Commentary

Estimating the risks of faecal transplants

Recurrent Clostridium difficile infection (RCDI) is a severe and often fatal condition, killing an estimated 14,000 Americans per year. Treatment with faecal microbial transplantation (FMT) has been shown to be vastly superior to traditional antibiotic treatments, with success rates of around 90%. In studies performed so far, the stool (or its cryopreserved microbial content) of a healthy donor are introduced into the colon of the patient via a nasogastric/nasoenteric tube or the rectum via enema or during endoscopy (upper or lower), and more recently via cryopreserving donor microbes in acid-resistant oral capsules. The speed at which this unorthodox therapy has been adopted (particularly in the USA) has surprised many people and governing bodies. Details on the risks of the procedure have been difficult to ascertain and Baxter and Colville in this issue of the Journal have performed an up-to-date review of the evidence of safety of the procedure. They assessed 109 publications involving 1555 patients, the vast majority for RCDI. Their major conclusion was that the quality of the reported data is poor and that determining precise estimates of risk is problematic. Nevertheless certain conclusions may be drawn—the first being that the overall rate of severe complications is low. They identified only three patients whose death may have been due to FMT, two of whom had experienced a procedure-associated complication and had been seriously ill before treatment.

Although this treatment originated in fourth-century China, the first western use was in the 1950s and the first randomized controlled trial (RCT) in 2013. Already more than 500 US centres offer FMT, most supplied by frozen donations from the not-for-profit stool bank organization in Boston known as OpenBiome. FMT for RCDI has now been cautiously endorsed by the American Academy of Gastroenterology and by the European Society of Microbiology and Infectious Diseases. In the UK the National Institute for Health and Care Excellence approved FMT for RCDI last year, and the Medicines and Health Products Regulatory Agency temporarily classed FMT as a medicinal product for this indication only (with numerous exemptions). The US Food and Drug Administration, under pressure from patients and clinicians, has granted FMT a temporary exemption as an investigational drug (IND) for RCDI (nevertheless it encourages IND application). The caution is understandable because, although research efforts are underway, no good long-term data or registries yet exist.

The available literature suggests that adverse events are rare, and that the short-term success rate relative to vancomycin is far better. No serious complications related to FMT have been reported in the only two RCTs that had a control group treated with vancomycin. Mild adverse events attributable to FMT include diarrhoea, constipation, cramping, belching, nausea, abdominal pain, bloating, transient fever, and dizziness, and are transient and self-limiting. Most studies do not actively seek these, and therefore their true frequency is difficult to define. So far FMT for RCDI appears relatively safe in immunocompromised patients as well as in the elderly.

The risk of infection transmission is significantly reduced by screening, which is always mandatory; and sample use should, where possible, be delayed by several months to monitor donors. Rare reported cases of Gram-negative sepsis post procedure seem to be secondary to underlying illness deterioration, rather than transmitted through the inoculum. Endoscopic procedure- or sedation-related complications are rare, but when they occur they may be serious or fatal, and are reported after both upper-gastrointestinal endoscopy and colonoscopy (but not after FMT delivery via enema). Baxter and Colville (Table V) report perforation or tear (related to endoscopy) in 0.25% of cases and an overall mortality of 0.25% related to FMT. When compared to other therapeutic endoscopic procedures, these risks are similar and certainly not prohibitive. In future, endoscopy-related risks could further be reduced by routine availability of oral capsulated frozen stool or by using selected microbes.

There are still some hypothetical long-term concerns about transmitting pre-clinical diseases linked to the donor’s microbiome that are not fully explored in Colville and Baxter’s review. There is one anecdotal report of C. difficile patients who recovered from the disease but then gained substantial weight, perhaps from the microbiome of the donor, who in parallel also recovered from the disease but then gained substantial weight. More concerning is the potential transmission of mood disorders such as anxiety and depression. Although not demonstrated in humans, gut microbes can produce a range of neurochemicals including dopamine, gamma-aminobutyric acid, and serotonin, potentially causing an imbalance in these neurotransmitters. These risks suggest that the whole process of faecal transplantation should be carefully monitored, and donors followed up, but even with all these caveats it is clearly less dangerous than using further antibiotics for treating conditions such as RCDI.

Although FMT is being applied to the whole spectrum of CDI, there are insufficient data from trials on early cases and very resistant CDI. Current expert consensus and guidance support use in RCDI only. The optimal method of inoculum delivery is unclear and has not been confirmed in an RCT, with the
majority favouring delivery via colonoscopy. This approach has a slightly higher but non-significant response rate, and is potentially favoured because stool is deployed at the site of pathology — not degraded by gastric or pancreatic secretions. As further studies and long-term outcomes are published, the demand for faecal transplant will undoubtedly spread to other more prevalent diseases and traits now linked to the microbiome, and trials are already ongoing for irritable bowel syndrome, inflammatory bowel diseases, hepatic encephalopathy, and autism. It also has potential to improve chemotheraphy and immunotherapy. Providing a treatment for obesity is a tempting target, but, despite success in animals, small-scale trials have so far been inconclusive.13,14 Regulatory bodies so far have been reluctant to approve FMT for non-life-threatening conditions, as they are hard to classify and control. Although FMT has been proposed as a cure-all for many diseases, these claims are exaggerated, particularly when altering well-adapted ecosystems. Additionally, as with other organ transplants, we may need to account for host genetic factors (which do play a role in allowing specific gut microbes to establish).15 Using banked autologous faecal transplants could also reduce risks.

Access to the Internet and the ease of the do-it-yourself procedure means that patients with chronic complaints may perform FMT themselves with unpredictable consequences and risks. To improve success rates and reduce risks, we urgently need more expertise, centres, and screening, as well as good long-term trials and long-term monitoring procedures.

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References

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