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Faecal microbiota transplantation for primary Clostridioides difficile infection

SHORT CASE REPORT

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Background

Faecal microbiota transplantation (FMT) is recommended for recurrent *Clostridioides difficile* (*C. difficile*) infection. The recommended treatment for primary *C. difficile* infection is antibiotics. We present a patient who requested FMT for primary *C. difficile* infection.

Case presentation

A patient in her sixties developed primary *C. difficile* infection following antibiotic therapy atter surgery for small bowel volvulus. The patient refused antibiotic treatment and contacted a research group that had just concluded a

randomised phase III trial assessing FMT for primary *C. difficile* infection. The trial had not yet been published, and FMT was not included in guideline recommendations for this indication. After joint decision-making involving the patient, her general practitioner, gastroenterologists and the research group, the patient received FMT and experienced complete remission of *C. difficile* symptoms within two days of treatment.

Interpretation

This case illustrates how to evaluate experimental versus established treatments in light of new evidence and patient preferences that do not align with guideline recommendations.

A woman in her sixties presenting with an acute primary *Clostridioides difficile* infection declined the recommended antibiotic treatment. She approached our research group directly, requesting a treatment that had demonstrated efficacy in a recently completed randomised trial. The trial was unpublished and the treatment was not part of the recommended guidelines.

A woman in her sixties with type 2 diabetes mellitus, structural scoliosis with reduced lung capacity (forced vital capacity 40 %), osteoporosis, hypercholesterolemia and a Leiden mutation experienced diarrhoea the day after discharge from hospital. She had undergone surgery with bowel adhesiolysis and detorsion for a small bowel volvulus, and was experiencing watery, yellow stools up to twelve times daily and increasing fatigue. She did not have a fever or abdominal pain. During her hospital stay she received perioperative intravenous antibiotic prophylaxis with doxycycline 400 mg and metronidazole 1000 mg, as well as four oral doses of erythromycin 250 mg postoperatively over the first two days to promote gastric motility. Routine blood tests by her general practitioner (GP) were unremarkable, but a stool sample on day 18 post-discharge was positive for toxin-producing *Clostridioides difficile* (*C. difficile*).

The GP prescribed oral metronidazole 500 mg three times daily for 10 days, in line with Norwegian primary care guidelines for primary *C. difficile* infection (1).

The patient declined the prescribed antibiotic therapy due to difficulty swallowing tablets, reluctance to increase her medication burden, and concerns about potential side effects of metronidazole.

The patient had read in the media about the Clinical Effectiveness Research Group at the University of Oslo and Oslo University Hospital, which was investigating faecal microbiota transplantation (FMT) for primary *C. difficile* infection (2). Four weeks after the onset of diarrhoea symptoms, she contacted a member of the research group by phone. She was still having ten to twelve watery stools daily and reported a reduced general condition.

We informed her that FMT is not recommended in Norwegian or international guidelines for primary *C. difficile* infection but that we had new, unpublished data from a randomised trial suggesting FMT is not inferior to antibiotics. The procedure and practical administration of FMT were explained to the patient, and she elected to undergo this treatment. Her GP confirmed her clinical course, test results and understanding of treatment options.

Five days later, FMT was administered using a healthy donor's stool from a regional stool bank at the University Hospital of North Norway, Harstad. The patient's local hospital had participated in the recently completed randomised trial (3) and had access to the treatment (Figure 1).

Figure 1 Faecal microbiota from a healthy stool donor, ready for use. Photo: Peter Holger Johnsen, University Hospital of North Norway, Harstad

The procedure followed the same administration protocol as in the study: a 200 ml faecal microbiota suspension comprising faeces, saline and glycerol, frozen to –80 °C, was thawed in a 37 °C water bath and delivered via rectal catheter in the gastroenterology laboratory by a trained nurse. The patient received no pre-treatment, bowel preparation or sedation. She was repositioned on the examination table to ensure distribution of the suspension throughout the colon (Figure 2) (4). The patient was discharged on the same day. She reported that the suspension had an unpleasant odour but felt that the procedure had gone well.

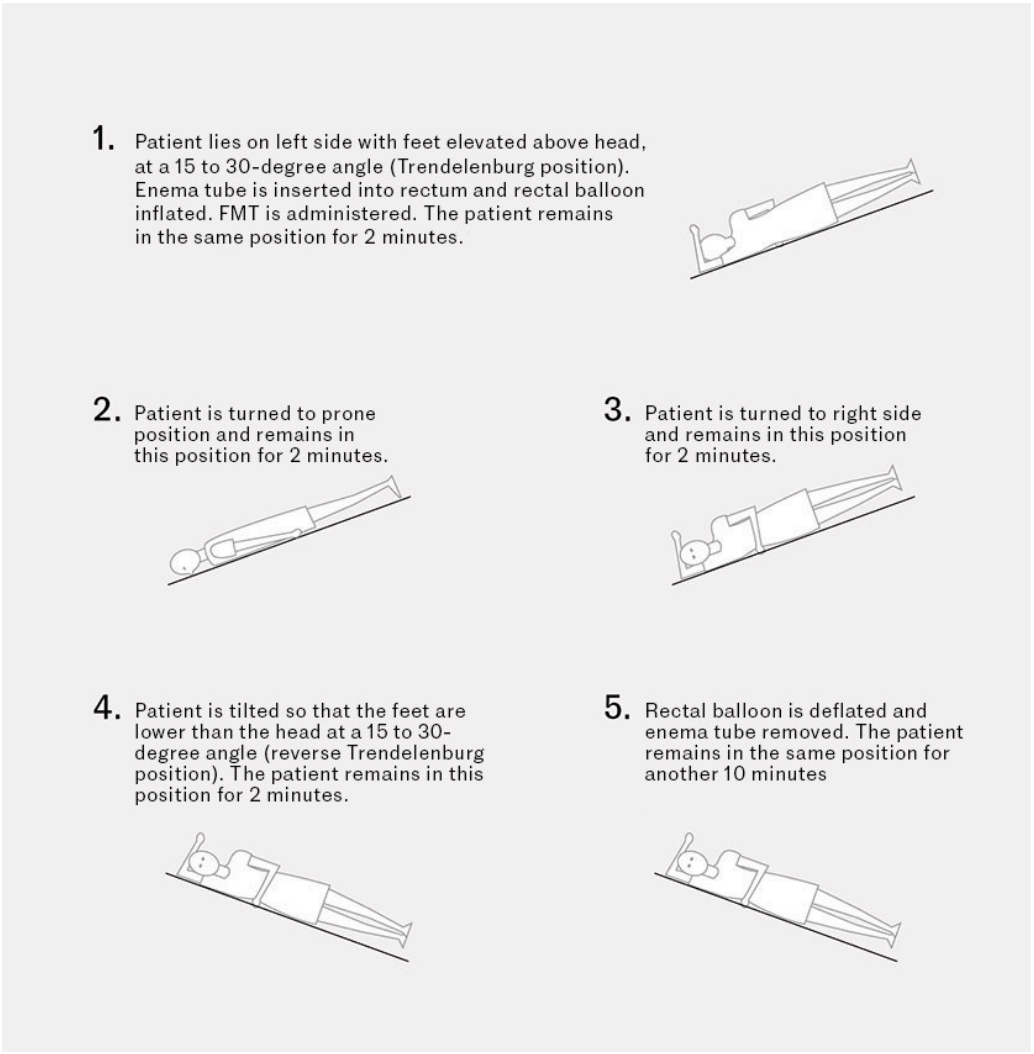

Figure 2 The patient was repositioned on the examination table according to a tested procedure to ensure distribution of the faecal microbiota suspension throughout the colon (4).

The patient experienced complete remission of symptoms, with normal stool consistency, colour and frequency within two days of treatment. At the one-week check-up with her GP, she reported being 'completely well again.' She had no recurrence of *C. difficile* infection at her last check-up two months after the FMT treatment.

Discussion

Watery diarrhoea (≥ 3 loose stools per day) following recent antibiotic treatment, together with confirmed toxin-producing *C. difficile* in the stool, as in our patient, is diagnostic of acute *C. difficile* infection. The patient declined antibiotics, which is the first-line treatment according to national guidelines (1).

FMT has been recommended for several years as a third-line treatment for recurrent *C. difficile* infection (1, 5). For a primary infection, FMT is not recommended due to the lack of large-scale clinical trials.

The treatment was not recommended in clinical guidelines for this reason, and could therefore be considered experimental at the time the patient contacted the research group. Experimental treatments should generally only be offered in clinical trials.

However, we had unpublished knowledge relevant to the treatment decision: shortly before the patient contacted us, we had completed a large-scale randomised phase III trial comparing standard antibiotic therapy for *C. difficile* infection with FMT (3). The patient's request was discussed from a medical and ethical perspective in the research group, and with her GP and a local gastroenterologist. Particular emphasis was placed on the patient's refusal of the antibiotic treatment recommended in guidelines. Shared decision-making is an important component of evidence-based practice (6).

We concluded that the new trial was relevant to the patient's clinical problem. In the trial, 67 % of patients treated with faecal microbiota suspension were cured, compared with 61 % receiving standard antibiotic therapy (a difference of 6 percentage points; *p*-value for non-inferiority < 0.001) (3). The trial also demonstrated that FMT did not lead to more adverse events than antibiotic treatment (3). We considered the results to be definitive. The trial's high-quality design, adequate sample size and well-defined endpoints support the validity of the results (3).

An experimental treatment is a novel intervention that has not been rigorously tested in randomised trials that compare it with current recommended therapy (7, 8). When we assessed this patient, we were aware of the results from the new trial (3). In addition, two smaller clinical studies had indicated that FMT is at least as effective as antibiotics for primary *C. difficile* infection and that the treatment is not associated with severe adverse effects or complications (9, 10). Other studies have shown that FMT is generally safe (11). We therefore concluded that the treatment could no longer be considered experimental, even though the results of our new trial had not yet been published in full in a scientific journal.

Overall, we determined that it was ethically justifiable and clinically appropriate to offer the patient FMT on the basis of shared decision-making and informed consent. We considered this intervention to be at least as effective as antibiotic treatment, that the risk of adverse effects or

complications was no higher, and that the treatment should no longer be regarded as experimental. We considered discussing the case with a clinical ethics committee but concluded that this was unnecessary, as we were confident in our reasoning. The patient responded well to treatment and experienced complete remission shortly thereafter. The randomised trial was published soon afterwards (3).

We would like to thank research coordinator and registered nurse Siv Isaksen for the prompt and smooth facilitation of faecal microbiota transplantation for the patient.

The patient has consented to publication of the article.

The article has been peer-reviewed.

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