Challenges and Opportunities for Treating *Clostridium difficile* in 2022

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IN A symposium session presented at United European Gastroenterology (UEG) Week 2022, experts delved into the challenges presented by *Clostridium difficile* infection (CDI) and the opportunity that faecal microbiota transplants (FMT) can provide. Benjamin Mullish, Gastroenterology and Hepatology Division of Digestive Diseases, Imperial College London, UK, and Georgiana-Emmanuela Gîlcă-Blanariu, Grigore T. Popa University of Medicine and Pharmacy, Iași, Romania, shared novel research and real-world experience. The symposium examined all aspects of CDI from the importance of understanding pathways of pathophysiology to the logistical challenges that pioneering an FMT clinic can present.

UEG 2022

THE BURDEN OF *CLOSTRIDIUM DIFFICILE* INFECTION

Mullish, a thought-leader on the topic of CDI, introduced the challenge of the infection and the impact it has on individuals and populations. In the USA, more than 500,000 cases of CDI are diagnosed per year; however, more concerning is the apparent shift in epidemiology, with CDI increasingly affecting the young and healthy, a population without typical risk factors. The infection still presents considerable risk of morbidity and mortality, resulting in huge implications for healthcare resourcing and patient quality of life. Novel challenges in the microbiology of CDI include hypervirulent strains and high rates of non-responsiveness to antibiotics and infection recurrence. All these aspects of CDI make it difficult to treat. New therapies such as FMT offer opportunities for improved outcomes; however, challenges regarding expense, logistics, and availability prevent FMT from acting as a silver bullet for treating patients with CDI.

UNDERSTANDING THE PATHOMECHANISMS OF *CLOSTRIDIUM DIFFICILE* INFECTION

Mullish questioned the audience on how to better respond to and treat patients. Mullish's answer was simple: treatment options and new therapies can be improved by better understanding the underlying mechanisms of pathology behind CDI. Mullish broke down these into three mechanism categories: bacterial factors, host–bacterial interaction, and host factors. Mullish went on to discuss novel research that demonstrates how increased understanding can lead to innovative treatment options.

The essential bacterial factor that Mullish wished to highlight was the *C. difficile* adhesin proteins, called surface layer proteins (SLP). Anti-SLP antibodies can be detected in the serum of patients with CDI. Previous experiments in mice have demonstrated a protective immune response against CDI after rectal SLP exposure. This was further confirmed

by detectable serum Ig following exposure. A further study where SLP was genetically engineered to be constitutively expressed in lab animals resulted in a protective response against CDI.

Mullish then focused on the host–bacterial interaction, more specifically gut microbial metabolites. Firstly, p-Cresol is a metabolite produced by *C. difficile*. *C. difficile* is one of only four gut-residing bacteria that can produce the organic compound. When formed, p-Cresol kills other Gram-positive bacteria in the gut, therefore giving *C. difficile* a competitive advantage in this environment. Although it is not currently a druggable target, p-Cresol has the potential to be a target for future therapies aiming to undermine the competitive advantage of *C. difficile*. Furthermore, p-Cresol could become a sensitive and specific potential diagnostic factor. Mullish then highlighted succinate, a chemical produced by bacterial fermentation in the gut. *C. difficile* can exploit succinate for energy to produce butyrate. FMT from a healthy human microbiota reduces the availability of luminal succinate for *C. difficile* to exploit. Here, FMT acts as a source of competitive niche exclusion for the carbon energy source *C. difficile* requires.

Small chain fatty acids (SCFA) are produced from undigested protein and carbohydrate elements and exert a net anti-inflammatory effect over the gut. Previous investigations have suggested that SCFAs have anti-*C. difficile* effects, which are induced by the inhibition of toxin production. FMT is associated with the restoration of SCFAs, as well as the variety of biofluids in the gut back to pre-morbid levels in patients with CDI.

The final group of metabolites that Mullish drew attention to were the bile acids. Primary bile acids are metabolised to secondary bile acids by enzymes, 7-α-hydroxylase, and bile salt hydroxylase, in the gut. Primary bile acids exert pro-*C. difficile* effects, whereas secondary bile acids have anti-*C. difficile* effects, inhibiting growth and toxin activity. Both enzymes for metabolising bile acids are found lacking in the gut of patients with CDI. Furthermore, secondary bile acids can be used as a predictive tool for the recurrence of CDI. Mullish shared research that they carried out as part of their own PhD, which demonstrated that FMT can restore secondary bile acids, and that FMT therapies are associated with restoral of the pre-morbid gut bile enzyme profile.

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Finally, Mullish delved into the interactions of host factors such as Igs, glycans, and microRNAs. Evidence has shown that hosts secrete different IgAs pre- and post-FMT. Additional studies have demonstrated significant differences in serum glycan before and after FMT, with a marked simplification of glycans relating to Igs. Researchers were able to demonstrate changes in host microRNAs, as well as transcriptional changes and differences in protein production linked to changes in the level of toxins post-FMT. Mullish summarised their presentation by highlighting how FMT can impact CDI on multiple levels, from changing metabolites in the gut to optimising elements of host physiology.

PIONEERING FAECAL MICROBIOTA TRANSPLANTS CLINICS

The challenges of treating CDI were also explored by Gîlcă-Blanariu. In their presentation, however, Gîlcă-Blanariu focused on the logistical challenges that surround the provision of FMT treatment. Gîlcă-Blanariu discussed the barriers that they had experienced and overcome when introducing the first FMT clinic to Romania. Over the last year, studies have established FMT as both safe and efficacious, with overall success rates of approximately 90% for treating recurrent CDI (at least two episodes). Furthermore, emerging evidence suggests that FMT is an effective option for treating first-line CDI.

Gîlcă-Blanariu began their presentation by discussing the key steps involved in implementing and running an FMT clinic in Romania. Gîlcă-Blanariu highlighted the necessity of learning and training from experts around the globe who already have practicing FMT clinics; the complexity of conceiving national guidelines for FMT practice; identifying clinical and legal frameworks; and the logistics of building an electronic database for managing details of donors and FMT recipients. Although the projected steps were at initial assessment clear and achievable throughout the project, Gîlcă-Blanariu and their team encountered numerous unexpected challenges to the provision of FMT for patients with CDI.

The COVID-19 pandemic delayed training activities planned at an FMT facility in Birmingham, UK, forcing the training to occur online. This also delayed the creation of national guidelines surrounding FMT practice so that they could include updated advice about COVID-19 safety.

Legal framing also presents a unique challenge. FMT is not yet formally regulated in Europe, with regulations differing in classification as a medical treatment versus a transplant across different locations. This resulted in the need for insurance coverage, which led to the practice being defined as an advanced therapeutic medicinal product by Romania. A proposal for regulation has recently been made in July 2022 to the European Commission (EC) to define FMT as a transplant.

Gîlcă-Blanariu and their team encountered further issues with the understanding of FMT amongst medical practitioners. In a survey of medical students, only 34% of the respondents were classified as having a medium level knowledge of FMT. Furthermore, 75% of respondents were worried about the risk of transmitting a disease undetected by donor screening to recipients. This level of understanding in the field indicates a general lack of knowledge about the benefits FMT can provide. This lack of understanding extends to, and

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is multiplied in, the general population. This misconception can hugely impact the number of willing donors, making programmes difficult to initiate and run.

The presentation closed with a summary by the session chair Juazos Kupinskas, Department of Gastroenterology & Institute for Digestive Research, Lithuanian University of Health Sciences (LSMU), Kaunas, Lithuania, who explained that lack of knowledge, logistical barriers, expense, and unforeseen challenges result in underserving patients with CDI, and in a lack of access to the proven effective treatment of FMT.

CONCLUDING COMMENTS

CDI is a globally ubiquitous challenge, which demonstrates concerning epidemiological profiles of increasingly younger and healthier populations. Research has demonstrated that FMT can fight infection on multiple pathological mechanistic levels. However, logistics, expense, and educational and regulatory barriers can make FMT clinics difficult to establish and run. Further investment in research, education, and provision is needed to make treatment accessible to all the populations that need it.