3-1-2023

Effect of fecal microbial transplantation on Clostridioides difficile infection: Dysbiosis, metabolites and health related quality of life

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Open Forum Infectious Diseases

Open Forum Infectious Diseases 2023; 10: 3
doi: 10.1093/ofid/ofad113

Insight

Effect of fecal microbial transplantation on *Clostridioides difficile* infection: dysbiosis, metabolites and health related quality of life

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The gut-brain axis

A complex bidirectional communication system exists between the gastrointestinal tract and the brain, called the "gut-brain axis" [1]. The growing recognition of the microbiome's importance in modulating health has prompted an extension of this term to the "microbiota-gut-brain axis", which represents a complex network of communication between the gut, microbiota, and the brain that modulates immune, gastrointestinal, and central nervous system (CNS) functions [1-3]. Mechanisms of communication include: (1) neurotransmitters; (2) microbial byproducts or metabolites including short-chain fatty acids (SCFA) and bile acids; (3) cytokines and immune cell activation; (4) neural networks including enteric nervous system (ENS) and vagal nerve activation; (5) and hypothalamic-pituitary-adrenal (HPA) axis modulation [4-8].

Central to the discussion herein is the integral role of both neurotransmitters and microbial metabolites within the microbiota-gut-brain axis:

- The gut microbiota can produce key central neurotransmitters such as gamma-aminobutyric acid (GABA), norepinephrine, dopamine, and serotonin, which have important influences that extend beyond the gut to the brain [9]. Accumulating evidence suggests that manipulation of neurotransmitters by bacteria may have important physiological implications [9-11]. Notably, modulation of glutamate and GABA, which are the major excitatory and inhibitory neurotransmitters found in the CNS, respectively [12, 13], may play a role in the development of various mood, cognitive, and behavioral functions [11, 14-17].
- The metabolome, which can be defined as the complete complement of all small molecule metabolites [18], is another way the microbiome plays a central role in gut-brain communication. This occurs via a number of different metabolites including SCFAs, bile acids, and tryptophan, which can activate several mechanisms in the brain.

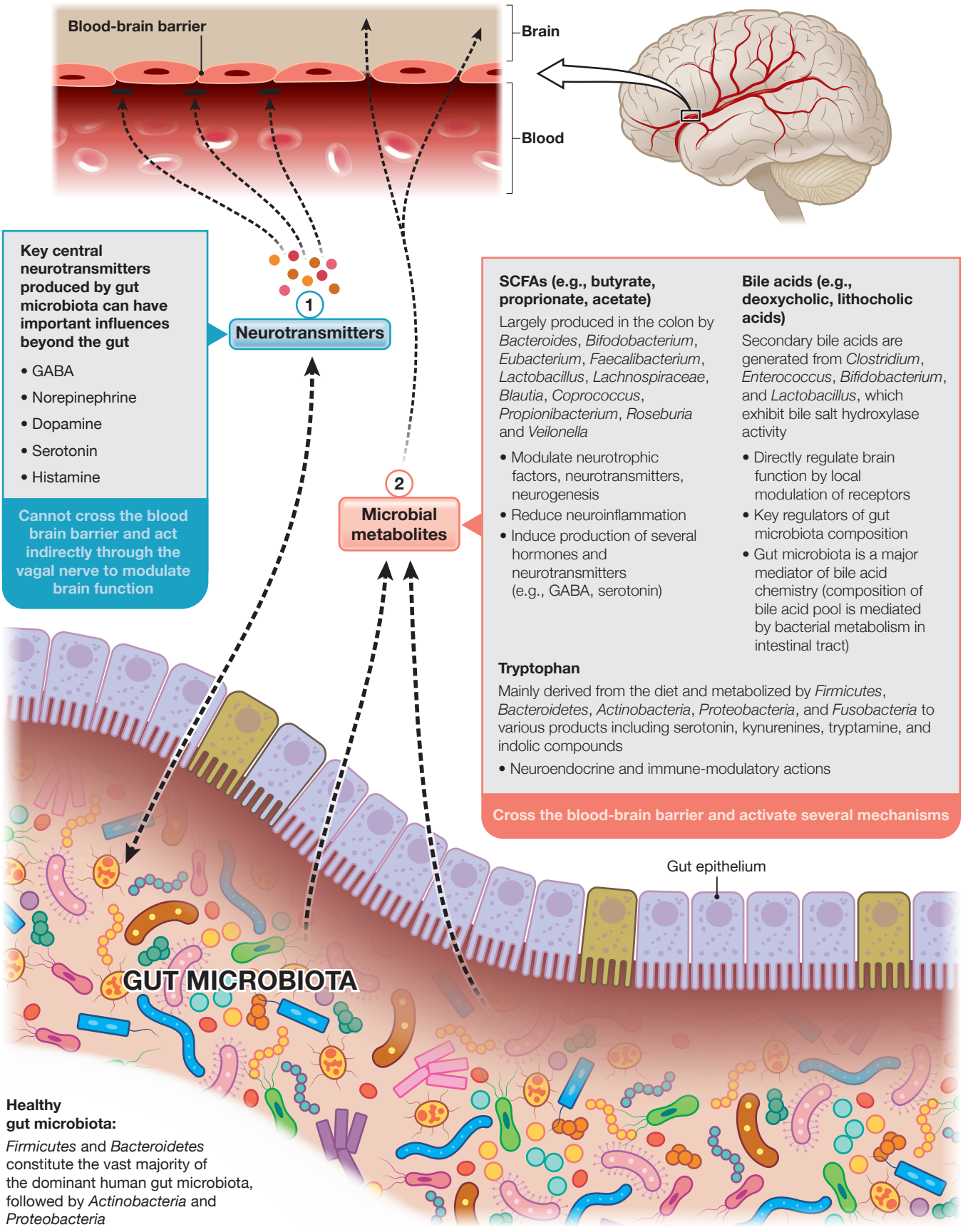
Dysbiosis in *Clostridioides difficile* infection

Clostridioides difficile infection (CDI), the most common cause of antibiotic- and healthcare-associated infective diarrhea in the US [19, 20] characterized by a disrupted microbiome [21-23], has health-related quality of life (HRQOL) implications [24-31]. Most *Clostridioides difficile* infection patients admit their daily activities are impacted [29, 32, 33] and the psychological and emotional impact is high; patients describe a wide array of emotions that they have experienced throughout their infection, including:

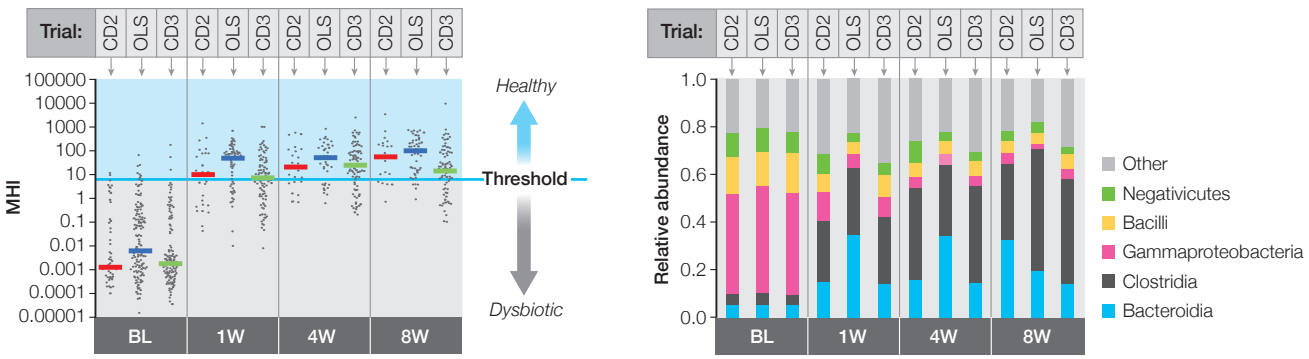
- Feelings of shame, humiliation, embarrassment, stress, depression, anxiety, and frustration [28, 31-37].
- Fear or worry related to worsening CDI, getting sick again, having uncontrolled symptoms for a longer period of time, never being cured, or infecting others [29, 31, 33, 34, 37].
- Concern about hospitalization due to a lack of trust in the ability of hospitals to adequately control and manage infections [34].
- Feelings of loneliness and worry when hospitalized [31]

Patients often intentionally take steps to evade certain social situations; this can have a profound impact on social lives as it can lead to the avoidance of venues or events outside of the home, including restaurants, public bathrooms, vacations, weddings, funerals, and more [26, 29, 31, 33, 34, 37, 38].

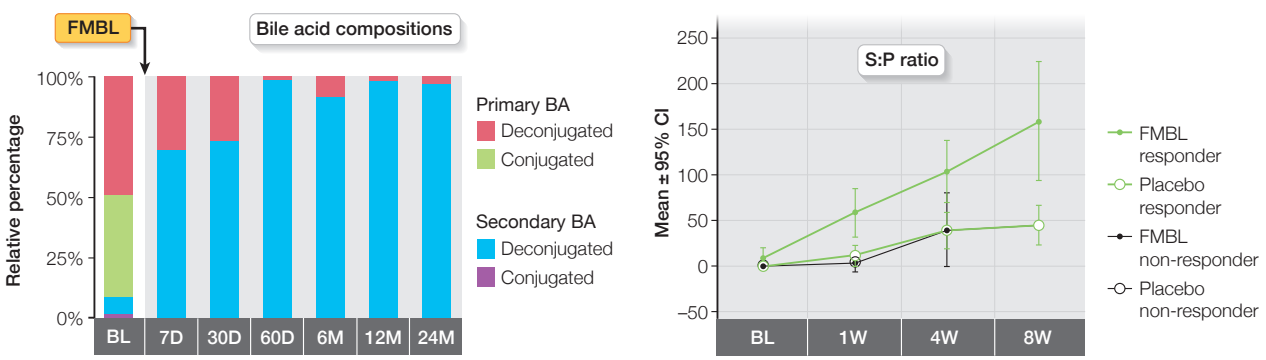
Microbiota-gut-brain axis communication mechanisms



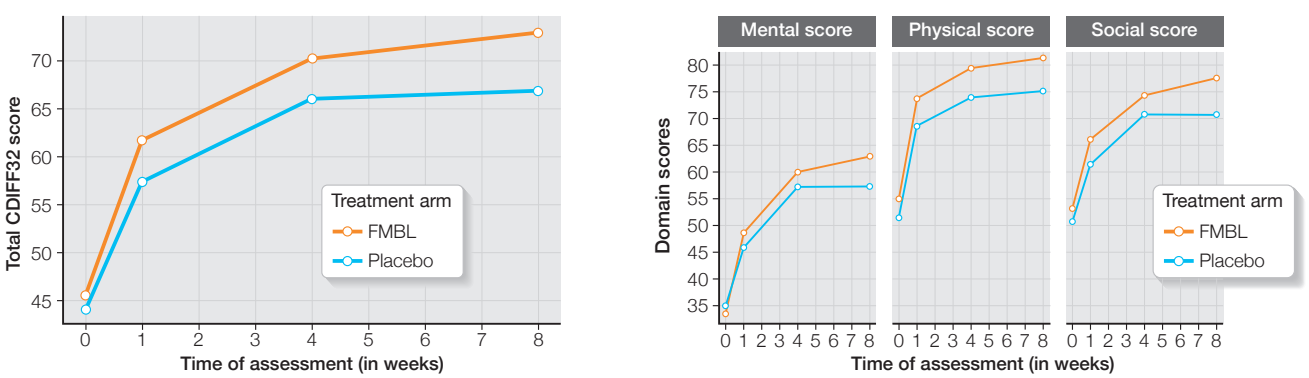
REBYOTA™ (fecal microbiota, live-jslm; FMBL) has been successful in the treatment of recurrent CDI



Bile acids are rapidly restored to healthier compositions after FMBL treatment with a significant secondary to primary bile acid (S:P) ratio increase relative to non-responders



FMBL treatment leads to sustained improvements in Cdiff32 with statistically significant differences in the adjusted mental domain and total score



Legend:

CD2 = comparative phase II, **OLS** = open label study, **CD3** = comparative phase III study, **BL** = baseline, **1W** = 1 week, **4W** = 4 weeks, **8W** = 8 weeks

HRQOL assessments

Several instruments are used to assess HRQOL in the clinical setting, including the widely employed 36-item Short Form 36 (SF-36) Health Survey [39] and the EQ-5D [40]; however, there was a need to develop and validate a disease-specific instrument to assess HRQOL changes related to CDI with a focus on recurrent CDI. As such, the Cdiff32, a disease-specific scale that contains 32 items related to the physical, mental, and social health in patients with CDI, was introduced in 2016 [41]. This standardized tool has since been utilized in clinical trials [41] and is the HRQOL instrument to use in patients with CDI.

Fecal microbial transplantation

Fecal microbial transplantation (FMT) has been proposed to improve neurological and psychological symptoms in CDI by likely modulating the gut-brain axis [42, 43]. Its effectiveness is largely due to the following:

- Direct microbiological mechanisms: successful FMT administration is marked by an eradication of key Proteobacteria species and a corresponding restoration of key Bacteroidetes and Firmicutes species, helping to prevent colonization and/or outgrowth of C. difficile [21, 44]
- Gut microbial bile acid metabolism: FMT restores the capacity of the microbial community to convert primary bile acids (which stimulate spore germination) into secondary bile acids (which inhibit C. difficile germination and epithelial apoptosis) [45-47]
- Repopulation of SCFA bacteria: FMT leads to sustained increases in several butyrate producers, including members of the Clostridiales clade [47]

REBYOTA™ (fecal microbiota, live-jslm; FMBL) improves HRQOL

REBYOTA™ (fecal microbiota, live-jslm; FMBL) (Rebiotix Inc., Roseville, MN, a Ferring company) is a recently FDA approved live biotherapeutic containing Bacteroidetes and other key species that has demonstrated safety and efficacy in adults with rCDI [48-50]. In the 6-month pivotal PUNCH CD3 clinical trial, FMBL-treated patients had more profound and sustained improvements at week eight compared to placebo with statistically significant differences in the adjusted mental domain and total score [51]. Similar results were found among FMBL responders versus placebo responders at week eight for the mental domain of Cdiff32; even among the few clinically non-responders, there were numerical improvements in all domains of Cdiff32 for FMBL-treated patients but not placebo-treated patients [52].

Conclusion

- Neurotransmitters and microbial metabolites play important roles within the microbiota-gut-brain axis
- A disrupted microbiome along with associated alterations in microbial metabolites has been implicated in CDI
- While CDI is characterized by significant diarrheal disease, it has underappreciated HRQOL implications
- FMBL promotes a more diverse and balanced microbiota composition that has direct antimicrobial actions
- A healthier microbiome increases SCFA production and promotes conversion of primary to secondary bile acids
- FMBL improves various aspects of HRQOL, which can be seen as early as one-week post-treatment

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InSight title:	**Effect of fecal microbial transplantation on *Clostridioides difficile* infection: dysbiosis, metabolites and health related quality of life**
Sponsor:	This InSight is sponsored by **Ferring Pharmaceuticals.**
DOI:	https://10.1093/ofid/ofad113

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Open Forum Infectious Diseases

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Conflict of Interest Statement:

KG: an employee of University of Houston College of Pharmacy, consultant for Ferring Pharmaceuticals, received research grant from Acurx, Summit, Paratek Pharmaceuticals and Seres Therapeutics. **PF**: an employee of Yale University School of Medicine, consultant, speaker's bureau and advisory board for Ferring/Rebiotix, consultant and advisory board for Seres Therapeutics, consultant for Merck and Co. and advisory board for Takeda Pharmaceuticals. **ED**: an employee of Washington University School of Medicine, advisor/consultant for Abbott, Ferring Pharmaceuticals, Merck, Pfizer, Seres Therapeutics, Summit, received grant/research support from Ferring Pharmaceuticals, Pfizer and Synthetic Biologics. **AG**: an employee of Ferring Pharmaceuticals. **GT**: an employee of GST Micro LLC, consultant to Ferring Pharmaceuticals, Spero Therapeutics and Paratek Pharmaceuticals.