

## EDITORIALS



## Faecal transplants

Still need good long term trials and monitoring

Tim Spector *professor*<sup>1</sup>, Rob Knight *professor*<sup>2</sup>

<sup>1</sup>Department of Twin Research and Genetic Epidemiology, King's College London, London SE1 7EH, UK; <sup>2</sup>Departments of Pediatrics and Computer Science and Engineering, University of California San Diego, USA

Recurrent *Clostridium difficile* infection is a severe and often fatal condition, affecting up to 3000 people in the United Kingdom and 100 000 in the United States, where it kills an estimated 14 000 a year.<sup>1</sup> About a quarter of patients experience a recurrence after an initial mild infection because treatment with antibiotics destroys the diversity of the normal gut microbes and allows *C difficile* to flourish.

The standard of care is antibiotics such as vancomycin and metronidazole, with or without bowel lavage or probiotics. However, a meta-analysis that included two randomised controlled trials and multiple case series covering 516 patients found an 85% success rate with a new non-drug treatment compared with only 20% success for vancomycin.<sup>2</sup> That treatment is called faecal microbial transplantation, whereby the liquidised stool (or its cryopreserved microbial content) of a healthy donor is introduced to the colon of the patient through a nasogastric tube or the rectum. A third recent randomised trial was stopped early because of the overwhelming superiority of faecal transplantation, with 90% success rate compared with 26% for vancomycin.<sup>3</sup> So far, such transplants seem relatively safe in immunocompromised and elderly patients.<sup>4 5</sup>

Although faecal transplants are being used in people with the whole spectrum of *C difficile* infection, insufficient data exist on their effect in early or very resistant infections, and there are few comparisons between the many different inoculation methods and routes, including the recent cryopreserving of donor microbes in acid resistant oral capsules.<sup>6</sup>

The first randomised trial was published in 2013, and under pressure from patients and clinicians the Food and Drug Administration effectively granted it a temporary exemption from its status as an investigational drug. Over 500 US centres now offer faecal transplantation, with most using frozen donations from the not for profit stool bank organisation in Boston, OpenBiome. Faecal transplantation for *C difficile* infection has now been cautiously endorsed by the American Academy of Gastroenterology and European Society of Microbiology and Infectious Diseases. While the European and Australian regulators have yet to make a decision, the UK National Institute for Health and Care Excellence approved it last year. The Medicines and Healthcare Products Regulatory

Agency has temporarily classed faecal transplants as a medicinal product (with exemptions from many of the usual barriers). The caution is understandable because no good long term data or registries yet exist, although efforts are under way. However, the available literature suggests that adverse events are rare.

In contrast to the US, the UK has only around seven centres (including one private) that offer the treatment. As further studies and long term outcomes are published, use of faecal transplant seems likely to spread to other commoner diseases and traits now linked to the microbiome. Trials are already ongoing for irritable bowel syndrome, inflammatory bowel diseases, hepatic encephalopathy, and autism. It also has potential in assisting chemotherapy. A treatment for the global problem of obesity is a tempting target, but despite success in animals, small scale trials in obese humans have thus far been inconclusive, although they have improved insulin sensitivity.<sup>7</sup>

Gut microbes play an important, wide ranging role in our immune systems and health. Reduced species diversity is observed in many common chronic diseases, associations between the microbiome state and many diseases have been observed in humans, and compelling mouse experiments link the microbiome to specific mechanisms in allergy and infection.<sup>8</sup> Despite these scientific advances, regulatory bodies are reluctant to approve faecal transplants for non-life threatening conditions as they are hard to classify and control.

As well as the obvious risks of infection (reduced by screening), there are longer term potential risks, and two anecdotal reports exist of patients with *C difficile* who recovered from their disease but then gained substantial weight, perhaps from the microbiomes of their overweight donors.<sup>9</sup> More worrying is the potential transmission of anxiety and depression. Although unproved in humans, gut microbes can produce a range of neurochemicals, including dopamine,  $\gamma$ -aminobutyric acid, and serotonin. Microbes transferred to a new host could therefore cause an imbalance in these neurotransmitters.<sup>10</sup> These risks suggest that faecal transplantation should be carefully monitored and donors followed up, but even with all these caveats it is clearly better than further antibiotics for treating conditions like *C difficile*.

Although advocates suggest that faecal transplantation could be a cure-all for many diseases, these claims are probably too optimistic. Current evidence suggests that transplants may not be able to correct a well adapted ecosystem. Additionally, as with organ transplants, we may need to account for host genetic factors (which have a role in allowing specific gut microbes to establish).<sup>11</sup> Using family donors is one method; another is using previously banked autologous faecal transplants, which is now being tested in high risk patients before bone marrow transplantation.<sup>12</sup> Autotransplant of microbes happens already in bariatric surgery and could be responsible for the procedure's rapid clinical benefits.<sup>13</sup>

As well as refining faecal transplants to include most of the key beneficial microbes, we urgently need more expertise and centres, proper screening of donors, and good long term trials and monitoring procedures in order to provide sensible advice. Otherwise, especially given the ease of performing the procedure at home following instructions on the internet, patients with many chronic complaints may lose patience and take matters into their own hands with unpredictable consequences.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare TS received fees for giving a talk on the microbiome to employees of Unilever and is author of *The Diet Myth*. RK received fees for speaking at a symposium on nutrition and the human gut microbiome for Nestlé and is author of *Follow Your Gut*.

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- 1 Leffler DA, Lamont JT. Clostridium difficile infection. *N Engl J Med* 2015;372:1539-48.
- 2 Drekonja D, Reich J, Gezahegn S, et al. Fecal microbiota transplantation for Clostridium difficile infection: a systematic review. *Ann Intern Med* 2015;162:630-8.
- 3 Cammarota G, Masucci L, Ianiro G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs vancomycin for the treatment of recurrent Clostridium difficile infection. *Aliment Pharmacol Ther* 2015;41:835-43.
- 4 Mittal C, Miller N, Meighani A, et al. Fecal microbiota transplant for recurrent Clostridium difficile infection after peripheral autologous stem cell transplant for diffuse large B-cell lymphoma. *Bone Marrow Transplant* 2015;50:1010.
- 5 Agrawal M, Aroniadis OC, Brandt LJ, et al. The long-term efficacy and safety of fecal microbiota transplant for recurrent, severe, and complicated Clostridium difficile infection in 146 elderly individuals. *J Clin Gastroenterol* 2015 Aug 26. [Epub ahead of print.]
- 6 Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, capsulized, frozen fecal microbiota transplantation for relapsing Clostridium difficile infection. *JAMA* 2014;312:1772-8.
- 7 Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* 2012;143:913-6.
- 8 Rosenbaum M, Knight R, Leibel RL. The gut microbiota in human energy homeostasis and obesity. *Trends Endocrinol Metab* 2015;26:493-501.
- 9 Alang N, Kelly CR. Weight gain after fecal microbiota transplantation. *Open Forum Infect Dis* 2015;2:ofv004.
- 10 Dinan TG, Stilling RM, Stanton C, Cryan JF. Collective unconscious: how gut microbes shape human behavior. *J Psychiatr Res* 2015;63:1-9.
- 11 Goodrich JK, Waters JL, Poole AC, et al. Human genetics shape the gut microbiome. *Cell* 2014;159:789-99.
- 12 Trubiano JA, George A, Barnett J, et al. A different kind of "allogeneic transplant": successful fecal microbiota transplant for recurrent and refractory Clostridium difficile infection in a patient with relapsed aggressive B-cell lymphoma. *Leuk Lymphoma* 2015;56:512-4.
- 13 Tremaroli V, Karlsson F, Werling M, et al. Roux-en-Y gastric bypass and vertical banded gastroplasty induce long-term changes on the human gut microbiome contributing to fat mass regulation. *Cell Metab* 2015;22:228-38.

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