were initiated on probiotics was 3 days after CDI diagnosis. Therefore, we do not attribute the difference in time to resolution to the use of probiotics, rather these patients had a prolonged recovery from CDI and probiotics were added in desperation when patients did not show response to traditional antibiotic therapy.

We analyzed our dataset in different ways to further explore if probiotics made a significant difference in CDI resolution. When we compared group 1 (patients never on probiotics) to group 2 (patients on probiotics for at least 24 hours prior to CDI diagnosis), the median time to disease resolution was 4 days and 3 days, respectively (p < 0.63) (Figure 3b). We then combined group 1, group 3, and group 4 together, representing a cohort who had not been on an established probiotic regimen prior to developing CDI. The median time to CDI resolution for these groups when analyzed together was 4 days. Once again, there was no significant difference when compared to group 2 (on probiotics at least 24 hours prior to CDI diagnosis)
randomized, retrospective chart review. We were reliant on probiotics versus no probiotics. This study adds to the growing body of literature recommending combinations of strains of probiotics that can be used. Unlike FDA-approved medications, probiotics are not standardized and there are dozens of single-strains and doses. However, we used a reputable and popular strain at the time of this study which was the Delphi panel recommended using Lactobacillus acidophilus CL1285 and Lactobacillus casei LBC0R to prevent CDI [16]. He found that 80% of patients remained diarrhea-free for at least 12 months. Spinler et al. administered this same kefir to a CDI mouse model in an effort to explore the mechanisms of its protective effect. 17 Spinler unexpectedly found that the kefir drastically increased disease severity, with all of the mice receiving Lifeway kefir having more weight loss and quicker health decline than the comparator group.

There are studies showing benefits of probiotics in the management of CDI, but we must regard these results with reservations. One study was biased by its failure to control for type, duration, and dose of antibiotics and another study only found a benefit in a post-hoc analysis of only patients on high doses of oral vancomycin [12], a CDI treatment strategy that has seen impact in shortening the time to CDI resolution. Patients who were started on probiotics at least 24 hours after CDI diagnosis had a significantly longer time to CDI resolution than the other groups. But they were started on probiotics around the time when other groups were experiencing CDI resolution. Like previous studies that saw no benefit in the use of probiotics to prevent CDI, we saw no benefit in preventing severe CDI or shortening time to disease resolution. We recommend against the use of probiotics in this setting as probiotics ultimately increase pill burden and cost to patients without added benefits of mitigating CDI.

References


