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Expanded Evidence for Frozen Fecal Microbiota Transplantation for *Clostridium difficile* Infection: A Fresh Take

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In recent years, *Clostridium difficile* infection (CDI) has emerged as an increasingly common and frequently severe clinical entity (1). In 2011, *C. difficile* was responsible for nearly 500,000 infections and approximately 29,000 deaths in the United States (2). Since the emergence of hypervirulent strains in the early 2000s, CDI has also become less responsive to standard therapy. Recurrent CDI is particularly problematic; about a quarter of patients will develop recurrent infection (3). The proportion is even higher among older adults and those with certain comorbidities. In a subset of patients, CDI continues to recur, and is often refractory to extended courses of antimicrobial agents. Increasingly, clinicians are using fecal microbiota transplantation (FMT) ("stool transplant") in these circumstances (1,4).

By transplanting donor stool into a patient with recurrent CDI, FMT restores the colonic microbiota to a more healthy state. Successful use of FMT to treat CDI was first reported in 1983 (5). Although the procedure initially received slow acceptance, FMT is performed routinely today, especially after recent data demonstrating efficacy of FMT for recurrent CDI (6). At present, the best evidence for FMT is for recurrent CDI, although there is growing evidence for use in severe, complicated, and refractory CDI (7).

Compared to many other medical procedures, FMT is not technologically complicated. However, the actual FMT process is complex because of logistical barriers related to identifying and screening donors and coordinating the timing of stool collection and preparation. Other issues include cost and insurance coverage—who pays for the donor screening and the FMT procedure, especially if done by colonoscopy? Inconvenience and cost have prevented more widespread use and, as a result, many patients who might benefit from FMT cannot easily access this therapy. These and other organizational barriers have expanded interest in using frozen stool for FMT (8).

In this issue of *JAMA*, Lee and colleagues present the results of a randomized noninferiority trial conducted at 6 academic medical centers in Canada comparing frozen and thawed to

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fresh FMT to treat patients with multiply recurrent CDI or refractory CDI (9). Recurrent CDI was defined as “recurrence of CDI symptoms for >/= at 48 hours within 8 weeks following the completion of at least 10-day CDI treatment.” Refractory CDI was defined as “persistent or worsening of diarrhea characteristic of CDI and one of the following: ongoing abdominal pain, fever (temperature > 38.0 C), or peripheral white blood cell (WBC) counts $>15.0 \times 10^{9}$/L despite treatment with oral vancomycin at a dose of 500 mg 4 times daily for at least 5 days.” Study participants were randomly assigned to receive frozen (n=114) or fresh (n=118) FMT via rectal enema. Primary outcome measures included clinical resolution of diarrhea without relapse at 13 weeks and adverse events. The non-inferiority margin was set at 15%.

A total of 219 patients (frozen: n = 108, fresh: n = 111), were included in the modified intention-to-treat (mITT) and of these patients, 178 (frozen: n = 91, fresh: n = 87) were included in the per-protocol populations. In the per-protocol population, the proportion of patients achieving clinical resolution of diarrhea in the frozen group was 83.5% and 85.1% for the fresh group (difference, −1.6%; 95% CI, –10.5% to infinity). In the mITT population, clinical resolution was observed in 75.0% of the frozen group and 70.3% of the fresh group (difference, 4.7%; 95% CI, –5.2% to infinity). Noninferiority thresholds were met, and there were no observed differences in adverse events between the treatment groups.

The results presented by Lee et al offer the best evidence to date supporting the use of frozen stool, with their finding that use of frozen stool for FMT resulted in a rate of clinical resolution of diarrhea that was no worse than that obtained with fresh stool for FMT, and will likely expand the availability of FMT for patients with recurrent CDI. The ability to use frozen stool eliminates many of the logistical burdens inherent to FMT because stool collection and processing need not be tied to the procedure date and time. This study also provides greater support for the practice of using centralized stool banks, which could further remove barriers to FMT by making available to clinicians safe, screened stool that can be shipped and stored frozen and thawed for use as needed. In theory, procedure costs may also be decreased, since comprehensive donor screening is expensive.

Although the current results add to an increasing number of reports in the literature and help guide clinical practice, several questions remain. In particular, there is growing interest in using FMT in other settings (ex. severe, complicated, and refractory CDI), not just recurrent CDI. Of note, the study population in the investigation by Lee et al. included patients with refractory CDI, but the numbers are too small to make meaningful conclusions. Additional high quality clinical studies are needed to answer these questions, and frozen stool may help facilitate such investigation. The current collective understanding of the microbiome remains incomplete, but given demonstrated associations between the gut microbiota and conditions such as obesity, inflammatory bowel disease, diabetes, and colon cancer, there is also increased interest in expanding the therapeutic scope of FMT (10).

Government regulation related to FMT has been another important and difficult hurdle for clinicians. Although the U.S. Food and Drug Administration (FDA) no longer requires an Emergency Investigational New Drug application when FMT is used for treatment of CDI, clinicians are still expected to obtain informed consent from patients (11). However, the

regulatory status of central stool banks (such as OpenBiome [Medford, Massachusetts]) that provide frozen stool for use in FMT currently is undergoing revision, as the FDA has published revised draft guidance (now in draft form for nearly two years) that, if adopted, would not allow such programs to operate (12). Specifically language in the draft guidance states the donor must be personally known to either the patient or treating physician, a criterion not met by most stool banks.

Although the results of Lee et al. will likely make FMT more accessible for a larger number of patients, the most fundamental question about recurrent CDI remains—how can clinicians prevent CDI in the first place? Antibiotic use is still the strongest predictor for the development of CDI, especially with multiple agents, or prolonged use. With about 50% of hospitalized adults receiving antibiotics at any given time (13), targeted measures to curtail antimicrobial use remain essential. Recurrent CDI is only one of many poignant reminders of the ongoing need for meaningful investment in antimicrobial stewardship and prevention of healthcare associated infection.

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