Rapid resolution of COVID-19 after faecal microbiota transplantation

Recent publications demonstrate that SARS-CoV-2 may undergo prolonged shedding in stool, and that gut microbiome perturbations associate with COVID-19 severity.[1 2] Faecal microbiota transplant (FMT) restores a damaged gut microbiome and may impact on immune responses,[3] including in the respiratory system ('gut–lung axis')[4]; such microbiome-immune signalling may result in lung-epithelial resistance to SARS-CoV-2.[5] We describe two interesting cases of patients treated with FMT primarily to treat *Clostridioides difficile* infection (CDI), but which coincidentally were performed just before initial symptoms of coexisting COVID-19 (figure 1).

Patient 1: an 80-year-old man with multiple comorbidities, including prior CDI, was admitted to hospital with pneumonia/sepsis. Following meropenem treatment, pneumonic features resolved, but CDI relapse occurred. Sequential vancomycin treatment and nasojejunal FMT were administered. On the day of FMT, he developed further fever and C-reactive protein (CRP) increased; repeat microbiology cultures were negative, but SARS-CoV-2 PCR was positive (figure 1). He commenced on remdesivir and convalescent plasma (CP). Unexpectedly, 2 days after FMT, the fever never recurred and his CRP decreased, without further pneumonia exacerbation.

Patient 2: a 19-year-old man with ulcerative colitis on immunosuppression was admitted to hospital because of a relapse of CDI. Vancomycin therapy was administered, and symptomatic improvement occurred; colonoscopic FMT was administered to prevent further recurrence. Fifteen hours post-FMT, he developed fever up to 39°C, with CRP and interleukin-6 (IL-6) levels increased; SARS-CoV-2 PCR returned positive. Subsequently, other than two isolated episodes of fever, his temperature did not exceed 36.6°C, and CRP and IL-6 normalised.

Retrospectively, we performed SARS-CoV-2 PCR stool testing in both

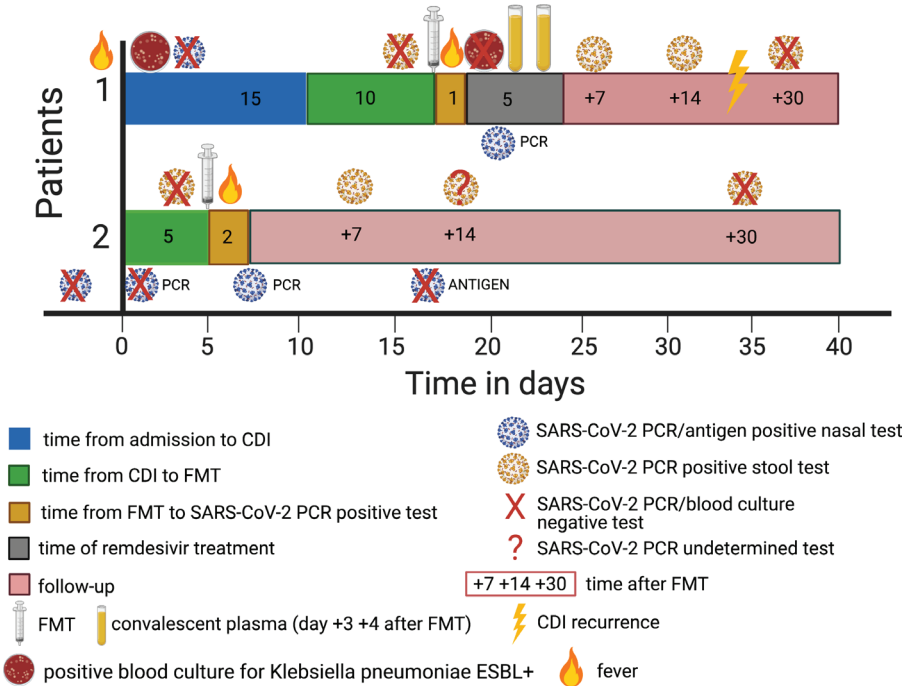

Figure 1 Timeline of the procedures performed in patients with CDI, which coincidentally occurred during COVID-19 early stage infection. Created with BioRender.com. CDI, *Clostridioides difficile* infection; ESBL, extended-spectrum beta-lactamase, FMT, faecal microbiota transplant.

patients. Pre-FMT samples were negative, but tests from day +7 post-FMT were positive in both patients. Further SARS-CoV-2 PCR stool tests in post-FMT samples gave the following results: patient 1—day +14 positive, day +30 negative; patient 2—day +14 undetermined, day +30 negative. Stool donors were twice negative for SARS-CoV-2 on nasopharyngeal swab during stool donation; all donated faecal material also tested negative on PCR. Both patients were SARS-CoV-2 negative before hospital admission.

Our main conclusion from these cases is that FMT appears safe and of comparable efficacy in treating recurrent CDI in patients with coexisting COVID-19. A further more speculative question is as to whether FMT may impact the clinical course of COVID-19. Both patients had risk factors for severe features/adverse outcomes of COVID-19, that is, frailty/comorbidities for patient 1 and immunosuppression in patient 2. However, both patients experienced mild clinical courses, with one possible explanation being that FMT mitigated more adverse outcomes, potentially through impacting microbiome-immune interactions. Apart from FMT, patient 1 received also remdesivir and CP; however, clinical benefits from remdesivir usually occur after a median of 10 days,[6] and clinical trials show limited benefits of CP in COVID-19.[7] Furthermore, patient 2 received no targeted therapy against COVID-19. Mean SARS-CoV-2 RNA presence in faeces of infected patients is 27.9 days (maximum of 47 days) after first symptom onset,[8] which appears far longer than in our patients. Our experience is consistent with two further reported cases in which FMT, primarily administered to treat CDI, appeared safe and associated with rapid resolution of coexisting COVID-19.[9]

Our findings provide early evidence regarding the use of FMT in recurrent CDI in patients with COVID-19. Furthermore, these data let us speculate that gut microbiome manipulation may merit further exploration as an immunomodulatory strategy in COVID-19. Based on our experience here (and other data demonstrating gut microbiome-immune interactions in humans[10]), we are progressing to a clinical trial to assess the impact of FMT added to standard COVID-19 treatment on the risk reduction of disease progression (NCT04824222); this should commence recruitment shortly.

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