Nursing Perspective

FECAL MICROBIOTA, LIVE-JSLM (RBL; REBYOTA®) FOR PREVENTION OF RECURRENT *CLOSTRIDIOIDES DIFFICILE* INFECTION: WHAT GASTROENTEROLOGY NURSES NEED TO KNOW

OPEN

Candace Cotto, RN
Kathy Baker, PhD, APRN, ACNS-BC, FCNS, FAAN
Echo Fallon, PharmD, RPh
Sharon Rimon, MSN, FNP-BC

Clostridioides difficile infection (CDI) is a major burden on patients and the healthcare system, causing an estimated 500,000 infections and 15,000 to 30,000 deaths per year in the United States (Guh et al., 2020; Lessa et al., 2015). CDI also causes substantial

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About the authors: *Candace Cotto, RN, Medical Research Center of Connecticut, Hamden, Connecticut.*

Kathy Baker, PhD, APRN, ACNS-BC, FCNS, FAAN, Texas Christian University, Harris College of Nursing & Health Sciences, Fort Worth, Texas.

Echo Fallon, PharmD, RPh, Ferring Pharmaceuticals Inc., Parsippany, New Jersey.

Sharon Rimon, MSN, FNP-BC, Reddy GI Associates, Mesa, Arizona.

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Correspondence to: *Echo Fallon, PharmD, RPh, 100 Interpace Parkway, Parsippany, New Jersey, echo.fallon@ferring.com.*

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morbidity, with many patients experiencing sepsis within 12 months following CDI, and a small but notable proportion of patients needing to undergo colostomy or ileostomy (Amin et al., 2022; Feuerstadt, Nelson, Teigland, Dahdal, 2022). Unfortunately, CDI often recurs, with up to 35% of patients experiencing recurrent CDI (rCDI) after an initial episode, and up to 65% of patients experiencing a subsequent recurrence after prior rCDI (Johnson et al., 2021; Kelly, 2012; Smits, Lyras, Lacy, Wilcox, Kuijper, 2016).

Fecal microbiota, live-jslm (RBL; REBYOTA®; formerly known as RBX2660; Ferring Pharmaceuticals Inc.), is the first US Food and Drug Administration (FDA)-approved, single-dose, rectally administered, microbiota-based live biotherapeutic product (LBP) for preventing CDI recurrence in adults (starting at first recurrence), after completion of standard-of-care antibiotic treatment for CDI (REBYOTA, 2022). Each dose of RBL is derived from a single healthy donor, standardized to include a known concentration range of organisms, and undergoes rigorous pathogen screening (providers may document the RBL lot number in the patient's medical record but are not required to). RBL contains a diverse set of micro-organisms, including *Bacteroides* spp., and is believed to restore a healthy gut microbiota to mitigate dysbiosis associated with rCDI (Kwak et al., 2020). It can be administered by any healthcare professional in any care setting.

Because this is the first LBP approved by the FDA for prevention of rCDI and one that gastrointestinal (GI) nurses will potentially be administering in their practice, we feel it is beneficial to share information about, and our experiences with, RBL to guide nurses on the use of this and future similar products. A second microbiota-based agent, fecal microbiota spores, live-brpk (VOWST®; Seres Therapeutics, Inc.), is FDA-approved to prevent CDI recurrence in adults, and is an oral medication that patients administer at home (VOWST, 2023).

The efficacy and safety of RBL has been established across five clinical trials that enrolled over 1000 participants, which included 3 Phase 2 trials (PUNCH CD, PUNCH CD2, PUNCH Open-label) (Blount, Shannon, Deych, Jones, 2019; Dubberke et al., 2018; Dubberke, Orenstein, Khanna, Guthmueller, Lee, 2023; Langdon et al., 2021; Orenstein et al., 2016), and 2 Phase 3 trials (PUNCH CD3 and PUNCH CD3-OLS [NCT03931941; completed late 2023]) (Khanna et al., 2022). In the Phase 3 PUNCH CD3 trial, RBL demonstrated a statistically significant treatment success (absence of CDI-related diarrhea) rate at 8 weeks compared with placebo (70.6% vs. 57.5%). Sustained treatment success was high, with 92.1% of participants who responded at 8 weeks remaining free of rCDI at 6 months.

RBL is well tolerated with consistent safety through 2 years of follow-up (Lee et al., 2023). Gastrointestinal side effects are common and can include abdominal pain, diarrhea, abdominal distension, flatulence, and nausea. Most are transient, mild to moderate in nature, and occur within the first 2 weeks after treatment (Khanna et al., 2022). No infections have been reported in the clinical trial program for which the causative pathogen was traced to RBL. RBL is well-established as safe for use in a broad patient population, including older adults with numerous comorbidities (Tillotson et al., 2023).

Patients receiving RBL report a positive impact on their health-related quality of life (HRQL), including mental and physical aspects of HRQL (Garey et al., 2023). Patients with rCDI considered rectal administration to be quick, convenient, acceptable, and lacking any perceived issues with administration, such as bowel preparation (Feuerstadt, Oneto, Tillotson, Van Hise, 2023).

Practical Considerations for Using RBL

Patient Characteristics

RBL is indicated to prevent subsequent rCDI in adult patients who have been diagnosed with rCDI, including those at first recurrence (REBYOTA, 2022). Prior to receiving RBL, patients should complete their existing antibiotic course for CDI, have resolution of CDI-associated diarrhea, and have a washout period of 1–3 days after the last dose of antibiotic before RBL administration. Patients do not need to undergo any special preparation for RBL administration, including no need for bowel preparation or fasting.

Preparing for RBL Administration

If applicable, confirm that RBL is covered by the patient's insurance. After ordering, RBL will be shipped frozen (orange box, 150 ml suspension bag inside) with an administration kit (blue box) and delivered typically in 1–3 days. Long-term RBL storage (>5 days) requires an ultracold freezer. Allow 1 day for RBL to thaw in the refrigerator before administration (thus, allow for a total of at least 2–4 days between ordering and administration). RBL can be thawed in the refrigerator next to other medications, as no separate storage is required. RBL is stable for 5 days in the refrigerator (including thaw time).

On the day of administration, gather the administration kit (blue box, stored at room temperature) and RBL (orange box containing product bag, thawing in the refrigerator). Gather other relevant supplies, such as a disposable underpad and water-soluble lubricant. Ask the patient to empty their bladder and bowels, if possible, just before the procedure.

Administering RBL

Ask the patient to assume one of two positions: left-side laying position, with top knee bent and arms resting comfortably; or knee-chest position, with their knees and face resting on the table and buttocks elevated. Most participants in clinical trials received RBL in the left-side laying position. In the RBL administration kit, close the pinch clamp on one end of the tubing, and connect the other end of the tubing with the spike port to the RBL product bag. Lubricate the free end of the tubing, and insert the lubricated tube about 5 inches into the patient's rectum. Open the pinch clamp and raise the product bag to a height that allows for gentle gravity flow, but do not hang the bag on an IV pole. Adjust the height of the bag as needed for the patient's comfort during administration. Patients may report a sensation of slight pressure or cold. Do not allow the tubing to sag or loop, as this will prevent the entire dose from being delivered. The administration should take about 5 minutes.

After RBL Administration

Withdraw the tube, and have the patient remain in the same position for up to 15 minutes, if tolerable, which can help minimize cramping but is not required for efficacy. It is normal for some RBL to remain in the tubing; do not squeeze the RBL bag to instill the remaining product, as this could be uncomfortable for the patient. Dispose of the tubing and bag as recommended by your facility (e.g. in a medical waste bin). There is no specific cleaning procedure that must be followed after RBL administration; rather, follow the cleaning guidance for your facility (as each site did in the Phase 3 clinical trial).

More information can be found at rebyotahcp.com. For any questions, please call Ferring Pharmaceuticals Medical Information at 1-888-FERRING.

Discussion

CDI occurs due to a disruption of the normal GI microbiota (i.e., dysbiosis) that allows dormant *C. difficile* spores to germinate and produce exotoxins, which underlies the pathophysiology of CDI (Abt, McKenney, Pamer, 2016; Fernández-García, Blasco, López, Tomás, 2017). LBPs have been developed for the prevention of rCDI, with the goal of restoring the GI microbiota from the dysbiotic state to a normal state by introducing a healthier microbiota consortium (Sehgal & Khanna, 2021). The FDA defines an LBP as a biological product, such as bacteria, that is applicable to the prevention, treatment, or cure of a disease (US Food and Drug Administration, 2016). Indeed, LBPs have been shown to restore the gut microbiota to a healthier state in patients who had recent rCDI (Feuerstadt et al., 2022; Orenstein et al., 2022).

RBL is one such LBP that has demonstrated sustained efficacy through 6 months, consistent safety through 2 years, and ease of patient administration in over 1000 patients treated in clinical trials to date. This FDA-approved, single-dose, rectally administered microbiota suspension is indicated for prevention of rCDI in adults, following standard-of-care antibiotic treatment for rCDI. Any healthcare professional can administer this therapy in any care setting, and patient survey data suggest high receptivity to RBL as easy and quick. Besides LBPs, other emerging therapies for CDI or to prevent rCDI include narrow-spectrum antibiotics and vaccines against toxins produced by *C. difficile* (Gonzales-Luna, Carlson, Garey, 2023).

Implications for Practice

As RBL is indicated to prevent the recurrence of CDI, patients do not meet the diagnostic criteria of having active CDI at the time that RBL is given. Eligible RBL patients have completed their standard-of-care antibiotics for CDI and should no longer be experiencing CDI-associated diarrhea; hence this is why no specific terminal cleaning procedure was required for the pivotal Phase 3 clinical trial. Nurses should defer to any practice site-specific expectations related to use of RBL, including for post-administration cleaning or product disposal.

RBL can be administered quickly in any care setting without the need for intensive monitoring afterwards and does not require any specific patient preparation before administration, aside from antibiotic completion 1–3 days prior. It is generally well tolerated by patients and effective at preventing rCDI.

Patients should be counseled about the possibility of common adverse events after RBL administration, including abdominal pain, diarrhea, abdominal distension, flatulence, and nausea. Most of these GI adverse events are transient, mild to moderate in nature, and occur within the first 2 weeks after treatment. Patients should also be counseled to not use systemic antibiotics in the short term after receipt of RBL (e.g., up to 8 weeks after administration), unless deemed necessary by their health care provider. If patients experience signs and symptoms of rCDI after RBL (e.g., persistent diarrhea for 2 consecutive days), particularly in the outpatient setting, they should contact their health care provider (REBYOTA, 2022).

Conclusion

LBPs such as RBL are becoming more frequently administered in GI care settings. As a result, GI nurses must be knowledgeable about and skilled in the administration of LBPs. Nurses also play an important role in

educating patients and caregivers about these products and the disease. Collectively, improved familiarity with LBPs and their proper use among nurses can contribute to successful prevention of rCDI in their patients.

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