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Commentary

# Shedding light on dark matter – faecal microbiota transplantation in Europe

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Faecal microbiota transplantation (FMT) is an emerging treatment modality. FMT entails the transfer of the intestinal microbiota from a healthy donor to a recipient to beneficially alter the intestinal microbiota and change the course of recipients' disease. Having shown high cure rates compared to antibiotic therapy, FMT has become a routine treatment for recurrent *Clostridiodes difficile* infection (rCDI) [1]. In many other microbiota-related diseases including gastrointestinal, metabolic and immunological disorders, the potential of FMT is still in an experimental phase [2]. In addition, FMT allows researchers to study causality of the gut microbiota in human disease [3]. Although the demand for safe FMT is growing, current clinical use, organisation and dissemination of FMT are unknown.

Baunwall and colleagues therefore set out to describe the clinical use and potential for FMT in Europe [4]. A total of 42 hospital-based FMT centres within the European Union were identified. Of these FMT centres, 31 centres from 17 countries replied to a digital survey organised by the United Gastroenterology European (UEG) working group for stool banking and FMT. The survey inquired FMT-related clinical activities, organisation and regulation of approached centres. A total of 1874 FMT procedures were reported, more than half of which (57%) were performed for the treatment of rCDI. Authors state that the reported number of FMTs for rCDI covers only 10% of annual cases of multiple, rCDI in Europe. The significant underuse of FMT in rCDI emphasizes the need to raise clinical awareness for FMT as recommended treatment for rCDI and increase European FMT activity by 10-fold.

The FMT centres in Europe operate with high safety standards and adhere to international consensus guidelines as well as formal or informal regulations from health authorities. Nevertheless, the survey showed a wide variation in donor screening, production and delivery of FMT among the European centres. Safety and accessibility of FMT are relevant concerns for clinical use of FMT. These can largely be overcome by establishing centralised FMT centres or faeces banks as proposed by Baunwall and colleagues. Although cost effectiveness of large FMT centres remains to be determined, these centres can facilitate FMTs via strict standards for donor screening, production, storage and handling. While this infrastructure would benefit FMTs to treat rCDI, it is yet to be determined if such standardised preparations are effective for indications that are more likely to benefit from fresh, (anaerobically) processed FMTs [5]. In such cases, local centres are to be preferred over centralised large centres.

The preferred delivery method for FMT was colonoscopy, followed by rectal enema and nasoduodenal tube. In 2019, 6/31 FMT centres offered FMT in encapsulated form, half as glycerol-based frozen FMT capsules and half as lyophilized FMT capsules. FMT capsules achieve comparable cure rates for rCDI compared to more traditional means to administer FMT and are quite patient friendly [6,7]. Capsules can be self-administered and, if disease conditions allow, FMT capsule treatment does not necessarily require a hospital visit. Long-term storage can be efficiently realised and capsules provide the opportunity for repeated treatment (*e.g.,* maintenance therapy) and targeted delivery, which might be important for specific indications [8,9]. Production methods for FMT capsules vary and protocols best preserving viability and diversity of donor microbiota still need to be optimised. Nevertheless, encapsulated FMT provides many advantages and opportunities and deserves close attention from initiatives that aim to foster and increase use of FMT for the treatment of rCDI and beyond.

A question which remains to be answered is whether live microbes are necessary for the clinical efficacy of FMT [10]. Other components in FMT such as bacterial remnants, metabolites and bacteriophages could modulate the microbiota as well and might broaden applicability of FMT for patients currently excluded from FMT (*e.g.,* immunocompromised patients). To further standardize the FMT treatment, the active components need to be identified. FMT can be used to identify these promising microbial or metabolic leads, which could replace FMT in time as pre-, pro- or postbiotics. Indeed, ongoing studies are investigating the efficacy of rationally selected bacterial consortia produced under GMP as alternative for FMT to

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treat rCDI. In time, treatments like these will probably replace the use of FMT.

There are some minor limitations of the study. Authors identified FMT centres via their joint networks and via the trial registry clinicaltrials.gov. In addition, only hospital-based FMT centres were included, leading to an underrepresentation of smaller or peripheral FMT centres. Therefore, the estimated FMT activity in the European union is a conservative measure and will likely be higher. In addition, the results from the survey reflect the situation in 2019 and current practices and FMT activity might have changed. Especially with the recent outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), many FMT centres were forced to temporarily cease activity and implement additional donor screening measures.

Nevertheless, FMT and similar treatments have an exciting future ahead. By mapping the current FMT landscape in Europe, Baunwall and colleagues provide important guidance for future clinical practice; for decision-makers to regulate FMT and for upscaling FMT and FMT centres in Europe.

## Author Contributions

KW and HH contributed equally to writing and revising this commentary.

## Declaration of Interests

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