Searching for superstool: maximizing the therapeutic potential of FMT

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Faecal microbiota transplantation (FMT), a highly effective treatment for *Clostridium difficile* infection, is now being explored for complex diseases, but innovative trial design and collaborative approaches are essential for unlocking its therapeutic potential. If 'superstool' capable of treating a complex disease exists, then FMT trials should aim to find and use it.

Faecal microbiota transplantation (FMT), which is highly effective for treating *Clostridium difficile* infection (CDI)[1], is now being explored as a therapy for complex diseases such as IBD[2], metabolic disease and autism spectrum disorders. However, even for CDI, which has a fairly straightforward aetiology, the mechanism by which FMT cures the infection is not well understood. Studies of FMT are challenging in part because of the immense biological complexity of stool[3] and its wide variation from person to person[4], so how should we design clinical trials when both the condition and the therapy are complex? We propose that the diversity of the therapeutic material, that is, the person to person differences in donor stool, is a double-edged sword: donor stool heterogeneity is both a major challenge facing FMT research and an opportunity for transformative science and medicine.

Despite the wide inter-individual variation in stool, stool from any well-screened donor seems highly effective for treating CDI. Thus, as all stool for CDI is 'superstool', it has been natural to think about FMT as a single, well-defined therapy. Nevertheless, thinking about FMT this way obscures the potential challenge of donor stool heterogeneity when treating more complex diseases[2,5]. For complex diseases, 'superstool' might be rare, if it exists at all, and it might not be as remarkably effective as FMT is for CDI. For example, in a trial in 2015 using FMT to treat IBD, 6 stool donors were used[6]. One of these donors produced stool that was apparently more effective than placebo, whereas the patients treated with stool from any of the other 5 donors responded at a rate similar to placebo treatment. If these results were not due to chance, and that one donor produced 'superstool', then the important conclusion is that FMT from at least some donors may be an effective therapy for IBD. The aggregate result — that FMT, averaged over donors, is no more effective than placebo — only obscures the therapeutic potential of FMT.

Consideration of all FMT as a single, monolithic 'drug' will hide any heterogeneity and could substantially impair clinical trials[2,5,7]. Instead, FMT must be approached as a fundamentally different therapeutic modality in which each donor produces a unique drug and each condition might respond differently to each drug (FIG. 1). Consider a dating analogy in which everyone in your pool of potential dates passes a background check, and then you randomly go on dates from that pool. This strategy, analogous to randomly selecting stool donors, is clearly not optimal for dating. Instead, an adaptive approach seems intuitive: you should leverage all your knowledge about the dating pool to maximize the probability that you go on a good date.

Adaptive FMT clinical trials similarly provide an opportunity to overcome the challenges posed by donor heterogeneity. We used a mathematical model and simulated clinical trials to show that a simple adaptive trial design, using no information beyond what arises during the trial itself, can mostly overcome the challenge of donor heterogeneity[7]. Like a matchmaker who has seen many dates succeed or fail, an adaptive trial protocol can help clinicians better predict which donors will maximize successful outcomes for patients in a trial. For example, if the first patient in a trial treated with stool from donor A does not respond to FMT, should you use donor A again or switch to donor B? A common answer is that donor A must be used multiple times before a rational decision to switch can be made. In fact, our mathematical analysis showed that, to maximize the number of patients with successful outcomes, a donor with one failure and no successes should immediately be dropped, even when used with only 1 patient[7]. In the dating analogy, this conclusion is intuitive: if you go on a bad first date with person A, you have a better chance of a good date with the new person B, rather than hoping that person A just made a poor first impression. It is worth noting that an adaptive design that identifies 'superstool' and uses it to treat as many patients as possible does not compromise the scientific integrity of the trial. The goal of an FMT clinical trial should be to determine if any stool is effective, not to determine if FMT averaged over all donors is more effective than placebo.

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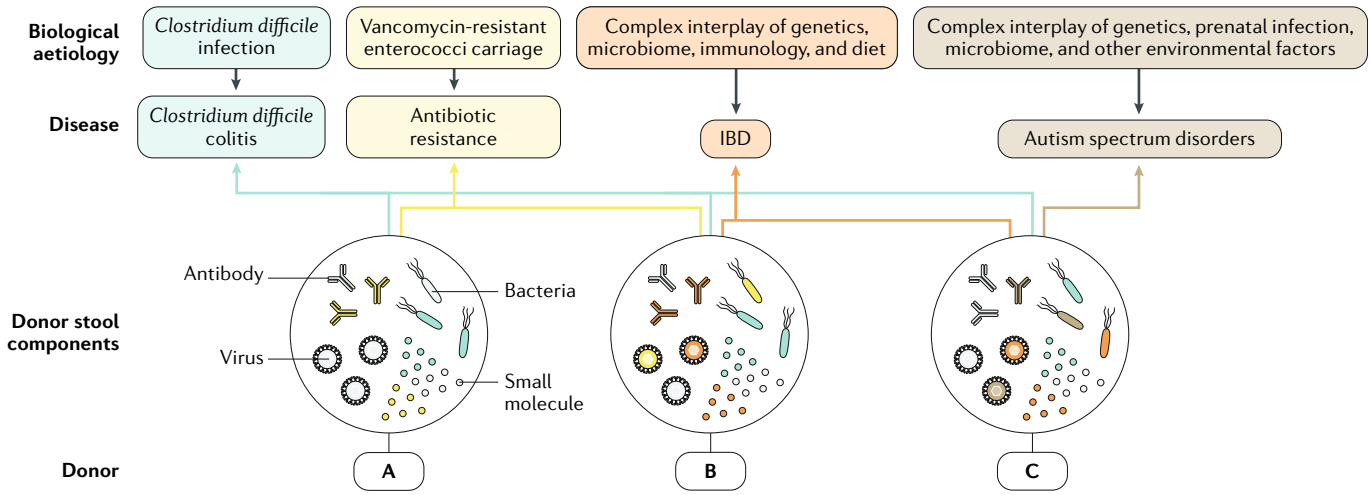

Fig. 1 | **Model of donor stool heterogeneity in treating complex diseases.** Donor stool components include antibodies, bacteria, small molecules, viruses and other as-of-yet unspecified factors. Different varieties (colours) of those components could have different abilities to treat different conditions (matching coloured lines).

Adaptive designs can do more than improve the outcomes of individual trials, especially if data are integrated across multiple trials, and donors and patients are well characterized[8,9]. Adaptive designs could eventually help researchers identify donor characteristics, perhaps bacteriological or immunological, that make a donor's stool particularly effective for treating a particular condition. Comparing donor stool performance across trials for different diseases could even provide clues about the aetiologies of those conditions and the therapeutic mechanism of FMT. To generate more sophisticated hypotheses that can move us away from whole stool FMT and toward defined, specialized and specific therapeutics, we need to aggregate information across donors and clinical trials[2].

To minimize the potential pitfalls of FMT research and leverage its unique ability to answer clinical, translational and even basic scientific questions, we make three recommendations. First, researchers should use adaptive trials to overcome the challenge of donor stool heterogeneity and deliver the best possible therapy in the treatment arm, beginning the search for 'superstool'. Second, reports of FMT trials should include sufficient information about the donors used in the trial to enable researchers to evaluate what part donor heterogeneity could have played in the results. This information should include the number of donors in the trial, how many of the patients assigned to each donor reached each endpoint, how donors were screened, whether donors were used in previous studies, and information about the donor age, sex, race, diet, any microbiome survey of their stool, and the length of time they have been a donor. Third, researchers should use local or national stool banks. Standardized methods for collecting stool, processing stool, and screening donors will improve comparability and reproducibility of research results.

Additionally, although the study of FMT for multifactorial diseases is driving the field forward, we encourage research on FMT for less complex diseases, such as drug-resistant pathogen carriage[10]. Scientifically, it will be useful to have a model disease for FMT other than CDI, which seems unusual in the uniform success of using FMT to treat it. FMT research and the search for 'superstool' should be interdisciplinary and innovative, involving clinicians and statisticians to develop the highest yield adaptive clinical trials, basic scientists to identify the critical components of efficacious stool, and bioethicists and data scientists to determine how to productively and ethically share information across trials. FMT holds tremendous potential as a treatment and as a tool to understand disease pathogenesis, especially if adaptive trials can be used to generate and test sophisticated hypotheses about disease aetiologies and the therapeutic mechanism of FMT.

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Competing interests
The authors declare no competing interests.