Expert centres for faecal microbiota transplantation: The guarantee for safe and effective use of faecal transplants

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Editorial

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Faecal microbiota transplantation (FMT) is a promising treatment for microbiota-related diseases.[1] Nowadays, it is recommended for recurrent *Clostridioides difficile* infection (rCDI) after at least two recurrences.[2] Indeed, in the last 30 years, rCDI has become a public-health problem with a high morbidity and mortality rate, increasing incidence and substantial cost.[3,4] For more than 10 years, FMT has appeared as an efficient treatment to prevent rCDI, with a reported rate of efficacy at two months of about 90% in both randomised controlled trials and retrospective studies.[5–7]

In this issue, Terveer et al. present in great details the first four years' experience of the Netherlands Donor Feces Bank (NDFB) – a nationwide organisation that centralises faeces collection, reviews FMT requests and performs prospective long-term follow-up.[8] This work of great value embraces all aspects and difficulties that can be faced when performing FMT: from the complex task of selecting a donor to the need for long-term follow-up and risk factors associated with FMT failure.

The authors first describe the process of donor selection and testing. Indeed, in clinical practice, finding a safe donor is maybe the most challenging issue when considering FMT. With only 2% (16/871) of all initial candidates eligible for faeces collection, donor selection appears as a poorly effective process. Moreover, even after proper selection, nearly all active donors experience one or more transient medical events that result in donations being stopped temporarily, limiting the number of transplants available from one donor. This shows that more efficient ways of donor selection are needed.

Selecting the right indication for FMT is also mandatory in order to prevent improper use and delay in the diagnosis of another condition. After their evaluation, the authors reported the rejection of 27% of all FMT requests mainly because of an alternative diagnosis of chronic diarrhoea, unravelling inflammatory bowel diseases (IBD) associated with the carriage of *C. difficile*. Indeed, when considering FMT, one has to be sure that a true rCDI is present. Proper microbiological diagnosis with a two-stage testing algorithm is recommended to differentiate between *C. difficile* carriage and infection. An interval of more than two months between two episodes favours a new CDI rather than a recurrence and should be treated by antibiotics first. In particular, as illustrated by the main causes of rejection of FMT requests reported here, two situations should question the diagnosis of refractory or recurrent CDI: non-responsiveness to anti-CDI antibiotics and elements suggestive of IBD that should be systematically sought. Bringing together microbiologists, gastroenterologists and infectious disease specialists in a multidisciplinary expert panel, as in the NDFB, allows a deep understanding of the clinical situations assessed, and this should be encouraged.

The reported cure rate at two months post FMT was 89%, and no related serious adverse events were reported, confirming, if needed, the very good benefit/risk ratio of FMT in rCDI in daily practice.

With 9% deaths at one year, the clinical profiles of patients selected for transplantation reflect the fragile profile of patients usually affected by this condition. While FMT is recommended after at least two recurrences of CDI,[2] the authors reported a mean of 4.2 (range 1–10) CDI episodes before FMT was considered. One can question why FMT was considered so late in the disease course of some patients. Given the high morbidity of rCDI and the good safety and tolerance of FMT, efforts should be made to increase access to this treatment and to inform practitioners about this therapeutic.

However, despite a high rate of efficacy, FMT can fail. An understanding of the risk factors associated with post-FMT recurrence is needed. Given the relatively low number of treatment failures, only large and prospective cohorts will have the statistical power to assess this question. Here, the two main factors associated with FMT failure were post-FMT antibiotic use for non-CDI indication and immunosuppression. Indeed, these two conditions are associated with

sustained microbiota perturbation and immunological imbalance that favour CDI.[9,10]

Interestingly, no other patient or faecal suspension characteristic was associated with FMT failure. In particular, the possibility of storing faeces transplants for a prolonged time (up to two years) without compromising FMT effectiveness and safety is of great importance to assure transplant provision.

Thus, a high level of expertise is now mandatory to ensure the proper use and safety of FMT. With the perspective of various new indications (e.g. IBD, hepatic encephalopathy, multi-drug-resistant bacteria decolonisation), requests for FMT are likely to increase significantly in the near future. This upcoming change of scale will need a robust operative pipeline. As demonstrated by Terveer et al., a centralised faeces bank allows efficient and safe use of FMT. While coping with donor selection issues and transplant provision, faeces bank can also implement large prospective cohorts to ensure long-term treatment evaluation. Following the NDFB experience, FMT platforms are now setting up in various countries, including the UK, the USA and France. By combining microbiological, clinical and pharmaceutical skills, these expert centres aim to guarantee good medical practice and high-quality research on FMT.

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