Taylor & Francis
Taylor & Francis Group

Expert Review of Gastroenterology & Hepatology

ISSN: 1747-4124 (Print) 1747-4132 (Online) Journal homepage: https://www.tandfonline.com/loi/ierh20

Artificial stool transplantation: progress towards a safer, more effective and acceptable alternative

Emma Allen-Vercoe & Elaine O Petrof

To cite this article: Emma Allen-Vercoe & Elaine O Petrof (2013) Artificial stool transplantation: progress towards a safer, more effective and acceptable alternative, Expert Review of Gastroenterology & Hepatology, 7:4, 291-293, DOI: 10.1586/egh.13.16

To link to this article: https://doi.org/10.1586/egh.13.16

Published online: 10 Jan 2014.

Artificial stool transplantation: progress towards a safer, more effective and acceptable alternative

Expert Rev. Gastroenterol. Hepatol. 7(4), 291–293 (2013)

Emma Allen-Vercoe

Author for correspondence: Department of Molecular and Cellular Biology, University of Guelph, 50 Stone Road East, Guelph, ON, N1G 2W1, Canada Tel.: +1 519 824 4120 ext. 53366 eav@uoguelph.ca

Elaine O Petrof

Department of Medicine, GIDRU Wing, Kingston General Hospital, Queen's University, 76 Stuart Street, Kingston, ON, K7L 2V7, Canada

"RePOOPulate, produced to order through bacterial culture, was instilled into two patients with severe, recurrent *Clostridium difficile* infection via colonoscope as part of a proof-of-principle trial, with resolution of disease in both cases."

Clostridium difficile infection (CDI), once considered a rare cause of antibiotic-associated diarrhea that was easily treated, has recently risen to the status of hospital 'superbug', greatly feared by patients and a grave concern for their attending physicians [1]. Over the past two decades, alarming increases have been seen in both the incidence and severity of CDI [2], and traditionally at-risk patients, such as the hospitalized elderly, continue to account for a large number of cases [3]. More recently, a worrying trend towards community-acquired infection, including in otherwise healthy, younger people, has been noted [4,5]. Of particular concern are the escalating rates of recurrent CDI, defined as complete resolution of disease during appropriate therapy, followed by a subsequent relapse of infection when treatment is stopped [5].

CDI is a disease that generally results as a consequence of destruction of the normal gut microbiota through antibiotic exposure for unrelated infections [6]. Loss of the gut microbiota, which is vitally important as a competitive barrier against infection with opportunistic pathogens [7], creates a suitable niche for the overgrowth of *C. difficile*; under these conditions the bacterium secretes several exotoxins, the net effect of which is to destroy the colonic epithelium, leading to severe diarrhea [6]. All antibiotics have the potential to damage the healthy gut microbiota and thus invite the risk of CDI; however, use of broad-spectrum antimicrobials presents a particular threat for development of this infection [6].

Recurrent CDI is generally treated with tapered and/or pulsed courses of either metronidazole or vancomycin, both of which are able to kill actively growing *C. difficile* bacteria [1]. However, *C. difficile* can effectively evade antibiotic destruction through its ability to sporulate; endospores are highly resistant to killing by antibiotics as well as by many disinfectants [8], and can persist in the environment for long periods of time, creating a reservoir for reinfection and thus an increased risk of recurrent CDI [8,9].

The treatment of a disease that is largely caused by the effects of antibiotic exposure with yet more antibiotics is counter-intuitive, akin to attempting to remove weeds from a lawn by setting fire to the grass. In this light, it is not surprising that the standard therapies for CDI are failing and that the incidence of recurrent CDI is rising. A more insightful approach to the management of the disease would involve the replenishment or replacement of the protective gut microbiota; crowding out the dandelions with healthy new turf. Indeed, the practice of fecal bacteriotherapy, commonly referred to as 'stool transplant', is thought to work through

Keywords: *Clostridium difficile* infection • fecal bacteriotherapy • gut microbiota • microbial ecosystem therapeutics

EXPERT REVIEWS

 10.1586/EGH.13.16 ISSN 1747-4124

this principle [10]. Typically, stool from a healthy donor is instilled into the GI tract of a patient via enema, colonoscopy or nasogastric tube. The success rate of this approach for the treatment of CDI has recently been highlighted by a randomized control trial comparing vancomycin treatment with fecal bacteriotherapy, where vancomycin treatment alone resulted in resolution of recurrent CDI in 31% of patients compared with an 81% success rate with stool [11].

> "...the Microbial Ecosystem Therapeutics approach represents a feasible, safer, more controllable alternative to feces for the treatment of recurrent *Clostridium difficile* infection."

While the success of fecal bacteriotherapy for recurrent CDI would seem to invite its more widespread use, there are many barriers to the approach. The 'ick factor' and the psychosocial stigma of using a human waste product in a clinical setting are obvious impediments to the practice, but even if these can be overcome, there are some further considerations to be taken into account:

- Donor stool is typically screened for a panel of known pathogens; however, there is still a risk to the patient of infection with undetected pathogens. Although such a situation has yet to be reported in the literature, it remains a risk. Importantly, an additional risk of the spread of as-yet unknown pathogens through stool donation (which may contain as many as 1000 different microbial species) must be considered;
- It is usually advised that donor stool be instilled as a freshly prepared product [12], and since the bulk of the gut microbiota consists of fastidious, strictly anaerobic bacterial species [13], the 'shelf-life' of fresh stool is limited if specialized laboratory equipment is not used. Although this issue can be mitigated to a certain extent by the use of preserved (frozen) stool [14], there may be a trade-off between bacterial viability under these conditions and the increased practicality of using a preprepared product;
- The lag-time between sampling for screening and subsequent stool donation may be too long to allow the use of fecal bacteriotherapy in an emergency situation;
- Removal of a complex mixture of donor microbes from a 'transfaunated' patient in the event of any adverse outcomes, especially when the exact identity of the microbes being instilled is unknown, would be difficult at best.

Despite these issues, the effectiveness of fecal bacteriotherapy for the treatment of recurrent CDI cannot be ignored. Knowing this, our group recently developed an improved approach to fecal bacteriotherapy, using innovative anaerobic culture techniques to isolate a subgroup of bacterial species from a fecal sample donated by a screened, supremely healthy individual. Isolated species were characterized and banked, and a synthetic ecosystem of 33 strains, termed 'RePOOPulate', was developed from a subset of isolates that had been pre-screened for susceptibility to antibiotics. RePOOPulate, produced to order through bacterial culture, was instilled into two patients with severe, recurrent CDI via colonoscope as part of a proof-of-principle trial, with resolution of disease in both cases [15].

The use of a synthetic ecosystem such as RePOOPulate, which we have termed 'Microbial Ecosystem Therapeutics' (MET) [16,17], offers many distinct advantages over stool for treatment of recurrent CDI:

- The RePOOPulate formulation does not look or smell like stool, increasing acceptance of the product by both patients and medical staff;
- The product can be produced (and reproduced) to order and as required, and can potentially be packaged in an oral, freeze-dried formulation using technology that is currently available and widely used in the probiotics industry;
- The exact composition of the synthetic stool is known and can be controlled; should any adverse effects be noted in a patient, antibiotics could confidently be used to remove the introduced microbes;
- MET can be thought of not only as curative therapy, but also as a potential prophylactic for patients at risk of contracting *C. difficile*, for example, elderly patients hospitalized for elective surgery. In the pilot study, it was additionally noted that the curative effect seen was durable, lasting in both patients through subsequent exposures to antibiotics for unrelated infections [15].

Given the improvements of the synthetic stool MET approach over fecal bacteriotherapy, the authors are keen to develop the concept further; for example, by developing different defined microbial ecosystems to match individual patient needs in a more personalized approach to treatment. However, regulatory hurdles are significant, in part because the MET approach is breaking new ground as a therapeutic. In Canada and elsewhere, stool for use as bacteriotherapy is regulated as a biologic drug; although RePOOPulate is no longer considered to be stool, it is prudent to consider it as a biologic alongside the stool from which it was originally derived, even though this may demand a different set of evaluation criteria than those for other live organisms indicated for medical use, such as probiotics. Inevitably, the manufacture and quality control of a live mixture of 33 strains will be problematic, although not insurmountable. Downsizing the synthetic ecosystem diversity will reduce production costs, and thus industry pressure to do this will be ever-present. However, studies of microbial ecosystem dynamics suggest that diversity is critical for ecosystem stability and function [18], thus reducing any MET product complexity will be a balance between ecology and economics. Next generation 'omics'-based approaches can be used to rationalize MET formulation; for example, metagenomics, metaproteomics and metatranscriptomics will undoubtedly help to guide this process by indicating which species are functionally redundant in a given ecosystem [19,20].

In summary, the authors believe that the MET approach represents a feasible, safer, more controllable alternative to feces for the treatment of recurrent CDI. The hurdles to overcome in order to classify a MET product for regulatory purposes are not insignificant, but are important to tackle to move the concept forward. MET and the emerging specialty of medical microbial ecology are new paradigms in medicine that, despite being complex in nature and thus hard to regulate, should be embraced as part of a brave new future.

Financial & competing interests disclosure

E Allen-Vercoe and EO Petrof have filed a patent on the MET-1 ecosystem (patent number: WO 2013/037068 A1). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Cohen SH, Gerding DN, Johnson S *et al.*; Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect. Control Hosp. Epidemiol.* 31(5), 431–455 (2010).

2 Lo Vecchio A, Zacur GM. *Clostridium difficile* infection: an update on epidemiology, risk factors, and therapeutic options. *Curr. Opin. Gastroenterol.* 28(1), 1–9 (2012).

3 Hensgens MP, Goorhuis A, Dekkers OM, van Benthem BH, Kuijper EJ. All-cause and disease-specific mortality in hospitalized patients with *Clostridium difficile* infection: a multicenter cohort study. *Clin. Infect. Dis.* 56(8), 1108–1116 (2013).

4 Khanna S, Pardi DS, Aronson SL *et al.* The epidemiology of community-acquired *Clostridium difficile* infection: a population-based study. *Am. J. Gastroenterol.* 107(1), 89–95 (2012).

5 Tschudin-Sutter S, Widmer AF, Perl TM. *Clostridium difficile*: novel insights on an incessantly challenging disease. *Curr. Opin. Infect. Dis.* 25(4), 405–411 (2012).

6 Denève C, Janoir C, Poilane I, Fantinato C, Collignon A. New trends in *Clostridium difficile* virulence and pathogenesis. *Int. J. Antimicrob. Agents* 33(Suppl. 1), S24–S28 (2009).

7 Walter J, Ley R. The human gut microbiome: ecology and recent evolutionary changes. *Annu. Rev. Microbiol.* 65, 411–429 (2011).

8 Leggett MJ, McDonnell G, Denyer SP, Setlow P, Maillard JY. Bacterial spore structures and their protective role in biocide resistance. *J. Appl. Microbiol.* 113(3), 485–498 (2012).

9 Sethi AK, Al-Nassir WN, Nerandzic MM, Bobulsky GS, Donskey CJ. Persistence of skin contamination and environmental shedding of *Clostridium difficile* during and after treatment of *C. difficile* infection. *Infect. Control Hosp. Epidemiol.* 31(1), 21–27 (2010).

10 Borody TJ, Khoruts A. Fecal microbiota transplantation and emerging applications. *Nat. Rev. Gastroenterol. Hepatol.* 9(2), 88–96 (2012).

11 van Nood E, Vrieze A, Nieuwdorp M *et al.* Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N. Engl. J. Med.* 368(5), 407–415 (2013).

12 Bakken JS, Borody T, Brandt LJ *et al.*; Fecal Microbiota Transplantation Workgroup. Treating *Clostridium difficile* infection with fecal microbiota transplantation. *Clin. Gastroenterol. Hepatol.* 9(12), 1044–1049 (2011).

13 Human Microbiome Project C. Structure, function and diversity of the healthy human microbiome. *Nature*, 486(7402), 207–214 (2012).

14 Hamilton MJ, Weingarden AR, Sadowsky MJ, Khoruts A. Standardized frozen preparation for transplantation of fecal microbiota for recurrent *Clostridium difficile* infection. *Am. J. Gastroenterol.* 107(5), 761–767 (2012).

15 Petrof EO, Gloor GB, Vanner SJ *et al.* Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: 'RePOOPulating' the gut. *Microbiome* 1(3), doi:10.1186/2049-2618-1-3 (2013).

16 Petrof EO, Claud EC, Gloor GB, Allen-Vercoe E. Microbial ecosystems therapeutics: a new paradigm in medicine? *Benef. Microbes* 4(1), 53–65 (2013).

17 Allen-Vercoe E, Reid G, Viner N *et al.* A Canadian Working Group report on fecal microbial therapy: microbial ecosystems therapeutics. *Can. J. Gastroenterol.* 26(7), 457–462 (2012).

18 Eisenhauer N, Scheu S, Jousset A. Bacterial diversity stabilizes community productivity. *PLoS ONE* 7(3), e34517 (2012).

19 Kolmeder CA, de Been M, Nikkilä J *et al.* Comparative metaproteomics and diversity analysis of human intestinal microbiota testifies for its temporal stability and expression of core functions. *PLoS ONE* 7(1), e29913 (2012).

20 Morgan XC, Huttenhower C. Chapter 12: human microbiome analysis. *PLoS Comput. Biol.* 8(12), e1002808 (2012).