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

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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

Key central neurotransmitters produced by gut microbiota can have important influences beyond the gut
- GABA
- Norepinephrine
- Dopamine
- Serotonin
- Histamine

Cannot cross the blood-brain barrier and act indirectly through the vagal nerve to modulate brain function

SCFAs (e.g., butyrate, propionate, acetate)
- Largely produced in the colon by Bacteroides, Blodobacterium, Eubacterium, Faecalibacterium, Lactobacillus, Lachnospiraceae, Bloa, Coprococcus, Propionibacterium, Roseburia, and Veillonella
  - Modulate neurotrophic factors, neurotransmitters, neurogenesis
  - Reduce neuroinflammation
  - Induce production of several hormones and neurotransmitters (e.g., GABA, serotonin)

Bile acids (e.g., deoxycholic, lithocholic acids)
- Secondary bile acids are generated from Clostridium, Enterococcus, Bifidobacterium, and Lactobacillus, which exhibit bile salt hydroxylase activity
  - Directly regulate brain function by local modulation of receptors
  - Key regulators of gut microbiota composition
  - Gut microbiota is a major mediator of bile acid chemistry (composition of bile acid pool is mediated by bacterial metabolism in intestinal tract)

Tryptophan
- Mainly derived from the diet and metabolized by Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Fusobacteria to various products including serotonin, kynurenines, tryptamine, and indolic compounds
  - Neuroendocrine and immune-modulatory actions

Cross the blood-brain barrier and activate several mechanisms

Gut epithelium

Microbial metabolites

Neurotransmitters

Blood-brain barrier

Brain

Blood

Healthy gut microbiota:
Firmicutes and Bacteroidetes constitute the vast majority of the dominant human gut microbiota, followed by Actinobacteria and Proteobacteria
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
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]

**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

References

Conflict of Interest Statement:

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