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Review

Regulation, risk and safety of Faecal Microbiota Transplant

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S U M M A R Y

From its origins as a left-field, experimental, and even "maverick" intervention, faecal microbiota transplantation (FMT) is now a well-recognised, accepted, and potentially life-saving therapeutic strategy, for the management of recurrent Clostridiodes difficile infection (rCDI). It is being investigated as a treatment for a growing number of diseases including hepatic encephalopathy and eradication of antimicrobial resistant organisms, and the list of indications will likely expand in the future.

There is no universally accepted definition of what FMT is, and its mechanism of action remains incompletely understood; this has likely contributed to the breadth of approaches to regulation depending on interpretation. In the UK FMT is considered a medicinal product, in North America, a biological product, whereas in parts of Europe, it is considered a human cell/tissue product. Regulation seeks to improve quality and safety, however, lack of standardisation creates confusion, and overly restrictive regulation may hamper widespread access and discourage research using FMT.

FMT is generally considered safe, especially if rigorous donor screening and testing is conducted. Most short-term risks are associated with the delivery method (e.g. colonoscopy). Longer term risks are less well described but longitudinal follow-up of treated cohorts is in place to assess for this, and no signal towards harm has been found to date. Rarely it has been associated with adverse outcomes including the transmission of antibiotic resistant bacteria, and even death.

It is vital patients undergoing FMT are well informed to the currently appreciated risks and benefits before proceeding.

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Introduction

The orthodox paradigm of infectious diseases management concentrates almost exclusively on pathogen eradication, ignoring the importance of the indigenous microbiota. However, this stance has shifted with the emergence of 'metagenomic medicine', with the gut microbiome now considered a distinct organ.

It has long been known that resident gut microbiota perform a fundamental role in excluding invading pathogens; the first description of colonisation resistance was reported in a mouse in 1954 [1]. Mice fed streptomycin were much more susceptible to experimentally induced Salmonella infections than their non-antibiotic exposed counterparts. This observation results from the antibiotic rendering the mouse 'vulnerable to the implantation of contaminating microorganisms by supressing or eliminating some of its normal inhabitants' [1].

The depletion of gut bacteria seen in humans treated with multiple courses of antibiotics and developing *Clostridioides difficile* Infection (CDI) is well described [2—5]. It follows, therefore, that attempting to modulate the altered gut microbiome by restoring diversity using faecal microbiota transplantation (FMT) is a logical therapeutic strategy. FMT involves the transfer of pre-screened donor stool into the gastrointestinal tract of a patient, aiming to increase microbiota diversity and restore the functionality [6].

There are a number of randomised controlled trials directly comparing FMT with either placebo or standard antimicrobial therapy (vancomycin or fidaxomicin) for the treatment of recurrent CDI [7—11]. These studies report efficacy rates of between 44 and 91% for a single treatment and up to 94% for two or more. These trials are complemented by numerous case series and other uncontrolled reports yielding similar cure rates [12]. The cure rates in controlled trials have been reported to be lower than those observed in open label studies, highlighting the importance of rigorously conducted research [13].

FMT has evolved from being perceived as a somewhat maverick treatment to an accepted and effective standard of care for particular patients, with a growing evidence base to support its use [14]. This progression in how FMT became established in the UK was cemented by the publication of an Interventional Procedure Guideline by the National Institute for Health Care and Excellence in 2014 [15]. FMT is now being touted almost as a miracle cure for many ailments with many novel indications under investigation [6].

Unfortunately, we know relatively little about the precise underlying mechanism of action of FMT [16,17]. Despite this, microbiome modulation appears to have captured the imaginations of clinicians and patients alike, and is perhaps an example of where adoption into clinical practice has preceded the basic science underpinning the treatment.

The indigenous microbiota are organised as consortia of highly specialised microorganisms coexisting in a complex community. As well as being highly variable and unique to their human host, these microorganisms have highly complex interactions, some synergistic, some antagonistic. In addition, microbiota composition and function is also significantly influenced by microbe-host interactions, including stimulation of various aspects of the innate and adaptive mucosal immune systems [18].

The highly variable nature of human stool and products derived from it results in a lack of standardisation in FMT practice, which extends to even fundamental parameters such as the amount of starting material and the route of administration [19,20]. Compounding the problem, many reported studies contain insufficient detail when describing key methodological parameters [21].

A number of guidelines and consensus statements have been published in an attempt to harmonise practice and techniques [22—25]. However, without high grade evidence that certain parameters are indicative that a product produced in a particular way is superior to others, individual groups and institutions have little motivation to change the methods that they have most experience with or find most convenient.

Ultimately FMT in its current form may be replaced with transplantation of defined microbial consortia or even microbial compounds that could be cultivated in the laboratory to produce 'clean' products, free of contamination by undesirable strains. This has the advantage of allowing scalability and eliminating many of the risks associated with FMT.

Regrettably, we are some way off being able to rationally design complex, fully synthetic therapeutic microbial communities [26,27].

How is FMT defined?

There is currently no universally accepted scientific or legal definition of FMT. However, it has been described as the transfer of biologic material containing a minimally manipulated community of microorganisms from a human donor to a human recipient (including autologous use) with the intent of affecting the microbiota of the recipient [28].

Although the exact mechanisms of FMT efficacy are poorly understood, in the context of treating patients with recurrent CDI the mode of action is thought to be mainly dependent on increasing bacterial diversity. The aim is to restore gut microbiota community structure and function to more closely resemble that of a 'healthy' person. This occurs by engraftment of donor bacteria not previously detected in the recipient prior to FMT. However, some argue that this is a rather simplistic view and the very concept of 'dysbiosis' is a flawed term [29].

Realistically, the active ingredient(s) and corresponding metabolic functions of FMT are not definitively established and it is likely that different mechanisms may play different roles for different diseases. For example, bile salt hydrolases produced by certain bacteria appear to play a significant role in influencing the efficacy of FMT in rCDI [30].

Faeces is a highly complex matrix comprising hundreds if not thousands of species of microorganisms. There are around 10^7 colonocytes, 10^{11} bacterial cells, 10^8 archaea, 10^8 viruses and 10^6 fungi per gram of wet human stool from healthy adults [31].

In addition to these microorganisms, faeces also contain a wide range of components which could plausibly exert therapeutic effect e.g. bacteriophages, metabolites, bile acids and other small molecules [16,32,33].

Table 1
Examples of different approaches to FMT regulation

Regulatory classification	Characteristics	Example jurisdictions
Biological agent	Stringent regulation, restricted use. Recognised as complex mixtures that are not easily identified or characterised, but should be standardised. Often derived/isolated from living organisms. Sensitive to external environmental factors (e.g. temperature, exposure to light)	USA (investigational), Canada (investigational), Australia
Human cell/tissue product	Tiered regulation according to risk: low risk tier covers tissues and cells that are not 'substantially manipulated' e.g. traditional transplants, higher risk tier covers products and therapies subject to additional processes and manipulation.	Netherlands, Belgium, Italy
Medicinal product (non-biologic)	Variable regulation according to jurisdiction. Product is well characterised and should have well defined structure/mechanism of action. Pharmacokinetic and dose-ranging studies inform appropriate dosage.	UK, Ireland, France, Germany, Switzerland
Medical procedure/unregulated	Considered normal practice of medicine. Decisions regarding donor screening and processing are delegated to clinicians/institutions. Regulatory oversight is devolved or involves self-regulation with voluntary reporting of adverse events.	Austria, Denmark, Sweden, Finland

This community of microorganisms and other stool components is highly variable, both amongst different people but also within the same person at multiple time points. This dynamic variation is influenced by a range of internal and external factors such as diet and exposure to antimicrobial and other drugs etc. [34]. It follows, therefore, that the chemical and biologic components of FMT products will also suffer from considerable variation between batches [35].

In this respect FMT is not like a drug or conventional medicinal product and the substantial degree of batch-to-batch variation would breach the normal regulatory requirements for consistency in product composition. Indeed, the main objective of Good Manufacturing Practice (GMP) is to ensure there is consistency between batches of the same product. This brings us to the question of how regulatory authorities define a medicinal product.

What is a medicinal product?

Article 1 of Directive 2001/83/EC as amended of the European Parliament defines a "medicinal product" as:

a) A substance or combination of substances presented as having properties for treating or preventing disease in humans, and;
b) The substance functions as a medicine i.e. it can be administered to humans either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis or is otherwise administered as a medicinal purpose.

Taking this definition at face value, FMT fulfils both these criteria, and that is the opinion of the UK Medicines and Healthcare Products Regulatory Agency (MHRA). The MHRA issued a position statement in June 2015 which confirmed that FMT falls within the definition of a medicinal product [36].

In the EU, a medicinal product can only be placed on the market if quality, efficacy and safety standards are met and a marketing authorisation has been issued. Currently there are no MHRA marketing authorisations for FMT products, thus material used for FMT is considered to be unlicensed in the UK.

Unlicensed medicinal products are often used in clinical practice; this is permitted by a derogation in the Medicines Directive (Article 5.1 of Directive 2001/83/EC relating to medicinal products for human use (Medicinal Products Directive). This allows member states to develop national provisions to allow supply of unlicensed products to meet the "special needs" of certain patients providing the supply is unsolicited.

Regulation of FMT

One could argue that FMT has similarities with probiotics which are generally considered foods or dietary supplements rather than drugs and thus have minimal regulatory requirements [37,38]. The Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO), defines probiotics as "live microorganisms that, when administered in adequate amounts confer a health benefit on the host" [39].

Although live colony counts contained within these products can be variable, traditional probiotics contain relatively few well-defined strains and can be grown in pure culture. This significantly limits risk and contrasts with FMT which involves thousands of bacterial species native to the gastrointestinal tract, but which are relatively poorly characterised and unstandardised. It is the lack of characterisation of microbial strains that precludes the classification of FMT as a probiotic according to expert consensus [39].

Some argue that FMT should be regarded as a human tissue or transplant product rather than a drug, with regulation under the EU Tissue and Cells Directive (EUTCD) (2004/23/EC) [40,41]. Under EUTCD faeces are classified as a 'combined substance' i.e. they contain both cells and other components. However, the definition of a 'combined substance' applies only where human tissues and cells are the active component of the substance and are being administered to patients because of it. Human cells are not considered to be an active component of FMT, and this definition does not apply.

This was determined by the Competent Authorities on Substances of Human Origin Expert Group of the European Union in 2012 which concluded that FMT is not covered by the European Human Tissue Directive 2004/23/EC of the European Parliament [42]. At the same time, the European Commission determined that individual Member States are free to regulate FMT on a national level. This decision has unfortunately led to haphazard regulation amongst member states, [43,44] and others lacking any regulatory standards [6,41].

The situation in the United States has evolved over the past few years. Initially FMT was unregulated, however in 2013 the FDA declared that FMT would be classed as biologic material and should not be performed without an approved investigational new drug (IND) application. The FDA cited both safety and efficacy concerns as their rationale for this declaration [6,43,44].

This provoked vigorous discussion amongst physicians, professional societies and patients and was considered by many as unnecessarily constraining access to FMT. The FDA responded to these concerns in July 2013 by relaxing their stance. The introduction of enforcement discretion allowed FMT to be used only to treat rCDI not responsive to standard therapy without an IND. This required that patients provide informed consent, emphasising the investigational nature of FMT and unknown long-term effects [43,44]. IND applications continue to be required for all other investigational uses of FMT.

Examples of the different approaches to FMT regulation in various countries are outlined in Table 1.

Safety and risks associated with FMT

FMT is generally considered safe with most short term risks attributable to the method of administration (endoscopic procedure) rather than FMT itself. The most common side effects are mild, self-limiting and include; transient diarrhoea, abdominal pain or cramps, bloating, flatulence and constipation [45,46].

Transfer of live microorganisms to recipients with underlying illness presents a greater potential risk, however a growing number of studies have shown FMT to be well tolerated in higher risk patient groups (such as the immunosuppressed), without excess side effects [47—50].

Many of the potential risks are mitigated by implementing a careful selection and screening process for prospective donors [22,24,51—53]. These would include obtaining a detailed medical history together with testing for a wide panel of infectious diseases. In some programmes this results in rejecting 97% of volunteers [53]. Many centres follow a Universal Stool bank model, distributing pre-screened frozen FMT preparations [24,44,52,54,55]. This model reduces costs through economies of scale and enhances safety through standardised processes, traceability, and monitoring.

Despite this, there are some notable failures which have resulted in obvious patient harm.

A recent example is the acquisition of an extended spectrum beta-lactamase (ESBL) producing E. coli from donated stool [56]. Whole genome sequencing of donor and recipient strains identified that the source originated from donor faeces. This resulted in blood stream infections in two patients enrolled in separate clinical trials in the US, and unfortunately one patient died. The donated stool was manufactured into capsules under a protocol which did not involve screening for ESBLs. In response, the FDA placed a national alert on its website and mandated additional screening to include ESBLs [57].

In a similar event, six infections caused by enteropathogenic E. coli (EPEC) and Shiga toxin-Producing E. coli (STEC) have occurred following investigational use of FMT that are suspected to be due to transmission from material used to make FMT products from different donors in the US. Two deaths in patients with chronic underlying health conditions were reported, although it is unclear if infection contributed to the deaths [58].

These events demonstrate the risk of administering FMT containing large quantities of unidentified micro-organisms, and the need to ensure continual review of screening and selection processes, including remaining vigilant for novel potential pathogens. Most donor banks have temporarily discontinued manufacture of FMT following the emergence of coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2). This virus can be found in the gastrointestinal tract [59], so presumably could be transmitted via FMT. Institutions will need to amend their procedures to minimise this risk.

Additionally, there are valid safety concerns about the use of FMT that extend beyond the transmission of potential pathogens and the complications associated with the procedure of administering the FMT material. In particular, there is a theoretical possibility of increasing the risk of certain non-infectious conditions in the recipient. These include a vast range of illnesses such as obesity, insulin resistance and other metabolic disorders, cancer, mood disorders and other neuropsychiatric conditions. Although many of the associations between gut microbiota and various conditions are fairly well established, there are many more conditions which appear to have quite tenuous links. Many of these links are poorly quantifiable and the conditions would take years or even decades to develop.

Long term safety data had been scarce until quite recently, however, there are now several studies that have followed up patient cohorts for several years, which do not suggest any cause for significant concern [60—63]. Nevertheless, establishing causality for many microbiome—disease associations definitively seems implausible.

To augment this data the American Gastroenterological Association (AGA) and Infectious Diseases Society of America (IDSA) have been funded by the National Institute of Health (NIH) to establish an FMT National Registry [64]. This aims to assess short and long term safety of FMT for up to 10 years with a target of 4000 patients.

The real and theoretical risks of FMT present certain ethical issues concerning the point at which FMT is offered to patients. FMT is now being proposed by some as a valid treatment option for patients with a first episode of CDI [65] despite current guidelines advising against this [22,24].

There is limited evidence emerging that FMT is superior to conventional drugs to prevent rCDI [11,66]. However given that these licensed drugs (e.g. fidaxomicin [67,68] and bezlotoxumab [69,70]) are established, have well described pharmacodynamics, pharmacokinetics and long term safety data, attempting FMT without making use of these would be a retrograde approach. Furthermore, trials of FMT are heterogeneous in design with different routes of administration, preparation, dosing, storage etc. Making it difficult to make comparisons and to pool data.

Conclusion

FMT is an effective treatment for patients with rCDI and potentially a wide range of other illnesses. It is now an established treatment in many countries and there are many clinical studies investigating its utility in many disease areas.

There is still much we do not understand about its underlying mechanism of action, which is likely to vary, depending on what is being used for.

Although generally well tolerated, there have been some serious adverse events, notably with the transfer of various pathogens. Some form of regulation of FMT should be considered positively, in order to improve patient safety. However, various countries have chosen to regulate activity in significantly different ways, often causing confusion and frustration. There are at least four different approaches to regulation, each with their own merits and disadvantages.

Restricting access to FMT through regulation has potentially resulted in a number of unintended consequences. There has been an increase in patients performing self-FMT in a medically unsupervised setting [71]. Instructions for performing home transplants are readily available on the internet [72]. This has the potential to significantly increase both procedural and infectious disease risks.

Increased regulation also places significant burden on those wishing to perform clinical research with FMT such as applying for an IND as a Clinical Trial of an Investigational Medicinal Product (CTIMP) in countries where FMT is classed as a drug. Many investigators may be discouraged from undertaking such research due to the complexity and often confusing requirements.

It is likely that FMT in its current form is a transitional conduit that will eventually be succeeded by well characterised, specific bacterial communities and/or their products.

Whatever the procedures for regulation, physicians must discuss potential short and long term risks of FMT [73].

Conflicts of interest

SDG has received personal fees from Astellas, Enterobiotix, Menarini, MSD, Pfizer and Shionogi.

DLS has undertaken paid consultancy for Norgine Ltd, Shionogi and Kaleido Biosciences and paid lectures for Falk Pharma, Norgine Ltd and Alfa Sigma.

All other authors report no competing interests.

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