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Real World Experience of Simple Administration of a Novel Fecal Microbiome Replacement for Prevention of Recurrent *Clostridioides difficile*

HEALIX

Richard L. Hengel MD[1]; Sujatha Krishan, MD[2]; Timothy E. Ritter, MD[3]; Jonathan A. Rosenberg, MD[4]; Kathy A. Baker Ph.D., APRN[5] ; Lucinda J. Van Anglen, BS, PharmD[6]; Kelly E. Hanna, PharmD[6]; Amy Guo, PhD[7]; Mielad Moosapanah, PharmD[7]; Sanghyuk Seo, PharmD, MS[7]; Kevin W. Garey, PharmD[8]

[1]Atlanta ID Group, Atlanta, GA; [2]DFW Infectious Disease, Dallas, TX; [3]GI Alliance, Southlake, TX; [4]GI Alliance, Highland Park, IL; [5]Harris College of Nursing and Health Sciences, Texas Christian University; [6]Healix Infusion Therapy, Sugar Land, TX; [7]Ferring Pharmaceuticals, Parsippany, NJ; [8]University of Houston College of Pharmacy, Houston, TX

Introduction

Clostridioides difficile infection (CDI) is a global healthcare concern, causing between 15,000–30,000 deaths and healthcare costs exceeding $4.8 billion annually [1]. Even with appropriate treatment of CDI with standard-of-care (SoC) antibiotic therapy, first recurrences continue in up to 35% of patients following an initial episode [2-5]. While treating the CDI, SoC antibiotics disrupt the gut microbiota, increasing the risk for further recurrent CDI (rCDI). Microbial restoration with live biotherapeutic products may restore the diversity and composition of the gut microbiota to decrease the likelihood of rCDI.

Fecal Microbiota, live-jslm (RBL) is a rectally administered, pre-packaged, live biotherapeutic approved in November 2022 for the prevention of recurrence of *Clostridioides difficile* infection (rCDI) in adults [6]. Clinical trial data indicates success in prevention of recurrence [7,8] for RBL, the first FDA-approved microbiota product. Study is warranted of whether RBL, a novel therapy in preventing rCDI, may pose challenges in routine clinical administration, particularly with Infectious Disease (ID), Gastroenterology (GI) or other specialties not commonly providing rectally administered therapies.

Objectives

The objective of this study is to develop and report implementation of a simple administration protocol of RBL for rCDI prevention in routine clinical practice.

Methods

Study Design: Retrospective, multicenter cohort study conducted in physician office infusion centers (POICs) in the United States.

Patient Population: All patients who received at least one dose of RBL from February 2023 through August 2023.

Protocol: A multi-disciplinary protocol was developed for provision of RBL through POICs. Development included the following:

- Protocol designed by Nursing, Pharmacy, Business Office (BO), Operations, and Purchasing
- Certificate of Medical Necessity (CMN) for insurance approval
- Order set
- Guidelines for use:
  - Referral and order management
  - Notification to BO and Clinical Team of a new urgent (STAT) order
  - Insurance approval and submission of co-pay assistance, if applicable
  - Scheduling of patient with coordination of antibiotic discontinuation
  - Acquisition of RBL
  - Pre-appointment confirmation
  - Appointment procedures with preparation and administration

Data collection: Electronic medical records (EMR), administration records and internal databases were queried, and the following data collected:

- Patient demographics, including payor detail
- History of present illness (HPI) for current and past episodes of CDI
- CDI stool test results and antimicrobial therapy
- Time from order to treatment
- Nursing assessment for RBL administration
- Adverse effects during the procedure

Data Analysis: Continuous and categorical variables were reported using mean ±standard deviation (SD) or median with interquartile range (IQR) and frequency (percentage), respectively.

Study Cohort

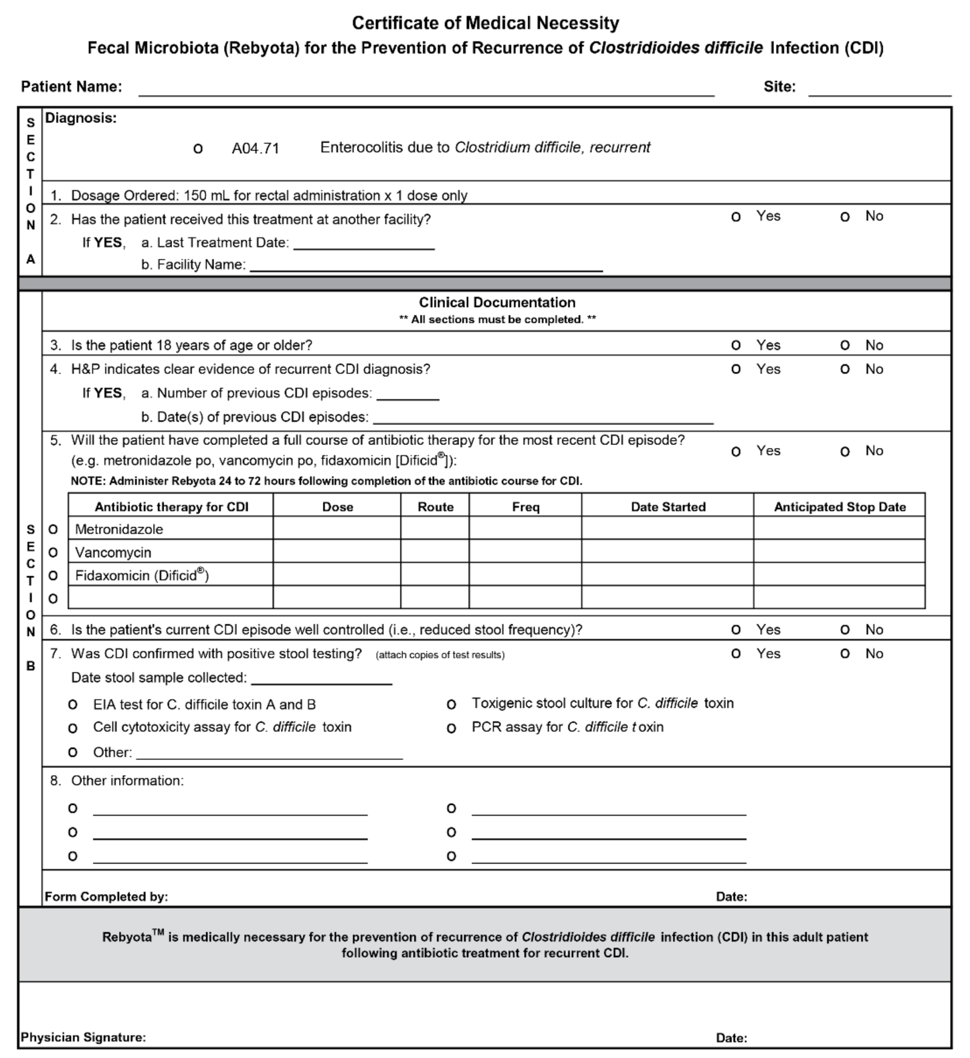
Table 1. Patient Characteristics

- 25 patients from 12 POICs in 8 states received RBL through 8/31/2023.
- Patients received treatment in GI POICs (n=14) and in ID POICs (n=11).

Characteristic	Results (N=25)
Age, years (mean±SD)	69±17
Age ≥65 years	17 (68%)
Female	17 (68%)
CDI episodes, including current, median (IQR)	4 (3-4)
SoC Antibiotic for the current episode of CDI	
Vancomycin	12 (48%)
Fidaxomicin	8 (32%)
Fidaxomicin and vancomycin	4 (16%)
Other*	2 (8%)
Health Insurance	
Commercial	9 (36%)
Medicare, Traditional	9 (36%)
Medicare Advantage Plan	7 (28%)

*vancomycin + metronidazole (n=1), unknown antibiotic (n=1); Data are presented as no. (%) unless otherwise indicated.

Figure 1. Certificate of Medical Necessity



Certificate of Medical Necessity

Fecal Microbiota (Rebyota) for the Prevention of Recurrence of *Clostridioides difficile* Infection (CDI)

Patient Name: ____ **Site:** ____

SECTION A

Diagnosis:

o A04.71 Enterocolitis due to *Clostridium difficile, recurrent*

1. Dosage Ordered: 150 mL for rectal administration x 1 dose only
2. Has the patient received this treatment at another facility? o Yes o No
   If **YES**, a. Last Treatment Date: ____
   b. Facility Name: ____

SECTION B

Clinical Documentation

**** All sections must be completed. ****

3. Is the patient 18 years of age or older? o Yes o No
4. H&P indicates clear evidence of recurrent CDI diagnosis? o Yes o No
   If **YES**, a. Number of previous CDI episodes: ____
   b. Date(s) of previous CDI episodes: ____
5. Will the patient have completed a full course of antibiotic therapy for the most recent CDI episode? (e.g. metronidazole po, vancomycin po, fidaxomicin [Dificid®]): o Yes o No
   NOTE: Administer Rebyota 24 to 72 hours following completion of the antibiotic course for CDI.

	Antibiotic therapy for CDI	Dose	Route	Freq	Date Started	Anticipated Stop Date
o	Metronidazole					
o	Vancomycin					
o	Fidaxomicin (Dificid®)					
o						

6. Is the patient's current CDI episode well controlled (i.e., reduced stool frequency)? o Yes o No
7. Was CDI confirmed with positive stool testing? (attach copies of test results) o Yes o No
   Date stool sample collected: ____
   o EIA test for C. difficile toxin A and B
   o Toxigenic stool culture for *C. difficile* toxin
   o Cell cytotoxicity assay for *C. difficile* toxin
   o PCR assay for *C. difficile* toxin
   o Other: ____
8. Other information:

Form Completed by: **Date:**

Rebyota™ is medically necessary for the prevention of recurrence of *Clostridioides difficile* infection (CDI) in this adult patient following antibiotic treatment for recurrent CDI.

Physician Signature: **Date:**

Table 2. Treatment Criteria

RBL Protocol Treatment Criteria
Primary Diagnosis: Enterocolitis due to Clostridium difficile, recurrent (ICD-10 Code: A04.71)
Patient Age (required to be ≥18 years)
Completion of Certificate of Medical Necessity, including the following:
History and Physical
Clear indication of current episode of recurrent CDI
No. of prior CDI episodes and dates
Positive stool test(s) for current episode, with type of test and dates
Antibiotic therapy for the current CDI episode
Antibiotic regimen and planned stop date (to plan for RBL administration)
Confirmation of control of symptoms with the current episode

Logistical Flow

Figure 2. Process Flow

1. Order written and submitted in EMR for RBL
2. Clinician compiles clinical notes and lab results to document medical necessity of RBL (must include HPI, positive stool test results, SoC antibiotic treatment)
3. Benefits verified STAT and case reviewed by clinical pharmacist
4. Authorization obtained STAT from insurance company as required.
5. Appointment scheduled upon insurance approval (typically plan for 48-72 hours following completion of SoC)
6. RBL is ordered 2-4 days prior to appointment*
7. RBL administered to patient

*RBL is ordered 2-4 days ahead of a confirmed appointment to allow for drug delivery and thawing. RBL must be thawed under refrigeration for 24 hours prior to use and may be stored for up to 5 days.

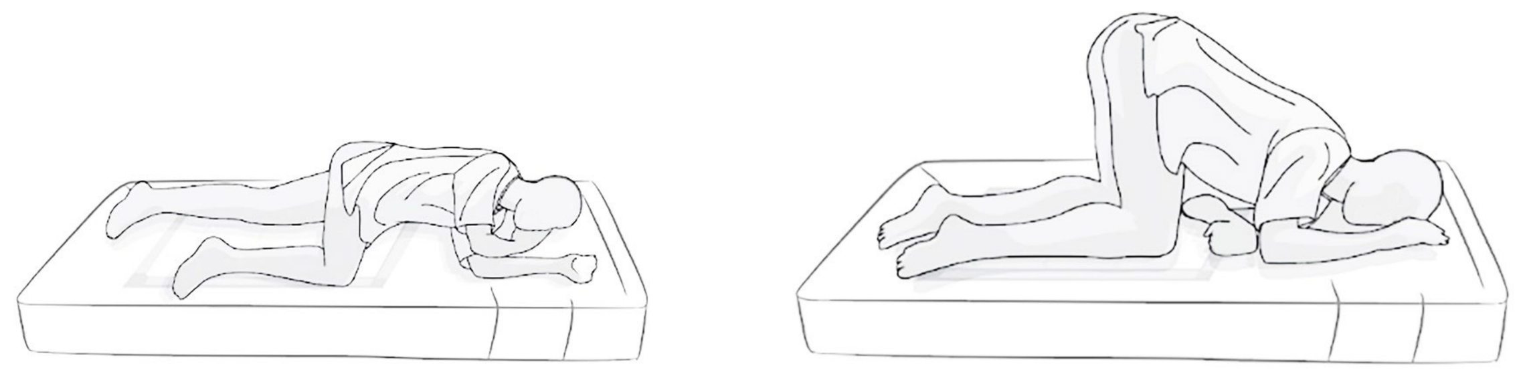
Table 3. Clinical and Administration Protocol

RBL Clinical Protocol
Appointment Coordination
Ensure the SoC antibiotic has been discontinued at least 24-72 hours prior to RBL administration.
Order RBL 2-4 days prior to the appointment for overnight delivery Tuesday through Friday.
Store RBL in the refrigerator immediately upon receipt. (Outside of a -70°C environment, RBL is stable for 5 days refrigerated.)
Pre-appointment Confirmation (24 hours prior)
Confirm patient does not have active diarrhea or continuing CDI symptoms.
Confirm the SoC antibiotic has been or will be discontinued at least 24-72 hours before the appointment.
Thaw RBL in the refrigerator for 24 hours prior to the appointment.
Request patient to empty bladder or bowel prior the appointment, but not to perform any bowel prep.
RBL Administration
Greet patient and room them in a private room with an exam table.
Have patient empty bladder and bowels if not done prior to appointment.
Don proper PPE and follow infection control guidelines for Clostridioides difficile.
Retrieve RBL from the refrigerator just prior to administration.
Place underpad on the exam table and position patient in a position as noted in Figure 3.
Prepare RBL for administration with attachment of provided tubing and apply lubricant to tip.
Administer single dose of RBL 150 mL immediately via gravity flow over 5 minutes.
Keep patient in the same position and observe for 15 minutes to minimize cramping.
Discharge patient from the clinic (may use bathroom prior to leaving if needed).

Abbreviations: PPE, personal protective equipment

Administration

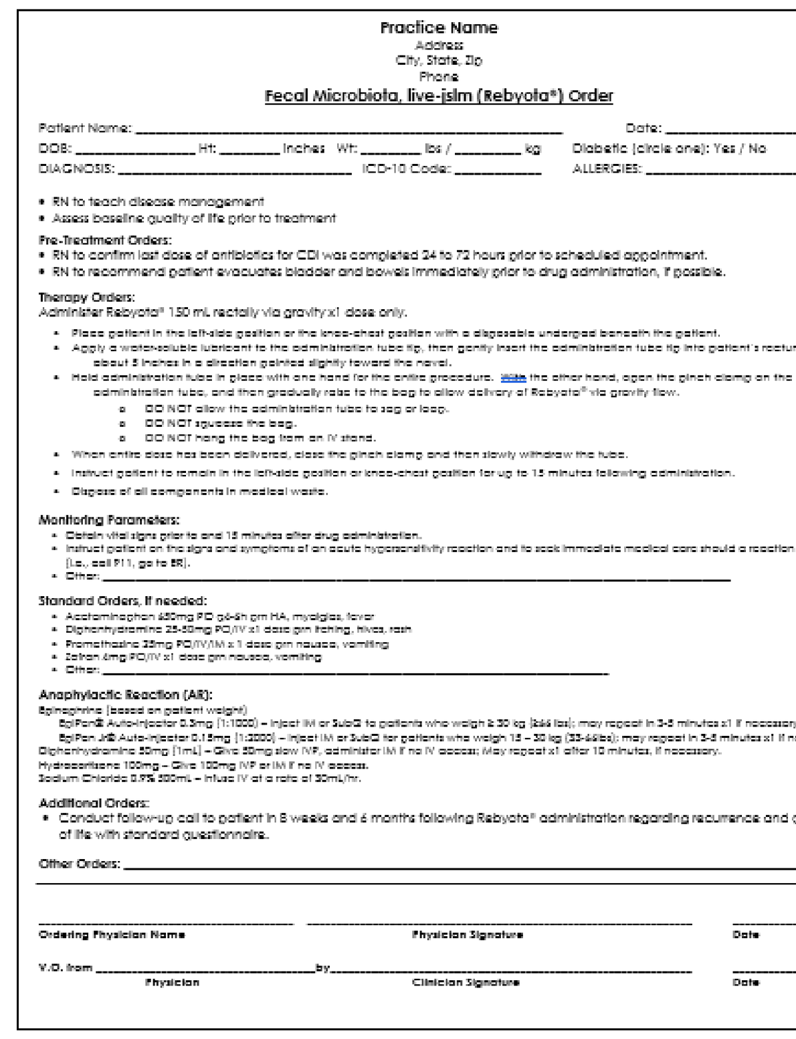
Figure 3. Administration Diagrams



Left-side position: Lie on left side with knee bent and arms resting comfortably.

Knee-chest position: Kneel, then lower head and chest forward until left side of face is resting on surface with left arm folded comfortably.

Figure 4. RBL Order



Practice Name

Address

City, State, Zip

Phone

Fecal Microbiota, live-jslm (Rebyota®) Order

Patient Name: ____ Date: ____

DOB: ____ Ht: ____ Inches Wt: ____ lbs / ____ kg Diabetic (circle one): Yes / No

DIAGNOSIS: ____ ICD-10 Code: ____ ALLERGIES: ____

- RN to teach disease management
- Assess baseline quality of life prior to treatment

Pre-Treatment Orders:

- RN to confirm last dose of antibiotics for CDI was completed 24 to 72 hours prior to scheduled appointment.
- RN to recommend patient evacuates bladder and bowels immediately prior to drug administration, if possible.

Therapy Orders:

Administer Rebyota® 150 mL rectally via gravity x1 dose only.

Monitoring Parameters:

Standard Orders, if needed:

Anaphylactic Reaction (AR):

Table 4. Administration Outcomes

Parameter	Cohort: No. of pts (N=25)*	Cohort: Result
Time from order to RBL administration, median days (IQR)	25	19 (17-30)
Instillation time via gravity flow, minutes, median (IQR)	12	6 (5-12)
Observation time, minutes	17	15
Administration position	16	-
Left lateral	-	15
Right lateral	-	1
Knee-Chest	-	0
Healthcare provider administering	22	-
Registered Nurse	-	16
Licensed Vocational Nurse	-	3
Nurse Practitioner	-	2
Physician	-	1
Adverse effects reported during the procedure	22	0
Reports of rectal leakage	22	0
Patients with bowel movement after the procedure	22	4

*Numbers noted for each parameter reflect those reported.

Discussion

This multicenter study involved the development of a simple protocol for administration of RBL, with subsequent analysis of the protocol. RBL is a rectally administered, pre-packaged, live biotherapeutic for the prevention of rCDI in adults.

- 25 patients received RBL following development and initiation of a protocol for use in 12 physician office infusion centers.
- Patients were older (69±17 years), majority female (68%) and most (64%) Medicare (Traditional or Medicare Advantage) recipients. Patients had a median of 4 episodes of CDI, including the current episode. Vancomycin was the most used SoC antibiotic for treatment of CDI.
- Protocol key success factors were:
  - Rapid compilation of required records for insurance approval following identification of rCDI. Median approval was 19 days from order to treatment.
  - Training for the nurses of the protocol and procedures for management, drug ordering, patient communication, and administration
  - Prompt order placement and receipt of RBL to meet appointments.
- The nurses confirmed completion of SoC at least 24-72 hours prior to administration of RBL.
- Administration of RBL was performed most often by registered nurses.
- RBL was instilled mostly in the left lateral position and completed in 6 minutes with 15 minutes of observation. No leakage or adverse events occurred.
- All patients adhered to appointments and received RBL as planned.

Conclusion

- **Development of a standardized protocol was critical in facilitation of RBL therapy in physician office infusion centers, particularly for nurses not familiar with rectal administration.**
- **Overall patient visit time and administration of RBL was brief and safe.**
- **RBL holds promise as a simple office-based therapy for the prevention of rCDI.**

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