

An ancient therapy modernized for *Clostridioides Difficile* therapy

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***Clostridioides difficile* is a type of bacteria that often affects people who have been taking antibiotics. Glenn S. Tillotson of GST Micro LLC explains how live biotherapeutic products have shown promise as a safe and effective treatment to help restore the normal gut microbiome**

The normal human gastrointestinal tract provides multiple functions essential for health. When the balance of the complex collection of microorganisms (the microbiome) is disturbed, this leads to a phenomenon called dysbiosis.

Microbes protect us against harmful bacteria, synthesize nutrients, and enable us to digest food. A damaged gut can lead to multiple conditions or contribute to various diseases, one of which is *Clostridioides difficile*, or 'C. diff.' This is the most common cause of antibiotic- and healthcare-associated infectious diarrhea in the US. According to the US Centers for Disease Control and Prevention, *C. diff.* causes approximately half a million infections in the US every year, resulting in 30,000 deaths.

C. diff. infection manifests as an infection of the lower gut with diarrhea, abdominal pain, and elevated temperature. An unusual feature of this infection is the recurrence of disease.

A quarter to a third of initial cases can recur, and of these, up to 60% can have further recurrences. The impact of the disease on patients is profound beyond the diarrhea, with mental derangement, exhaustion, and inability to function properly not uncommon. *C. diff.* produces toxins or poisons that cause massive damage to the cells in the gut. These toxins can produce toxic megacolon leading to surgery.

Current management recommends either of two antibiotics (vancomycin and fidaxomicin) as standard treatment for *Clostridioides difficile* infection. If the first choice fails, the second drug is recommended.

Since the recognition of *C. diff.* in 1935 by Hall & O'Toole, it has taken about 40 years for the association of this species as a cause of human illness caused by association with certain antibiotics. Several antibiotics are more frequently associated with *C. difficile* infection (CDI), with clindamycin, cephalosporins, and quinolones being the major 'villains.' These antibiotics cause significant damage to the gut, leading to a reduced richness and diversity in the gut microbiome, which allows *C. diff.* to flourish and cause an infection.

Paradoxically, *C. diff* bacteria are part of our normal gut microbiome and are found in 5-10% of people. They normally live harmlessly inside the bowel in balance with the rest of the microorganisms.

As mentioned, current approaches to CDI are less than satisfactory. So, researchers turned to an 'ancient' therapy described by Guo Hong in the fourth century as a remedy for 'stomach upset.' He described the 'yellow soup' derived from the feces of healthy stool. Further studies using human derived material were conducted over the period 1958-2010 and beyond, but these products were not screened for potential infectious organisms, causing multiple serious life-threatening infections in already seriously ill patients.

Fecal transplantation has seen an upsurge in the past ten to fifteen years, with the majority of studies using poorly or unscreened donors, an inconsistent production process, and clinical data derived from inadequately designed and conducted studies. These flaws led to the development of two products that differ in several respects. These are called live biotherapeutic products, LBP.

Live biotherapeutic products

As of late 2024, two products derived from humans—REBYOTA and VOWST— were thoroughly screened for 29 pathogens mandated by the US Food and Drug Administration. Moreover, both REBYOTA and VOWST are manufactured following a standardized process and have been tested in large clinical trials, where they were found to be clinically effective and safe.

REBYOTA

REBYOTA consists of a broad consortium of bacteria including Bacteroides organisms. It is given as a single dose as an FDA-approved microbiome-based treatment and administered as a single dose rectally via enema.

REBYOTA was studied in a large study called PUNCH CD3 involving 289 participants who had one or more *C. diff* infection recurrences. This study was a randomized double-blinded trial with patients receiving REBYOTA treatment or an inactive substitute (placebo). Neither the patients nor the researchers knew who received which therapy. Importantly, all patients were initially treated with antibiotics.

The study showed that 70.6% of the patients who received REBYOTA were prevented of having a *C. diff* recurrence compared to 57.5% of those who received the placebo. Of interest, the treatment was more successful than the placebo in older individuals, including those affected by other illnesses such as cardiac, kidney, and gastrointestinal diseases, compared with younger healthy patients.

Side effects were mild or moderate, and the product was tolerated well by all age groups. A later study evaluated the patient's quality of life, including physical and mental health parameters, showing a significant benefit for those treated with REBYOTA compared to

the people who were given the placebo. Indeed, an important observation was that quality of life improved in relation to the level of secondary bile acids, which increased with REBYOTA therapy. Fascinatingly, studies examining the efficacy of REBYOTA in patients on anti-psychotics, statins, and PPIs were unchanged with those not on these therapies.

VOWST

VOWST is also a microbiome-based treatment based on the spores of Firmicutes, which has recently been approved for use in the US. In contrast to REBYOTA, VOWST is given orally as four capsules for three days on an empty stomach after a bowel preparation. Its efficacy and safety were assessed in a large study where it was shown that administration of VOWST was superior to placebo in reducing the risk of the *C. diff* infection coming back (recurrence rate was 12% in the VOWST group and 40% in the placebo group). Similar quality-of-life improvements were observed with this therapy.

Thus supporting the benefits of restoring specific metabolites and key changes in life quality.

Restoring the normal gut microbiome

Live biotherapeutic products have been shown to be safe and effective due to the restoration of the normal gut microbiome, which is viewed as very beneficial. Live biotherapeutic products restore the essential metabolic processes for a healthy microbiome and avoid *C. diff* infection. *C. diff* infection is a particularly complex and difficult infection. Live biotherapeutic products are based on good science and an understanding of the complexities of the gut.

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