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Use of Fecal Microbiota, Live-jslm (RBL) in the Routine Clinical Management of Clostridioides Difficile—First Five Cases

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Abstract: *Clostridioides difficile* infection (CDI) is one of the most common healthcare-associated infections. The current recommended treatment regimen for an initial episode of CDI is fidaxomicin (200 mg twice daily for 10 days) or vancomycin (125 mg, four times daily for 10 days) as an acceptable alternative [1]. Unfortunately, in approximately 25–35% of cases, CDI recurs within 1–2 months of the initial infection [2–5]. After a first recurrence, patients are substantially more likely to have a subsequent recurrence, with approximately 50–60% of these patients experiencing multiple recurrent CDI (rCDI) [2]. We report our early clinical experience in a multi-center community infectious disease private practice setting with the initial five patients who received the live biotherapeutic product, REBYOTA (RBL). Methods: Five patients who had experienced multiple recurrent episodes of *C difficile* infection and had failed the standard antibiotic therapy were prescribed the live biotherapeutic product REBYOTA (RBL). The product was administered as a single dose via the rectum. The patients were followed for eight weeks for clinical response and adverse events. Results: Patients included three males and two females, aged 20–86 years with recurrences ranging from 3 to 6 in the previous 18 months. Four patients received standard vancomycin, two patients had vancomycin taper, two had fidaxomicin and one had bezlotoxumab (Zinplava). RBL was administered easily and in less than 10 minutes. No new symptoms occurred within seven days. No recurrence was reported at eight weeks. No adverse events were reported, including no bacteremia or fungemia. No patient incurred expenses other than deductible costs. Conclusion: In a real-world setting, our initial five patients found that RBL was easy and convenient to administer with normalization of formed stools and an excellent overall clinical response at eight weeks. Furthermore, no adverse events were reported.

Keywords: FMT; Recurrent CDI; Cdiff Prevention

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Introduction

Clostridioides difficile infection (CDI) is one of the most common healthcare-associated infections and, as such, aggressive action is required to combat this threat [6]. There are an estimated 467,400 cases of healthcare- and community-associated CDI cases with approximately 29,000 deaths annually in the United States. The estimated direct medical cost of CDI in the USA is USD 5.4 billion (2014 dollars) [7].

Patients with CDI often present with watery diarrhea and abdominal pain, but symptoms can also include fever, hypotension, or ileus in more severe cases [8]; complications can include sepsis or colectomy/ileostomy [9–11]. The current recommended treatment regimen for an initial episode of CDI is fidaxomicin (200 mg twice daily for 10 days) or vancomycin (125 mg, four times daily for 10 days) as an acceptable alternative [1]. Unfortunately, in approximately 25–35% of cases, CDI recurs within 1–2 months of the initial infection [2–5]. After a first recurrence, patients are substantially more likely to have a subsequent recurrence, with approximately 50–60% of these patients experiencing multiple recurrent CDI (rCDI) [2]. *C difficile* infection is defined by the CDC and IDSA as the occurrence of diarrhea eight weeks after therapy.

The inciting dysbiosis for CDI can arise for several reasons. Antibiotics are considered significant disruptors of the gut microbiota and have the strongest association with CDI [12,13]. Older age brings changes in the gut microbiota, which could be influenced by a change in diet, lifestyle, or immune senescence [14,15]. Dysbiosis of the gastrointestinal tract is driven by the replacement of the normal healthy microbiome of Firmicutes and Bacteroidetes by Proteobacteria such as *Escherichia coli*.

Restoration of the normal state requires engraftment of healthy organisms such as Bacteroidetes and Firmicutes; these provide the essential metabolites and other products which provide colonization resistance and inhibit the germination of *C. difficile* spores.

Given the underlying state of gut dysbiosis that fosters CDI, an ideal goal for patients with CDI is eubiosis, or restoring the gut microbiota to a healthy state [16,17]. Fecal microbiota transplantation (FMT) is the delivery of stool or a full microbiota from a healthy donor to a recipient to mitigate disease by modifying the structure and/or function of the gut microbiota [18,19].

Live biotherapeutic products (LBPs) have been developed as an extension of the initial FMT studies, in part to standardize products and measure outcomes. LBPs contain live microbes that are able to prevent, treat, or cure a disease [20].

Fecal microbiota, live-jslm (RBL; REBYOTA ^{TM}, Ferring Pharmaceuticals, New Jersey), is a biologically sourced, broad consortium microbiota-based LBP that is processed from the stool of healthy donors, standardized, and administered rectally [21].

Results from a phase 3 trial of RBL, analyzed with a Bayesian hierarchical model formally incorporating data from a phase 2b trial, showed a treatment success rate of 70.6% [22]. Clinical success was defined as the maintenance of being diarrhea-free and formed stools within a period of eight weeks. Long-term data (up to 24 months) after treatment with RBL in a phase 2 trial showed durable treatment success, with more than 90% of treatment responders remaining CDI-free at 6, 12, and 24 months [23,24]. In a phase 3 study, the CDiff32 quality of life instrument was used to ascertain the impact of the therapy based on baseline symptoms. The changes in three domains of quality of life were compared with those achieved with placebo; these assessments included physical, mental, social, and total domains with superior changes occurring in mental and total domains [25]. Although this instrument is not used daily, the questions can help as a guide regarding the change in a patients life quality [25].

In these five cases, stool quality was assessed following the Bristol stool scale with soft stools being ascribed scores of 4–5, while soft to liquid stools had scores of 6 or 7.

Here, we report our experience with five patients who received RBL.

Case 1: A 78-year-old female with a history of obesity, depression, and hypercholesterolemia. She reported a sinus infection to the primary care physician, which was empirically treated with co-amoxicillin-clavulanate 875/125 mg orally twice daily (BID) for seven days. Three days after the end of therapy, the patient experienced profuse diarrhea. Her stool was tested via EIA to be toxin B positive for *C. difficile*. The patient was prescribed oral fidaxomicin 200 mg BID for 10 days but had issues having her prescription filled and was thus given oral vancomycin 125 mg four times daily (QID) for 10 days. Eleven days later, the diarrhea returned. The patient was administered a vancomycin taper (125 mg BID for 7 days, 125 mg daily for 7 days, and 1 capsule every other day for 14 days). She reported improvement and had formed stools; however, she developed diarrhea again and became fearful of the infection returning. Her diarrhea continued; therefore, she was prescribed 10 days of oral vancomycin. Two weeks later, the diarrhea returned with 6–7 stools per day. The patient did not want fidaxomicin; thus, she was given oral vancomycin 125 mg BID for 10 days. At this point, the patient had experienced three CDI episodes in a few months. Diarrhea returned soon after the last vancomycin course; as such, she was given an oral vancomycin taper. While on the vancomycin, she would form 4–5 soft stools per day, typically registering around 4–5 on the BSS. This was better than active diarrhea, but it was not her pre-CDI baseline. Three weeks into the oral vancomycin course, she was tapered off the vancomycin, and 72 hours later, she was given RBL. By day three after the transplant, her stools had become less frequent and more formed. Over the next three weeks, the patients stools were less frequent and generally firmer. Over the next week, stools returned to normal. After nine weeks, the patient was still diarrhea-free, no adverse events were reported, and she reported "being back to normal".

Case 2: A 74-year-old female with a history of hypertension, hyperlipidemia, anxiety disorder, and lumbar stenosis. The patient was unsure of her initial infection five years ago but reported that oral metronidazole treatment resolved the initial CDI. A second CDI episode occurred soon after the first and was treated with oral vancomycin. Four years later, she underwent a dermatological procedure for which she received an unknown antibiotic. She reported diarrhea and due to her history, she was tested with a PCR followed by an EIA. With both being positive, she was prescribed fidaxomicin. The diarrhea was resolved with fidaxomicin followed by oral vancomycin taper. Six months later, soft stools returned with intermittent diarrhea, which tested positive for *C. difficile* toxin B via PCR. The patient was given oral fidaxomicin 200 mg bid for 10–14 days of fidaxomicin to lead into a washout for Rebyota. In total, the patient experienced six episodes of CDI over the last 5 years, with some diagnosis via PCR and some via EIA. Regardless, due to the history of recurrent CDI and risk factors to have it again, it was decided to administer RBL after a three-day washout period. Eight weeks later, the patient had no issues and formed stools; she reported no adverse events and according to the patient, her quality of life had improved.

Case 3: A 20-year-old male with Crohns disease who had experienced a perforated appendix and abdominal abscess and was hospitalized. Antibiotics were prescribed during hospitalizationm consisting of intravenous piperacillin/tazobactam, which was then de-escalated to oral ciprofloxacin for approximately two weeks total to treat this infection. After discharge, his Crohns disease was subsequently controlled with methotrexate and Adalimumab. Approximately 6 months after his discharge from the hospital and after he was stable from a Crohns disease standpoint, his diarrhea re-developed. GI tested his stool which was positive for *C. difficile* PCR. The patient received oral vancomycin four times a day followed by a taper. He developed diarrhea after stopping the taper, tested positive via PCR again and treated with fidaxomicin. Due to his high-risk nature of recurrence, he was prescribed intravenous bezlotoxumab during his fidaxomicin course. He recurred six weeks later. For this course, he took oral vancomycin for eight weeks. Even after this round of vancomycin, his stools were formed, but they were frequent (5–7 times per day) with considerable urgency. The patient was then given amoxicillin for sinusitis and diarrhea redeveloped within a couple days after the amoxicillin. The diagnosis was made via PCR and vancomycin was prescribed and tapered until he could receive a RBL. Six weeks into his vancomycin course, vancomycin was discontinued and

RBL was administered within a 72-hour washout period. One week later, the stools began to be more formed those than pre-RBL and less frequent. At four weeks post-RBL, the patient reported a changed stool color with a little intermittent diarrhea. The patient was tested and the *C. difficile* test was negative via GDH/EIA reflexed to PCR. After eight weeks, the patient was still free of symptoms and reported no adverse events.

Case 4: A 79-year-old male with a complex medical history including prostate carcinoma, diverticulosis, subarachnoid hemorrhage, hypertension, and hyperlipidemia. He was hospitalized two years ago, and according to the patient, it was for lethargy. At that time, he received treatment for frequent diarrhea suggestive of CDI with oral vancomycin 125 mg QID for 10 days. He did improve and was discharged. Subsequent episodes, three months and two months later, were positive for *C. difficile* toxin via EIA. Further courses of oral vancomycin four times a day for 14 days were given for both bouts. For the recent bout, diarrhea redeveloped; the stool tested positive via EIA and the patient was given a vancomycin taper. Toward the end of the taper, vancomycin was discontinued and 72 hours later, RBL was administered uneventfully. By day three post-RBL, the patient reported having had two loose stools, but all subsequent stools were formed and less frequent than pre-RBL. At eight weeks, the patient remained well, and according to the patient, he felt his quality of life had been restored.

Case 5: An 86-year-old male with a history of Parkinsons disease and bladder and prostate cancer. He had experienced an episode of diverticulitis with diarrhea and was prescribed ciprofloxacin and oral vancomycin. He continued to lose weight but did not report diarrhea. His stool tested positive for *C. difficile* toxin via EIA, which was treated with oral vancomycin 125 mg QID for 14 days. Due to his chronic weight decline, he was admitted for rehabilitation. He would have intermittent diarrhea; therefore, he was placed again on vancomycin followed by a course of oral vancomycin taper. This did not resolve the diarrhea completely, but it decreased the frequency. It is unclear how many bouts he has had, but he does have recurrent CDI and is at high risk for another bout. Once discharged from rehab, and toward the end of this taper, he was given RBL after a vancomycin washout period with no issues on administration. His strength and appetite improved in a few days and the frequency of his intermittent diarrhea also improved. Eight weeks later, his diarrhea had completely resolved, and he did not report any further problems regarding recurrences along with no adverse events being reported.

Discussion

The five cases described highlight the challenges of managing rCDI. Four of the patients were older and had a complex medical history. All had experienced multiple CDI episodes, ranging from 3 to 6 bouts over a short interval. A variety of treatments were given, including oral metronidazole, vancomycin tapers, fidaxomicin, bezlotoxumab, and the standard 10–14-day vancomycin regimens. All of these patients continued to have numerous recurrences. Predisposing factors were observed in this series of cases. Some patients received prior antibiotics for community-acquired infections or surgical prophylaxis, and four of the five patients were old (>65 years old). The younger 25-year-old patient had underlying inflammatory bowel disease in addition to receiving broad spectrum antibiotics.

RBL is a standardized screened human-derived LBP delivered via the rectum using an enema. It can be administered in an examination room and does not require an endoscopy suite. Delivery can be carried out by any healthcare provider and does not require a physician. It takes approximately 10 minutes to administer. It does need to be stored in an ultra-deep freezer. It can be stored in a $-20\ ^{\circ}$C freezer. Prior to use, it must be thawed in a refrigerator (36–46 degrees Fahrenheit). A recent survey of subjects who had received the product in a clinical trial were almost exclusively happy with the convenience and speed of delivery without the need for bowel preparation or an endoscopy suite [26].

In each case, resolution of symptoms in the eight weeks following RBL provided significant improvement in the patients quality of life, which was assessed using questions relating to mental and physical criteria.

The limitations of these cases are the relatively short follow-up period; however, all of the patients were evaluated at eight weeks as per the CDC guidelines for assessing recurrent infection. Although adverse events were not systematically collected, any unexpected conditions were reported. The eight-week period was appropriate to assess for recurrence and, importantly, any longer-term potential events such as bacteremia or fungemia were not observed.

RBL is easy to administer in a single procedure that does not require bowel preparation or colonoscopy. Orenstein et al. have shown a unique durable and safe response over a 24-month period [24]. The restoration of the normal flora containing Firmicutes and Bacteroidia provides the essential metabolites to prevent rCDI. RBL, providing the full microbiota, restores these essential metabolites. This series of challenging cases of rCDI demonstrates the rapid effectiveness of a microbiome restoration LBP such as RBL and its maintained efficacy over eight weeks.

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