Endoscopic Delivery of Fecal Biotherapy in Inflammatory Bowel Disease

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KEYWORDS

• Fecal Microbial Transplant (FMT) • Inflammatory Bowel Disease (IBD) • Dysbiosis • Microbiome • Recurrent Clostridium Difficile Infection (RCDI)

KEY POINTS

- The intestinal microbiome plays an important role in the pathogenesis of dysbiotic conditions, namely in inflammatory bowel disease (IBD).
- Fecal microbiota transplantation (FMT) has been shown to be efficacious in restoring a dysbiotic state in recurrent *Clostridium difficile* infection (RCDI) with use of upper gastrointestinal (GI), lower GI, or encapsulated stool product.
- There is tremendous excitement in our ability to manipulate dysbiosis in IBD with utilization of FMT, but it is currently not allowable for therapeutic purposes of IBD without a proper approval with Investigational New Drug application through the Food and Drug Administration.
- Further research with proper regulatory oversight is required to enhance our knowledge of the safety and efficacy of FMT in IBD.

INTRODUCTION

The intestinal microbiota has been shown to play an important role in several gastrointestinal (GI) disorders, including inflammatory bowel disease (IBD). Evidence supporting the role of bacterial flora in IBD includes the use of antibiotics targeting enteric flora in prevention of postoperative recurrence of Crohn's disease (CD).[1] As our understanding of what constitutes imbalances of the intestinal microbiota expands, we are able to treat to target for a more "harmonious" balance. One unique example of this manipulation is the use of fecal microbial transplantation (FMT) for treatment of recurrent *Clostridium difficile* colitis (RCDI). FMT has been used since the fourth century in China, and was first reported in the medical literature when Eiseman and colleagues[2] used fecal enemas in 4 patients for treatment of pseudomembranous colitis. The past decade has seen a steep rise in the incidence of RCDI,[3] bringing FMT to the forefront of both scientific communities and the lay public. Success of FMT in RCDI has been shown by retrospective

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Gastrointest Endoscopy Clin N Am 26 (2016) 707–717
http://dx.doi.org/10.1016/j.giec.2016.06.006
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reviews[4] and more recently by randomized controlled trials.[5] RCDI is prevalent in patients with IBD and also is a risk factor for negative outcomes. FMT use in the IBD population for RCDI has been shown to be both safe and efficacious.[6] The use of FMT to directly treat IBD, however, has shown mixed results. Given our ability to target the dysbiotic state with FMT, its use as targeted therapy has tremendous potential. Studies have involved a multidisciplinary approach, including gastroenterologists, infectious disease specialists, microbiologists, and patient volunteers. This overview discusses the practical considerations of FMT therapy with respect to our current understanding of safety and efficacy in IBD, screening for donors and recipients, specimen handling and storage, methods of delivery, and regulatory considerations.

REGULATORY GUIDELINES

Therapeutic use of FMT has not followed a traditional path toward investigation and approval. Practitioners in infectious disease and gastroenterology have used it in various forms for many years without formal regulatory guidelines, unprecedented for a biological product. Medical therapy centers presented early options for patients to undergo a therapeutic FMT procedure for indications such as obesity, irritable bowel syndrome, or IBD without regulatory oversight. These practices were primarily based on positive case series, although efficacy and safety were not entirely known. This changed in 2013 when the US Food and Drug Administration (FDA) announced that any practitioner who wished to perform FMT obtain approval through application for an Investigational New Drug (IND). This was subsequently amended to state that an FMT is allowable without an IND for the indication of RCDI only. All other indications would require an IND. It is important for practitioners to recognize that FMT has yet to fully be studied beyond the phase 1 and early phase 2 portions of drug approval. At the time of this publication, FMT is *not* allowable for therapeutic use in IBD unless an IND has been obtained. The most recent FDA draft guidance was issued in March of 2016.[7] This states that practitioners can use FMT for CDI not responding to standard therapies as long as full informed consent is obtained including the knowledge that FMT is an investigational therapy along with discussion of its reasonable foreseeable risks. The guidance mentions use of stool banks to obtain donor specimens and the regulatory oversight required when banks are used. It should be noted that the FDA is not changing its policy on enforcement discretion that allows for use of FMT without IND as long as

1. Full informed consent is obtained from the recipient that includes knowledge that FMT is an experimental treatment.
2. The stool is not obtained from a stool bank.
3. A licensed health care provider tests the donor's blood and stool for the purposes of FMT.

At of the time of this draft, the regulation is up for public discussion on the FDA Web site. Key issues are defining what constitutes a stool bank and how to regulate their distribution of FMT product, particularly across state lines.

DONOR AND RECIPIENT CONSIDERATIONS

Excitement within the scientific community over the therapeutic potential of FMT has translated to the lay public. Despite the apparent "ick factor" of the procedure, patients with IBD have demonstrated a willingness to undergo FMT, especially among those with more severe disease.[8] Despite this willingness to undergo the procedure, many patients still find it difficult to seek out a suitable donor. There is also tremendous