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Vowst™ to Prevent Recurrent *Clostridioides difficile* Infection

By: Reegan Cotey, Pharm.D.

Background: *Clostridioides difficile* infection (CDI) is associated with 20,000 deaths annually in the United States.[1] The Infectious Disease Society of America (IDSA) recommends either fidaxomicin or vancomycin to treat CDI.[2] The clinical outcomes of CDI are often suboptimal since these medications eliminate toxin-producing *C. difficile* bacteria but not the bacterial spores.[3] Furthermore, these therapies may contribute to disease recurrence by depleting protective Firmicutes bacteria responsible for the breakdown of primary bile acids in the gut. Accumulation of primary bile acids has been shown to promote *C. difficile* spore germination, leading to a repeat episode of CDI. In addition to antibiotic use, risk factors for recurrent CDI (rCDI) include age ≥ 65 years, history of CDI in the past 6 months, immunocompromised disease states, severe CDI, and specific *C. difficile* ribotypes (027, 078, or 24).[2] The IDSA provides recommendations for the treatment of rCDI. According to the IDSA, patients with a first CDI recurrence should receive adjunctive treatment with bezlotoxumab (Zinplava™), a monoclonal antibody that binds to and neutralizes *C. difficile* toxin B. This medication was approved by the Food and Drug Administration (FDA) in 2016.[4] Fecal microbiota transplantation (FMT) therapies are recommended following a second CDI recurrence.[2] Fecal microbiota, live-jslm (Rebyota™), an enema formulation, was the first commercially available FMT product. It was approved by the FDA in 2022 to prevent recurrence of CDI in individuals at least 18 years of age, following antibacterial treatment for rCDI.[5] Fecal microbiota spores, live-bprk (Vowst™), the first oral FMT product, was approved by the FDA in April 2023 for the same indication.[6]

Mechanism of Action: Disruption of the balance of gut microflora is thought to enhance the recurrence of CDI.[3] Vowst™ contains a bacterial spore suspension that is used to restore the gut microbiota and thus prevent rCDI.[6]

Clinical Trials: The clinical safety and efficacy of Vowst™ have been established via the ECOSPOR III and IV trials.[7,8] ECOSPOR III was a phase III, double-blind, randomized, placebo-controlled trial that included patients 18 years of age or older who had three or more episodes of CDI within 12 months, a positive *C. difficile* toxin test, and resolution of symptoms while receiving 10 to 21 days of standard-of-care antibiotic therapy.[7] Patients were stratified by age (<65 or ≥ 65 years of age) and CDI antibiotic treatment (fidaxomicin or vancomycin) before randomization. One-hundred and eighty-two patients were randomized in a 1:1 ratio to receive Vowst™ (n=89) or placebo (n=93). Treatment was administered as four oral capsules once daily over 3 consecutive days after standard-of-care antibiotic treatment.

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To limit inactivation of the bacterial suspension in Vowst™ by prior CDI antibiotic therapy, patients received 10 ounces of magnesium citrate the night before taking Vowst™. The primary efficacy endpoint was to demonstrate the superiority of Vowst™ compared to placebo in reducing the risk of rCDI up to 8 weeks after treatment completion. Recurrence was defined as the onset of three or more unformed bowel movements per day over 2 consecutive days, a positive *C. difficile* stool toxin assay, an investigator's assessment that treatment was warranted, and the persistence of diarrhea until antibiotic treatment was started. The safety of Vowst™ was compared to placebo up to 8 weeks after administration. Demographics and risk factors for CDI were balanced between groups. The percentage of patients with rCDI was significantly lower in the Vowst™ group compared to the placebo group (12% and 40%, respectively). The Vowst™ group had a 68% reduction in the risk of recurrence compared to the placebo group ($p<0.001$; relative risk, 0.32 (95% confidence interval [CI], 0.18-0.58). There was a lower percentage of rCDI in all cohorts for the age-stratified and antibiotic-stratified analyses in patients that received Vowst™ compared to placebo. Adverse events were reported in 93% of the treatment population, the most common being mild-to-moderate gastrointestinal disorders. The authors of ECOSPOR III concluded that the use of Vowst™ was superior to placebo in reducing the risk of rCDI with minimal side effects. ECOSPOR IV was a phase III, single-arm, open-label trial that enrolled adult patients in two cohorts.[8] Cohort 1 included roll-over patients from ECOSPOR III who had a CDI recurrence within 8 weeks after receiving either placebo or Vowst™, and cohort 2 included de novo patients with at least two CDI episodes inclusive of the current episode. Recurrence was defined as at least three unformed stools per day for 2 consecutive days, any positive result for *C. difficile* stool test for toxin production, and a response to CDI antibiotic treatment with vancomycin or fidaxomicin. The primary endpoint was the safety and tolerability of Vowst™ evaluated over 24 weeks. The secondary endpoint was CDI recurrence as determined by a toxin assay up to week 4, 8, 12, and 24 after initiation of therapy. A total of 263 patients were evaluated; 29 were in cohort 1 and 228 were in cohort 2. Regarding the primary endpoint, 141 (53.6%) experienced a treatment-emergent adverse event, most commonly, diarrhea. The sustained clinical response at week 24 was 86.3% (95% CI, 81.6%-90.2%). The investigators concluded that treatment with Vowst™ was well tolerated and was associated with a low rate of CDI recurrence.

Safety: The most common treatment-related adverse events of Vowst™ with an incidence ≥ 5% were abdominal distension (31.1%), fatigue (22.2%), constipation (14.4%), chills (11.1%), and diarrhea (10.0%).[6] Since Vowst™ is manufactured from human fecal matter, it may carry the risk of transmitting infectious agents and may contain certain food allergens.

Dosing and Administration: Vowst™ is formulated as an oral capsule.[6] The standard dose is four capsules by mouth daily for 3 consecutive days for a total of 12 capsules. Vowst™ therapy should be initiated 2 to 4 days after the completion of rCDI antibiotic treatment. The day before and at least 8 hours before the initial dose of Vowst™, patients should drink 296 mL of magnesium citrate. In clinical trials, patients with impaired renal function received 250 mL of polyethylene glycol electrolyte solution (GoLYTELY®) instead of magnesium citrate. Patients should not eat or drink for at least 8 hours prior to taking the first dose of Vowst™. All subsequent doses should be administered on an empty stomach before the first meal of the day.

Cost and Availability: Vowst™ (NDC: 71881-400-12) is supplied as a bottle of 12 capsules.[6] Each capsule contains a bacterial spore suspension with 1×10^6 to 3×10^7 Firmicutes spore colony forming units in 92 ± 4% (w/w) glycerol in saline. One bottle of 12 capsules costs $17,500.[9] Cleveland Clinic Specialty Pharmacy can order and dispense this product for outpatient prescriptions.

Formulary Status: Vowst™ was not added to the CCHS Formulary. Inpatients may use a home supply of Vowst™ in accordance with the Medication from Home Policy.

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What are the requirements for prescribing buprenorphine for opioid use disorder? Is a DATA 2000 waiver still required?

By: Haley Welch, Pharm.D.

The Drug Addiction Treatment Act of 2000, known as DATA 2000, required that practitioners who wanted to prescribe buprenorphine products including, Suboxone® (buprenorphine/naloxone) and Subutex® (buprenorphine), for opioid use disorder (OUD) obtain a DATA 2000 waiver. Applicants for a DATA 2000 waiver needed to complete an 8-hour training program for prescribing buprenorphine and meet specific qualifications to be approved by the Drug Enforcement Agency (DEA) and Substance Abuse and Mental Health Services Administration (SAMSA). This process limited the number of approved prescribers. Furthermore, DATA 2000 and its various amendments set limits on the number of patients treated for OUD with buprenorphine per prescriber or group of prescribers.

As of December 23, 2022, obtaining a DATA 2000 waiver was no longer required for practitioners who would like to prescribe buprenorphine for the treatment of OUD. The Omnibus Bill of 2023 contains the Mainstreaming Addiction Treatment (MAT) Act, which removed the DATA 2000 waiver requirement.

All licensed practitioners, except veterinarians, who have a DEA registration with Schedule II-V authority can prescribe buprenorphine for OUD where state laws allow. There are no longer limitations on the number of approved prescribers and the number of patients per prescriber who could receive a prescription for buprenorphine for OUD. The Omnibus Bill also includes the Medication Access and Training Expansion (MATE) Act which requires all prescribers of controlled substances to take an 8-hour substance use disorder (SUD) training session or attain other equivalent competencies upon receiving or renewing their DEA licenses.

Practitioners applying for a new or renewed DEA registration to prescribe Schedules II–V need to attest to one of the following requirements:

- Completion of at least 8 hours of SUD or opioid-specific training from an approved organization.
- Board-certified in addiction medicine or addiction psychiatry from the American Board of Medical Specialties, American Board of Addiction Medicine, or the American Osteopathic Association.
- Graduated, in good standing, within 5 years from a medical, advanced practice nursing, or physician assistant school in the United States and successfully completed an OUD or SUD curriculum covering approved Food and Drug Administration treatments.

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