Seeking safe stool: Canada needs a universal donor model

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Early in 2015, Health Canada opened the door to fecal microbiota transplantation, a promising treatment for patients with recurrent *Clostridium difficile* infection.[1] During fecal microbiota transplantation, stool from a healthy, screened donor is homogenized and filtered and is either infused into the patient by means of colonoscopy, nasoenteric tube or enema, or taken orally in an encapsulated formulation. The procedure restores the diversity of gut microbiota that confers protection against recurrent *C. difficile* infection.[2] The results are remarkable: the first randomized controlled trial of the procedure for recurrent *C. difficile* infection was stopped early because of benefit,[3] and a high-quality meta-analysis reported an 89% clinical cure rate.[2] Accordingly, medical societies and national health regulators such as the American College of Gastroenterology and the UK National Institute for Health and Care Excellence have adopted fecal microbiota transplantation as part of their guidelines.[4]

Fecal microbiota transplantation represents a novel approach for managing recurrent *C. difficile* infection.[2,5] *Clostridium difficile* infection is among the most common health care–associated infections in Canada and costs more than $280 million annually.[6] The incidence has increased over the past decade, reaching an estimated 37 900 episodes in 2012, with a corresponding rise in mortality.[7] With antibiotics, a patient's risk of recurrent infection is 20% after a primary episode and more than 60% after two recurrences.[2] The disease burden, combined with fecal microbiota transplantation's relative effectiveness, has catalyzed rapid clinical adoption of the procedure in other countries. The new Health Canada guidance now permits fecal microbiota transplantation outside of clinical trials for Canadians with recurrent *C. difficile* infection.

Although a welcome shift, the policy supports a model for delivering fecal microbiota transplantation that undermines its potential benefits. The guidance limits the procedure to a directed donor model, which requires the patient or physician to identify a stool donor (e.g., spouse). This model places responsibility on physicians for donor screening, material preparation, administration and monitoring for adverse events. By contrast, the universal donor model, currently allowed in the United States,[4] makes use of de-identified donors who are screened by a stool bank. Much like blood banks, stool banks provide a standardized and scalable product, and an adverse events registry. We evaluate these two models along the dimensions of patient safety, access to the procedure and cost to the health care system (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150672/-/DC1).

First, although fecal microbiota transplantation has shown remarkable therapeutic benefit, its safety profile includes both procedure-related (e.g., colonoscopy-induced perforation) and material-related risks.[4] Prospective long-term safety studies are ongoing, but no adverse events related to material used in the procedure were noted in a systematic review with follow-up ranging from three weeks to eight years,[8] nor in a multicentre case series of 77 patients with a mean follow-up of 17 months.[9] However, like blood, stool carries a risk of infectious disease transmission and potential transference of microbiome-mediated conditions.[8] Donor screening is vital for patient safety; however, there are no data to suggest that matching of donors and recipients is necessary to increase the procedure's effectiveness.[8]

Given this safety profile, the Canadian Association of Gastroenterology has advocated that fecal microbiota transplantation warrants standardized, rigorous screening protocols, as well as stringent monitoring and oversight.[5] If donor screening is conducted at the discretion of individual clinicians, time and resource constraints may result in less rigorous practices and protocol heterogeneity. The directed donor model also places the burden of monitoring on physicians and relies on their voluntary reports to Health Canada, which in turn

Key points

- New Health Canada guidance allows the use of fecal microbiota transplantation to treat recurrent *Clostridium difficile* infection outside of clinical trials in Canada.
- The guidance supports a directed donor model, which places responsibility on physicians to identify, screen and monitor stool donors.
- Evidence suggests that, compared with a regulated universal donor model, a directed donor model risks compromising patient safety and access while increasing costs to the health care system.
- In cooperation with patients, clinicians and scientists, Health Canada should develop regulations that support a robust universal donor model.

Competing interests: Carolyn Edelstein and Zain Kassam are employed at OpenBiome, a nonprofit stool bank that provides clinicians with preparations for fecal microbiota transplantation and supports research into the human microbiome and its role in medicine. Zain Kassam is co-founder of Finch Scientific and has a patent pending for the production of a stable fecal microbiota transplantation capsule. No other competing interests were declared.

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faces the challenge of overseeing a decentralized network of practitioners.

Universal stool banks can serve as centralized points for regulatory oversight, saving time and resources. Stool banks can be required to use standardized screening protocols that go well beyond what might be reasonably expected of an individual clinician. Nonprofit stool banks in the US, including OpenBiome, which two of us (C.E. and Z.K.) helped found, follow screening protocols that are a superset of those reported in the literature and recommended by the American Gastroenterological Association and other medical societies.[2] At OpenBiome, less than 3% of prospective donors qualify.[10] Individuals are most often excluded because of potentially microbiome-mediated conditions (e.g., obesity) or because of risk factors for infectious diseases similar to risk factors used by Canadian Blood Services. Those who pass are rescreened after stool collection to detect any changes in health status.[10] Because the universal model allows for material to be collected in advance of a fecal microbiota transplantation, this level of stringency remains pragmatic.

Universal stool banks can also simplify adverse event reporting and regulatory auditing, and they can support system-wide traceability by retaining fecal aliquots from collected stool samples for retesting after a suspected adverse event. Under the universal donor system, because stool from a single donor will likely be used to treat many patients, it is critical that robust monitoring systems are used.

Second, patient access to fecal microbiota transplantation requires the availability of suitable donors and clinicians. Under the directed donor model, the time involved in identifying and screening potential donors can delay care, and patients without access to young, healthy candidates may not find a qualified donor. Physicians may have a pre-existing relationship with donors, although these are commonly health care workers who are at higher risk for nosocomial infection.[11] Although the procedure is simple, considerable expertise and resources are required by providers to identify, screen and process stool donations. Only a small proportion of providers, concentrated at urban academic medical centres, are willing and able to perform all of these functions. Under the universal donor model, providers are responsible only for performing the procedure itself. Stool preparations can be cryogenically preserved without decreasing their effectiveness[12] and stored in health care facilities across Canada to avoid treatment delays.

Third, although fecal microbiota transplantation is cost-effective relative to antibiotic treatment with vancomycin or fidaxomicin, the donor model drives the potential savings for the health care system.[13] Donor identification is the most expensive component of the procedure. The cost per patient receiving treatment is substantially higher under a directed donor model than under a universal donor model, especially if many donor candidates must be screened to provide treatment to a single patient. Stool banks achieve economies of scale by spreading the costs of identifying and screening donors across many treatments. To ensure treatment costs remain low, Canadian regulations could be designed to restrict stool banks to operate as public or nonprofit entities.

Overall, the universal donor model offers advantages for promoting safe, cost-effective access to fecal microbiota transplantation. Health Canada should consider shifting its regulatory position to support such a model in Canada.

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