Lessons Learned from Faecal Microbiota Transplantation in Cirrhosis

Grace B. Hatton¹ · Shaolu Ran¹ · Thomas H. Tranah¹ · Debbie L. Shawcross¹

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Abstract

Purpose of Review We examine recent developments in the treatment of cirrhosis by gut microbiome manipulation specifically focusing on the phase 1 safety and feasibility trials of faecal microbiota transplantation (FMT). We interrogate the published data so far on its feasibility, safety and efficacy.

Recent Findings A large number of trials have demonstrated the efficacy of FMT in treating recurrent *Clostridium difficile* infection which is now considered standard of care. In cirrhosis, FMT is still being evaluated and there are a number of clinical trials underway. There are two phase 1 pilot safety studies that have been published with promising findings. However, the importance of rigorously testing donor stool for the presence of multi-drug resistant species has been highlighted and lessons have been learned.

Summary For those patients with cirrhosis, replacing an unhealthy gut microbiome with a healthy one offers a promising antibiotic-free treatment that may reduce bacterial translocation and endotoxemia.

Keywords Cirrhosis · Dysbiosis · Faecal microbiota transplantation · Gut dysbiosis · Hepatic encephalopathy

Introduction

Global Chronic Liver Disease Crisis

Cirrhosis reflects the clinical endpoint of advanced-stage liver disease, uncompromisingly characterised by a myriad of debilitating and largely irreversible symptoms. Typically, these symptoms range from immune dysregulation and infection to bleeding, fluid overload, hepatic encephalopathy (HE), end-organ failure and, ultimately, death. Treatment options are all the more limited with disease progression, and without access to liver transplantation, prognosis is invariably bleak. Equally, cirrhosis is gaining rapid traction as one of the biggest contributors to mortality worldwide [1].

Poor Outcomes in Chronic Liver Disease

In the UK, 70% of patients with cirrhosis die in hospital and while one in five of those who die have had five or more admissions to hospital in the last year of life, one in five are admitted only once and die during that first admission [2]. Cirrhosis is associated with an increased incidence of infection resulting in hospitalisation and complicating hospital admissions in up to 40% of cases [3]. Infection can lead to worsening liver function and precipitate complications including variceal bleeding, HE, acute kidney injury and multi-organ failure, contributing to high mortality [4]. Patients with cirrhosis admitted to intensive care have an overall survival until hospital discharge of only 51% [5].

Grace B. Hatton and Shaolu Ran contributed equally to this work.

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✉ Debbie L. Shawcross
debbie.shawcross@kcl.ac.uk

¹ Institute of Liver Studies, Department of Inflammation Biology, School of Immunology and Microbial Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK

Susceptibility to Infection and Anti-microbial Resistance in Chronic Liver Disease

The underlying mechanisms that contribute to the development and progression of chronic liver disease are complex and encompass the development of hepatocellular inflammation, fibrosis and cirrhosis with a variable time course. This usually spans one to three decades. The gut microbiome has prime importance in the pathogenesis of cirrhosis with the

evolution from a healthy gut microbiome to one characterised by dysregulation of gut microbial activity or ‘dysbiosis’ associated with the progression to end-stage cirrhosis. Dysbiosis is greater in patients with cirrhosis who develop complications related to their cirrhosis correlating with plasma endotoxin and 30-day mortality [6]. Many pre-cirrhotic liver diseases particularly alcohol and fatty liver disease [7] are associated with increased intestinal permeability and in cirrhosis, there is an imbalance between healthy and pathogenic gut bacteria with skewed microbiota populations in favour of increased numbers of pro-inflammatory and ammoniagenic species including *Enterobacteriaceae*, *Firmicutes*, *Archaea* and *Prevotella*. Bacterial translocation is a significant driver of cirrhosis-associated immune dysfunction (CAID) [8], although the mechanisms by which dysbiosis drives immune cell dysfunction remain unknown.

Patients with cirrhosis have enteric bacterial dysbiosis and translocation of bacteria across the gut epithelial barrier. This culminates in systemic inflammation and endotoxemia, inducing innate immune dysfunction, predisposing to bacterial infection. 35% of patients with cirrhosis acquire nosocomial infections compared with 5% of inpatients without cirrhosis. Patients with cirrhosis are at particularly high risk for developing antimicrobial resistance because they are frequently prescribed antibiotics (25% are on prophylactic antibiotics), undergo multiple invasive procedures (e.g. endoscopy, recurrent paracentesis) and require recurrent hospitalisations [9, 10]. Decompensated cirrhotics have a 37% 30-day readmission rate [11]. The Canonic study [12] investigated the prevalence of multi-drug resistant organisms (MDRO) in patients with decompensated cirrhosis and acute-on-chronic liver failure in different liver centres around Europe; between one quarter and two-thirds of patients enrolled had MDRO infections, especially *ESBL-Escherichia coli*.

With poor outcomes following infection, the propagation of antimicrobial resistance and increasing waiting list mortality for liver transplantation, there is an urgent unmet need for approaches that focus on reducing the rate of infection and preventing recurrent hospitalisations.

The Gut in Health and Chronic Liver Disease

The gut microbiome per se is the bacterial hothouse of our digestive system, and its characteristics vary widely from person to person [13]. These variations in microbiome composition have also been repeatedly shown to link with various pathologies. Reduced species diversity and bacterial numbers are associated with inflammatory bowel disease, coeliac disease, diabetes, metabolic syndrome and even Parkinson’s disease and dementia [14, 15]. This often reduced diversity of the gut microbiome in diseased states is predominantly characterised by an overabundance of opportunistic bacterial species including *Enterobacteriaceae* as well as *Escherichia*

coli, and loss of anti-inflammatory species and their metabolic products including *Firmicutes* and *Faecalibacterium* [16]. Numerous studies have also demonstrated that diet, stress, drugs and hormones play collectively strong roles in contributing to our gut microbial makeup—corroborating the microbiome’s susceptibility to manipulation by the environment as much as being pre-programmed by genetics. Indeed, the functional integrity of the microbiome as we increasingly understand it is phenomenally complex; so much so that it has prompted many clinicians to advocate its status as a metabolically active tissue in itself.

Current understanding of the composition and function of the gut microbiome and how this relates to the progression and outcomes in patients with cirrhosis remains in its infancy and is based on descriptive snapshots afflicted with confounders and lacking in robust clinical validation.

The term gut ‘dysbiosis’ has been coined to encapsulate the perturbations in the structure of the complex commensal communities of the gut microbiome. With the onset of cirrhosis, small bowel bacterial overgrowth and a more permeable gut epithelial membrane expose the liver to immune-activating bacterial degradation products via the portal vein. This is further exacerbated by underlying portal hypertension and endothelial dysfunction, whilst portosystemic shunting increases the delivery of these bacterial degradation products to the systemic circulation, evading the reticuloendothelial system. Endotoxins activate hepatic macrophages inducing the production of pro-inflammatory cytokines. This can ultimately culminate in hepatic injury and systemic inflammation contributing further to immune disarray, which predisposes individuals to infection and heralds the development of decompensating complications. The evolution of gut dysbiosis has been causally linked to the pathogenesis of cirrhosis and the progression to end-stage liver disease [6]. Patients with cirrhosis also have salivary dysbiosis associated with impaired salivary defences and systemic inflammation. Salivary dysbiosis has been shown to be greater in patients with cirrhosis who developed complications necessitating hospitalisation within 90 days [17].

Evidence Base for the Manipulation of the Gut Microbiome in Cirrhosis to Improve Outcomes

Therapeutic approaches to correcting dysbiosis have, as with the causes of dysbiosis itself, been multifactorial; targeting the replenishment of lost favourable bacterial species as well as supplementing the gut with prebiotic foodstuffs to encourage butyrate-producing anti-inflammatory bacteria to thrive. There are however limits to these endeavours; treating the complications of cirrhosis with broad-spectrum antibiotics also contributes to ongoing gut dysbiosis, augmenting disruption to the normally symbiotic population of intestinal bacteria and potentially predisposing to further opportunistic infections and small bowel bacterial overgrowth [6, 18, 19]. This

in turn adversely impacts on microbial diversity, composition and activity.

Manipulation of the Gut Microbiome (Changes in Diet)

It has been demonstrated that within a day of reaching the distal gut, a change in diet can measurably alter the gut flora and its metabolic end-products and therefore, regulation of diet itself creates an opportunity to alter the gut milieu [20]. Overall, protein intake positively correlates with microbiota diversity. In particular, consumption of plant protein has been linked to increased levels of *Bifidobacteriaceae* and *Lactobacillaceae* resulting in improved gut mucosal barrier integrity whilst animal protein has been linked to increases in abundance and activity of microorganisms capable of triggering inflammatory bowel disease, of which includes *Bacteroides*, *Alistipes* and *Bilophila* [20–22].

Animal models have shown that high-fat diet induces a shift in balance of gut microbiota leading to reduced levels of *Lactobacillaceae* and disproportionately more pro-inflammatory species, possibly through altered bile acid profiles [23, 24]. The Mediterranean diet, characterised by a low intake of saturated fat and cholesterol, and a high intake of mono- and polyunsaturated fatty acid, along with complex carbohydrates and fibre, has been shown to improve cardiovascular risk and reduce inflammation [25]. This effect may in part be mediated by the increase in butyrate-producing species and decreases in pro-inflammatory species that is associated with this diet [26].

The effects of dietary habits on clinical outcomes in cirrhosis was interrogated by Bajaj et al. when they compared cirrhotic and control groups in the USA with groups from Turkey. The Turkish diet was rich in fermented milk products, coffee, tea and chocolate, all associated with increased microbiota diversity. Furthermore, it was shown that coffee, tea, vegetables and cereals were protective against 90-day rehospitalisation rates [27••]. The effects of dietary intervention on the gut flora are worth considering when managing patients with cirrhosis.

Manipulation of the Gut Microbiome (Probiotics, Rifaximin)

Beneficial modulation of the gut microbiome to improve liver-related complications in cirrhosis has been explored through the use of indirect, non-specific means such as probiotic, prebiotic supplementation and the non-absorbable antibiotic rifaximin.

Probiotics are largely marketed as food supplements rather than licenced medicinal products but are used with the intent of conferring positive health-related effects by augmenting existing beneficial bacterial populations within the gut, thereby conferring increased microbial diversity. Equally, they may have a secondary role in inhibiting bacterial growth, including that of *Pseudomonas* spp. [28], methicillin-resistant

Staphylococcus aureus, *Shigella* spp. and *Escherichia coli* [29], thus potentially protecting against spontaneous bacterial peritonitis in decompensated patients. The evidence for probiotic use in treating gastrointestinal diseases remains largely conflicting; however, whilst numerous clinical trials argue that probiotic supplementation has yet to demonstrate significant benefit in such patients and namely those suffering from Traveller's diarrhoea and necrotising enterocolitis [30–32], others cite that specific strains may show promise in improving insulin sensitivity and reducing symptoms common in cirrhosis, such as hepatic encephalopathy [33, 34]. Arguably, however, one factor influencing this partial efficacy may be the intra- and inter-individual variability in gut motility, which in turn influences bacterial transit and the potential window of opportunity for beneficial bacteria species to exert their anti-inflammatory effects.

Prebiotics by comparison act as non-specific 'feedstock' for microbiota utilisation. There is some evidence to suggest their efficacy in treating dysbiosis by promoting *Bifidobacterium* spp. growth and which may lead to increased endogenous production of acetate and lactate, which act as substrates for beneficial butyrate-producing bacteria thought to be responsible for maintaining gut barrier integrity, such as *Roseburia* and *Eubacterium*. These species have otherwise been shown to be reduced in inflammatory bowel disease, highlighting a potential avenue for indirect modification of the gut microbiota in such diseased states by creating a preferentially favourable environment in which beneficial bacteria may thrive.

Rifaximin is a non-absorbable antibiotic which, in stark contrast to pre- and probiotic supplements, serves to non-preferentially eliminate enteric bacterial species, destroying potentially beneficial as well as harmful strains [35, 36]. Patients on the UK liver transplant waiting list treated with rifaximin have reduced all-cause admissions, episodes of spontaneous bacterial peritonitis and variceal bleeding, as well as reduced length of stay [37••]. Furthermore, the use of rifaximin by patients on the waiting list has been linked to reduced early allograft dysfunction following liver transplantation [38]. However, considerable concern remains regarding whether long-term antibiotic administration may drive antibiotic resistance. Indeed, in a recent study, 50% of patients prescribed rifaximin for HE developed rifampin-resistant staphylococcal isolates after as little as 1–7 weeks following rifaximin treatment [39••]. The question therefore is raised as to whether directly, as opposed to indirectly, modulating the gut microbiota utilising faeces from healthy donors may be a safer and more durable therapy.

FMT: Origins and Uses So Far

Direct targeting and manipulation of the gut microbiome is an increasingly promising feat of bioengineering and

personalised medicine. One emerging strategy to address dysbiosis therapeutically is with the administration of FMT, i.e. the transplant of a homogenised filtered faecal sample from a healthy donor directly into the gastrointestinal tract of a patient with dysbiosis. The first case of FMT's use in vivo was described in 1958 [40] as an adjunct in the treatment of pseudomembranous colitis, followed by the first successful report of treatment of inflammatory bowel disease in 1989. Following this, FMT has had reported success in correcting dysbiosis, improving gut microbial diversity and reducing disease morbidity and mortality in cases of irritable bowel syndrome [41], IBD [42], metabolic syndrome [43], uro-genital infections and recurrent *Clostridium difficile* infection, and is now recommended in many guidelines as a therapeutic modality for the latter [44]. There is irrefutable evidence for FMT in treatment of recurrent *Clostridium difficile* infection; however, its benefit in first presentation *Clostridium difficile* infection and severe *Clostridium difficile* infection requires more evaluation.

In addition, there appears to be the emergence of donors that produce outstanding results in transplanted inflammatory bowel disease patients—the ‘super donor’ phenomenon. If we can characterise the specific factors involved, then that will allow for more targeted bacteriotherapy [45•].

FMT in Cirrhosis

Fresh/Frozen FMT in Cirrhosis

End-stage liver cirrhosis inevitably leads to portal hypertension and HE, which frequently requires hospitalisation. The aim of FMT in cirrhosis is to disrupt the pathological pathways aforementioned by restoring the gut microbiome. Some of the postulated benefits that FMT may offer in patients with cirrhosis are shown in Fig. 1.

In a pioneering open-label randomised trial of 10 patients treated with FMT via enema, Bajaj et al. showed that FMT was safe and potentially efficacious in treating HE [46••]. The group demonstrated at least part restoration of gastrointestinal bacterial diversity through treatment with FMT in cirrhotic patients following antibiotic therapy. Just one dose of rectally administered FMT was shown to reverse this dysbiosis and supports the promising use of FMT in alleviating gut microbiota disruption secondary to antimicrobials. A rational donor was selected who had a high relative abundance of *Lachnospiraceae* and *Ruminococcaceae* within a universal stool donor bank. FMT was associated with improved cognitive function. Recurrence of HE was observed in 5 of 10 patients given the standard of care but none of the 10 patients who received FMT. FMT was associated with a relative increase in the butyrate-producing species *Lactobacillaceae* and *Bifidobacteriaceae*. This study however was criticised as patients were treated with broad-spectrum antibiotics prior to FMT and the favourable impact may have been related to the antibiotic administration (not given to the standard of care arm). This would still support FMT as having utility in restoring antibiotic-induced disruption in microbial diversity and function [47••].

Long-term safety and efficacy of FMT was studied within this population as the group was followed up for between 12 and 15 months (mean $\pm$ standard deviation, 12.9 ± 2.9 months for FMT and 12.8 ± 3.7 months for standard of care). Within the standard of care group, 2 patients were excluded (1 died and 1 had a liver transplant) and within FMT group, there was 1 death. The FMT cohort had no adverse effects on long-term follow-up and, even more strikingly, there were significantly less hospitalisations compared to the standard of care group (1 in FMT group vs 10 in the standard of care group), reduced HE events (0 in FMT group vs 8 in standard of care group) as well as improved cognition on assessment [48••]. On microbiota analysis, although there were differences in profiles between FMT and standard of care groups, the increase in

Fig. 1 Proposed benefits of faecal microbiota transplantation in cirrhosis

Lactobacillaceae and *Bifidobacteriaceae* were not sustained suggesting that the recipient microbiome may not need to absolutely reflect that of the donors in order to have a beneficial effect. Further evaluation of the mechanism by which FMT produces its beneficial effects will shed insight into this matter.

HE is associated with a perturbed gut-liver-brain axis with the presence of brain and systemic inflammation. The potential impact of FMT on the development of neuroinflammation in cirrhotic mice as well as germ-free mice colonised by both microbiota from pre- and post-FMT cirrhotic humans as well as non-cirrhotic humans was evaluated by Liu et al. in an elegant study. Here, the investigators compared the degree of neuroinflammation in cirrhotic mice in germ-free and conventional settings that were colonised by stool collected from human cirrhotics and human healthy controls. They observed that the former showed significantly higher levels of neuroinflammation and that stool transplanted into germ-free mice from human cirrhotics who had undergone FMT attenuated the neuroinflammation [49••]. Post-FMT stool was found to have a higher abundance of *Lactobacillaceae* and *Verrucomicrobiaceae* species, the latter which has been demonstrated to protect against immune-mediated liver injury strengthening the enteric barrier.

Encapsulated FMT in Cirrhosis

Encapsulated FMT offers a more practically feasible modality of treatment and is perhaps more acceptable for patients too. Furthermore, as maintained concordance of gut flora with that of the donors has been shown to be short-lived, regular FMT therapy has been suggested as prophylaxis against HE [50].

Bajaj et al. have recently published a phase 1 study, demonstrating that oral FMT capsules are safe and well tolerated in 10 patients with cirrhosis and recurrent HE [51••]. FMT was associated with improved duodenal mucosal diversity, anti-microbial peptide expression, lipopolysaccharide-binding protein and improved cognitive performance. Microbiota analysis showed increased *Ruminococceae* and *Verrucomicrobiaceae* species. Preliminary data is encouraging and warrants further validation in larger randomised placebo-controlled trials focusing on clinical endpoints.

Regulation and Problems Encountered So Far/Pitfalls

The exact role of FMT in restoring cirrhotic gut microbial functionality in a clinical setting still remains unclear. Indeed, what is the precise composition of FMT; how is it regulated with donor selection; and what are the long-term demonstrable effects of treatment for these patients?

When FMT use is appropriate to be employed in the natural history of chronic liver disease has yet to be decided. The efficacy as well as the cost of manufacture must be considered when compared to conventional treatment modalities. A ubiquitous issue will be the innate inability to regulate the composition of FMT with the variability between donors. Furthermore, how will FMT compare to targeted bacteriophage therapy [52••]? Treatment options for patients outwith of liver transplantation are limited and therefore FMT offers an innovative alternative particularly for patients who are ineligible for liver transplantation. However, an independent issue arises in that up to 25% of cirrhotic patients are on prophylactic antibiotics. This will inherently disturb enteric flora, particularly decreasing the proportion of important short-chain fatty acid-producing species and will confound the effects of FMT.

A number of studies have illustrated a potential donor-dependent effect on microbial diversity and systemic metabolic response with FMT [43, 53, 54], and underpinning the difficulties in achieving treatment standardisation with donor and sample confounding. The chronology of FMT's clinical impact is also widely variable, ranging up to several years following treatment completion [50, 55, 56].

Similarly, detailed interrogation of donor characteristics is somewhat lacking in the literature. Anand et al. studied the effects of ageing on FMT donor samples and demonstrated compositional alterations as part of their FMT microbiota analysis from donors aged over 60 years; the exact significance of this remains unclear, though did not appear to affect the clinical efficacy [57].

On a more severe note, emerging problems with FMT pertain to the inherent problems associated with regulation of donor selection, sampling and cohesion which have the potential to cause real patient harm. One such example is of emerging infections being transmitted through FMT, such as ESBL-producing *E. coli* [58]. Two cases have been reported of ESBL bacteraemia caused by FMT shown through genomic sequencing. One case tragically resulted in death. Subsequent investigation showed increased incidence of ESBL in stool culture of recipients from this particular donor, particularly in recipients who were treated for recurrent *Clostridium difficile* infection, a condition where the enteric barrier is similarly disrupted. As previously discussed, cirrhotic patients are at high risk of bacterial translocation given their state of shunting and impaired reticuloendothelial system, making them susceptible to these pathogens. FDA screening only mandated the screening for ESBL within an update on their protocol in 2019. As it is within the nature of microorganisms and viruses to mutate and alter their pathogenicity, our current screening protocols may not be able to cover all that is necessary. This carries huge clinical implications, given that these pathogens are being directly delivered into already immunosuppressed patients, leading to even higher

Table 1 Planned and FMT trials in progress in patients with chronic liver disease as registered on clinicaltrials.gov

Status*	Study title	Conditions	Interventions	Locations
Unknown†	Fecal Microbiota Transplantation for Decompensated Cirrhosis	Decompensated cirrhosis	Biological: FMT Other: traditional treatments	IEC of Chengdu Medical College, Chengdu, China
Completed	Trial of Faecal Microbiota Transplantation in Cirrhosis	Faecal microbiota transplantation Cirrhosis of the liver	Biological: Faecal microbiota transplantation Biological: placebo Drug: FMT Other: placebo	King's College Hospital NHS Foundation Trust, London, UK Hunter Holmes McGuire VA Medical Center, Richmond, Virginia, USA Virginia Commonwealth University Richmond, Virginia, USA
Completed	Oral Fecal Transplant in Cirrhosis	Hepatic encephalopathy Cirrhosis, liver		
Recruiting	FMT in Cirrhosis and Hepatic Encephalopathy	Cirrhosis Hepatic encephalopathy	Drug: faecal microbial transplant capsules Drug: faecal microbial transplant enema Other: placebo	Hunter Holmes McGuire VA Medical Center, Richmond, Virginia, USA
Completed	Fecal Transplant in Recurrent Hepatic Encephalopathy	Hepatic encephalopathy Cirrhosis	Biological: faecal transplant	Hunter Holmes McGuire VA Medical Center, Richmond, Virginia, USA
Active, not recruiting	Fecal Microbial Transplant for Alcohol Misuse in Cirrhosis	Cirrhosis Alcohol abuse	Biological: faecal microbial transplant Other: placebo	Hunter Holmes McGuire VA Medical Center, Richmond, Virginia, USA
Withdrawn	Fecal Microbiota Therapy Versus Standard Therapy in Decompensated NASH Related Cirrhosis: A Randomized Controlled Trial	NASH-related decompensated cirrhosis	Drug: faecal microbiota transplantation Drug: standard treatment Other: weight reduction	Hunter Holmes McGuire VA Medical Center, Richmond, Virginia, USA
Not yet recruiting	Investigational Microbiota Restoration Therapeutic for Hepatic Encephalopathy	Hepatic encephalopathy Cirrhosis, liver	Biological: RBX7455 Biological: placebo	Institute of Liver and Biliary Sciences, New Delhi, Delhi, India
Recruiting	Fecal Microbiota Therapy Versus Standard Therapy in NASH Related Cirrhosis	Non-alcoholic steatohepatitis	Biological: faecal microbiota transplant Other: standard medical treatment	Institute of Liver & Biliary Sciences, New Delhi, Delhi, India
Completed	Randomized Controlled Trial Comparing the Efficacy and Safety of FMT in Hepatitis B Reactivation Leads to Acute on Chronic Liver Failure	Acute on chronic liver failure	Drug: tenofovir Drug: faecal microbiota transplantation (FMT)	Institute of liver and Biliary Sciences, New Delhi, Delhi, India
Completed	Transplantation of Microbes for Treatment of Metabolic Syndrome and NAFLD	Diabetes mellitus Non-alcoholic fatty liver disease	Biological: autologous Biological: allogeneic	Michael Silverman, London, Ontario, Canada
Completed	Randomized Controlled Trial Comparing the Efficacy and Safety of FMT in Hepatitis B Reactivation Leads to Acute on Chronic Liver Failure	Acute on chronic liver failure	Drug: tenofovir Drug: faecal microbiota transplantation (FMT)	Institute of liver and Biliary Sciences, New Delhi, Delhi, India
Recruiting	Fecal Microbiota Transplantation in Severe Alcoholic Hepatitis- Assessment of Impact on Prognosis and Short-term Outcome	Severe alcoholic hepatitis	Other: faecal microbiota transplantation Other: standard of care treatment	Postgraduate Institute of Medical Education and Research, Chandigarh, India
Completed	A Comparison of Fecal Microbiota Transplantation and Steroid Therapy in Patients with Severe Alcoholic Hepatitis	Severe alcoholic hepatitis	Other: faecal microbiota transplantation Drug: steroids	Institute of Liver and Biliary Sciences, New Delhi, Delhi, India

* At time of writing

† Study has passed its completion date and status has not been verified in more than 2 years.

prospective rates of morbidity and mortality [59]. Furthermore, the virome is gaining increasing traction [60] and little is understood what implications FMT may pose through transmission of viruses and phages.

The UK-centric PROFIT trial [61] is one such example of a feasibility and safety study that has specifically addressed the evaluation of the mechanism of action of FMT in cirrhosis administered directly into the jejunum rather than the large bowel, with formal results due to be published in mid-2020.

FMT trials thus far have investigated by and large the preliminary safety and feasibility of FMT in diseased patients. As such, the optimal method of both manufacture and delivery of FMT remains unclear.

Conclusions

It is clear that FMT has a viable role not limited to that of gastrointestinal disease, or indeed, cirrhosis. Our emerging understanding of the gastrointestinal microbiome and its far-reaching implications on health and disease has allowed for FMT to take a central role as an emerging therapy and viable alternative to conventional treatments, as well as for those patients deemed unsuitable for receipt of liver transplantation. The number of clinical trials in setup or which are currently ongoing for the treatment of chronic liver disease (Table 1) illustrates the potential interest hepatologists have in this therapeutic arena but extreme caution is advocated in trial protocolisation for this immunocompromised population.

Caveats to FMT's widespread use include its lack of regulation and donor safety as well as efficacy. Despite this, the future remains promising for the use of microbial transplantation in mainstream medicine; the role of genomic profiling and personalised medicine specific to individuals is likely to inform this directly, as well as improved donor screening and even artificial FMT creation to address these ongoing health problems.

Compliance with Ethical Standards

Conflict of Interest Professor Shawcross has participated in advisory boards for Norgine Pharmaceuticals Ltd., Shionogi and Kaleido Biosciences and has delivered paid lectures for Norgine Pharmaceuticals Ltd. and for Falk Pharma. Dr. Hatton has delivered a paid lecture for Symprove Bioscience Ltd.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Abbreviations CAID, Cirrhosis-associated immune dysfunction; ESBL, Extended spectrum beta-lactamase; FMT, Faecal microbiota transplantation; HE, Hepatic encephalopathy; MDRO, Multi-drug resistant organisms

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