Biotechnology

SECTION EDITOR

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Editorial

Jana Kubátová describes how biotechnology is a large field "comprised of products consisting of organisms, cells, their parts, and molecular analogues of endogenous substances". The subject of her article represents a newly defined class of biotechnology product that falls under microbiome-based medicines.

One person's gut microbiota weighs approximately 2 kg and contains microorganisms (bacteria, archaea, phages, protozoa, viruses), human cells, mucus, enzymes, bile acids, metabolites, and undigested food remnants.[1] Microorganism activity is key to human nutrition and immunological functions and its composition can indicate the health of an individual. Faecal microbiota transplantation (FMT) is an innovative therapy where gut microbiota are transplanted from a healthy individual to restore the equilibrium of an unbalanced gut microbial population in an unhealthy individual – a practice that started centuries ago.

The topic of Jana's article might be considered distasteful, but FMT is important and beneficial to those who receive it – she specifies those suffering from *Clostridioides difficile* infection (CDI). She outlines how hospitals can conduct this non-standard procedure and how regulations define FMT as a drug or a transplant depending on the world region. She also outlines the advantages of using a medical writer for communications about FMT and how cultural differences are important to consider to avoid putting off lay people.

I want to thank Jana for discussing FMT and drawing my attention to something I had not thought about at all.

Jennifer Bell

1. Masucci L, Quaranta G. Fecal microbiota transplantation: What's new? Microorganisms. 2022;10(1):23. doi:10.3390/microorganisms10010023

"All that is gold does not glitter": Faecal microbiota transplantation

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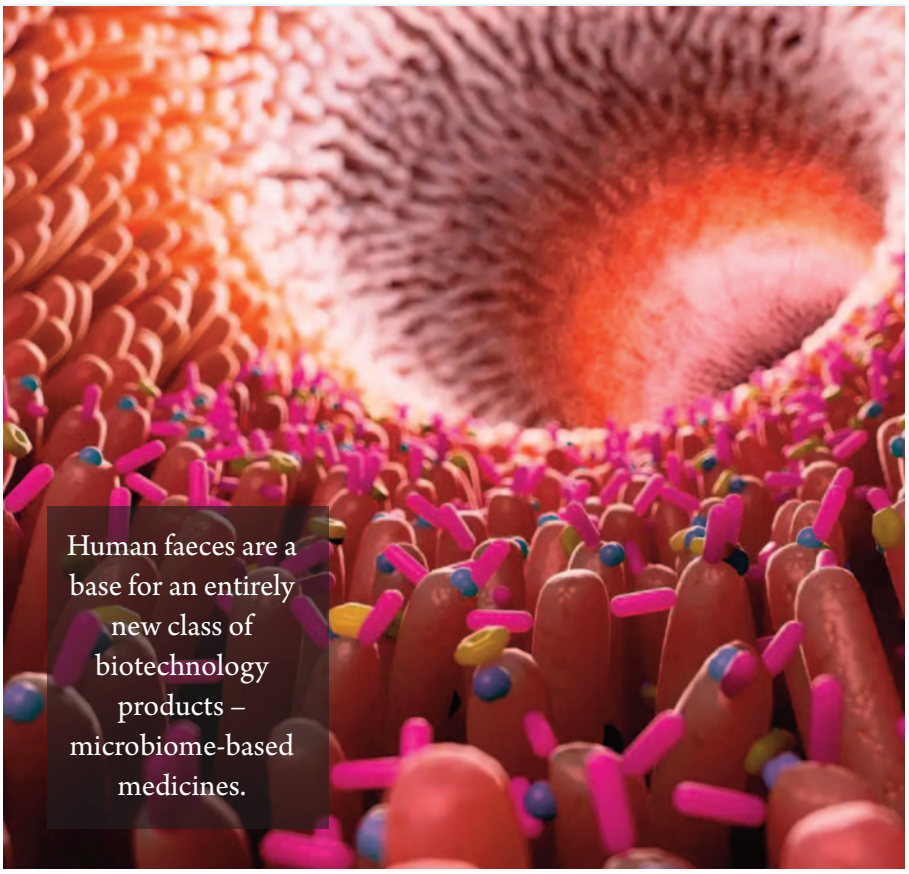
In ancient and medieval times, the therapeutic arsenal of natural healers, first physicians, and proto-pharmacists included excrement from various animal species. For instance, ancient Egyptian healers used hippopotamus and human excrement to treat gynaecological problems.[1] Ancient Chinese brought a fever down with "golden juice" from human faeces,[2] while ox excrement was used for the same purpose in medieval Britain.[3] The mixtures were applied to skin, mucosae, or even ingested. Let us try to overcome nausea. Humankind has always used faecal matter to treat diseases. What is surprising is that we have never stopped.



Human faeces are a base for an entirely new class of biotechnology products – microbiome-based medicines.

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Weird but mainstream

The large field of biotechnology is comprised of products consisting of organisms, cells, their parts, and molecular analogues of endogenous substances. Biotechnology products originate from the interconnection of natural and

Table 1. Healthy stool components[14]

Microorganisms or cells	Number per gram of wet stool
Bacteria	10^{11}
Viruses	10^{8}–10^{9}
Archaea	10^{8}
Colonocytes	10^{7}
Fungi	10^{6}

Table 2. The regulatory status of FMT products[6]

Country	Medicinal product (or equivalent)	Tissue and cells (or equivalent)	Therapeutic intervention	Classification undetermined / case-by-case
EU member states				
Austria				x
Belgium		x		
Croatia	x			
Czechia	x			
Denmark				x
Finland			x	
France	x			
Germany	x			
Ireland	x			
Italy		x		
Netherlands				x
Portugal	x			
Spain	x			
Sweden	x			
Non EU countries				
Australia		x		
Canada	x			
United Kingdom	x			
United States	x			

engineering sciences and aim to improve our life, health or environment.[4,5] Human faeces are a base for an entirely new class of biotechnology products – microbiome-based medicines.

The use of faeces is generally called "faecal microbiota transplantation" (FMT) and refers to the transfer of biological material containing faecal microorganisms from a human donor to a recipient's gastrointestinal tract (GIT) to modify gut microbiota composition.[6–8] Currently, FMT is used in conventional clinical practice to treat *Clostridioides difficile* infection (CDI). This bacterium causes severe nosocomial enterocolitis that could be fulminant. It frequently develops in immunocompromised patients and after the use of broad-spectrum antibiotics. Randomised controlled trials and observational studies have confirmed that FMT is highly effective in treating CDI and preventing its recurrence.[9] According to the European and American clinical guidelines, FMT is an option in recurrent CDI or when the infection is refractory to the standard therapy.[10–12] Compared to the standard therapy of recurrent CDI, FMT proved to be the most cost-effective method.[13]

Waste is a treasure

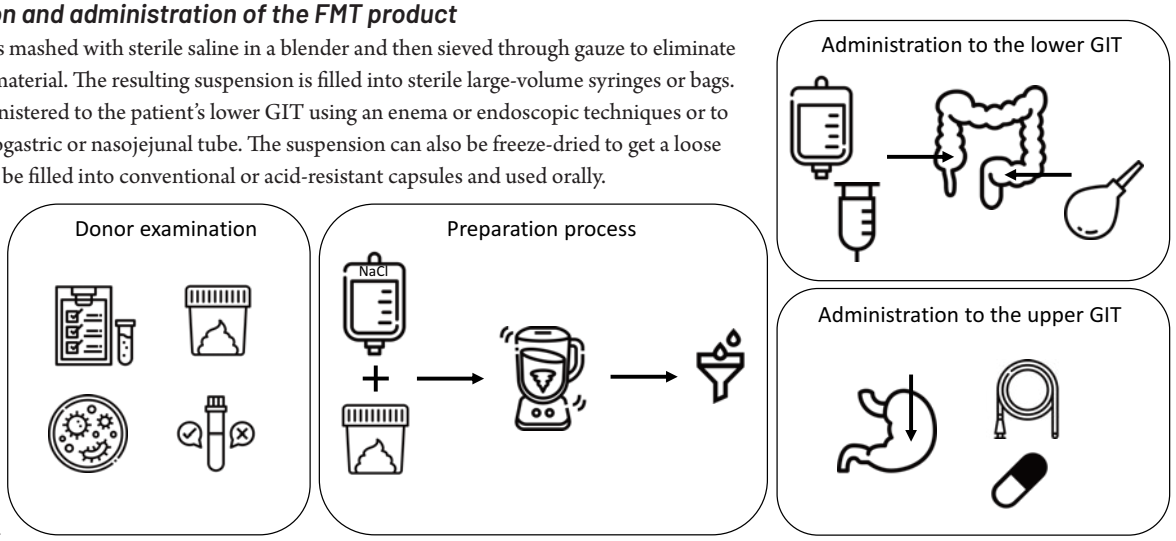
The healthy human stool consists not only of various living or dead microorganisms (bacteria, fungi, archaea) but also bacteriophages and other viruses, human cells, mucus, enzymes, bile acids, metabolites, and undigested food remnants (Table 1).[14,15] FMT increase microbial diversity and quantity in the recipient's gut. However, the mechanism of action is more complex. FMT starts multiple interactions between the microbiota and the recipient's intestinal environment and immunity.[16]

Hospital do-it-yourself

FMT product is prepared using a portion of stool from a healthy donor. The exact preparation

Figure 1. Preparation and administration of the FMT product

The biological material is mashed with sterile saline in a blender and then sieved through gauze to eliminate most of the undigested material. The resulting suspension is filled into sterile large-volume syringes or bags. A liquid product is administered to the patient's lower GIT using an enema or endoscopic techniques or to the upper GIT *via* a nasogastric or nasojejunal tube. The suspension can also be freeze-dried to get a loose solid material which can be filled into conventional or acid-resistant capsules and used orally.



Abbreviations:
NaCl, sodium chloride (saline).

Figure 1 was designed using free resources from Flaticon.com.

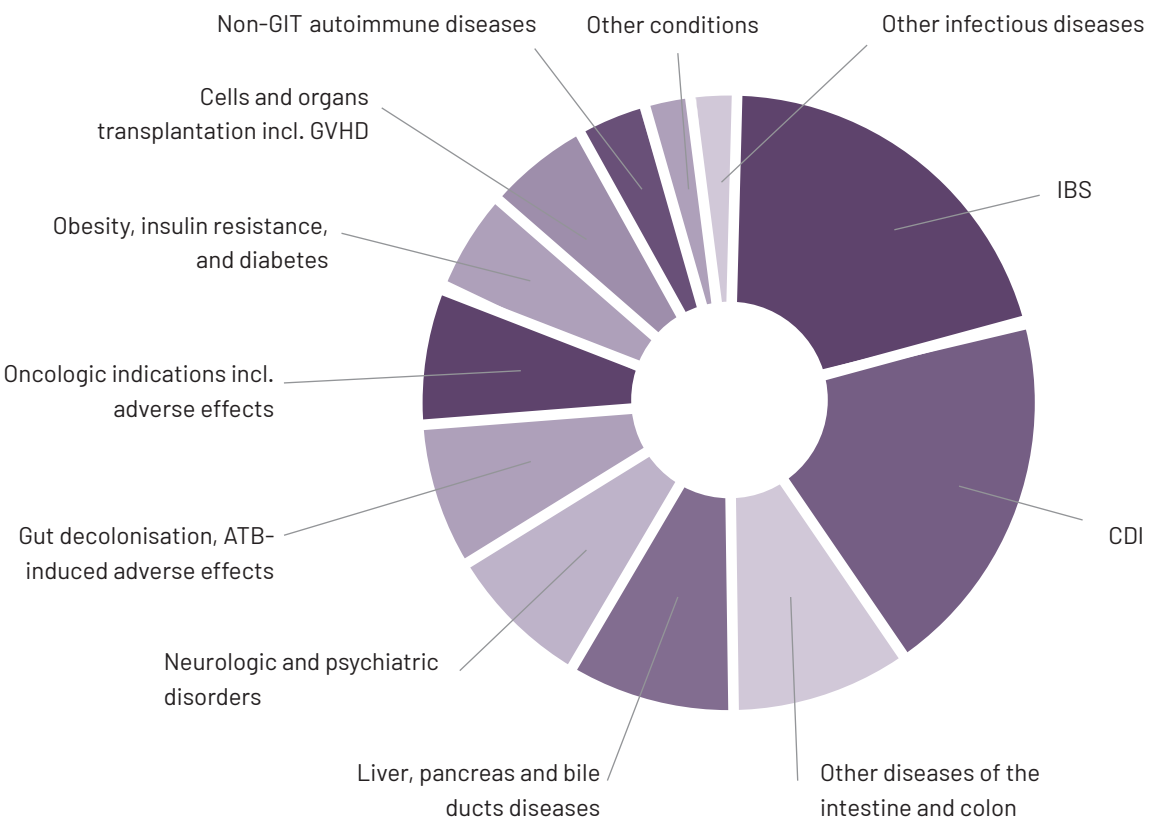


Figure 2. The spectrum of clinical trials focused on FMT

The term "fecal microbiota transplant" was searched on ClinicalTrials.gov (Beta Website), and the summary table was exported. Trials with the status "suspended" and "withdrawn" were excluded, while the indication was verified in the study description for the others. The trials were then sorted into broader indication categories. Studies focused on multiple indications were counted in more than one category.

Abbreviations: ATB, antibiotics; GVHD, graft versus host disease; IBS, irritable bowel syndrome.

method is not standardised, and facilities modify it according to their individual experience. Figure 1 gives an overview of the common way of preparation.

EMA distinguishes two ways of FMT product preparation. The "extemporaneous preparation" processes the stool minimally in on-site healthcare facilities. "Manufacture", on the other hand, is carried out in dedicated facilities, and the process includes multiple steps and uses more sophisticated technologies.[6]

> Altogether, it is easier to donate blood than stool.

Physicians' approval

FMT therapy is widespread, and more than 1800 hospital-based procedures were estimated to be performed in Europe in 2019.[17] Many countries have already adopted clinical guidelines for the rational and safe use of FMT (e.g. Australia, Austria, Canada, Czechia, Denmark, Poland, Romania, South Korea, and the United Kingdom).[18–26] However, these guidelines are mostly an expert consensus of medical societies without the point of view of relevant regulatory authorities.

A drug or a transplant?

The regulations of products influencing human health often fall behind clinical practice. In 1958, the first modern scientific article about FMT was published.[27] Currently, there is still no internationally agreed classification of FMT products.

The first attempt to define the product from the regulatory point of view was made by FDA in May 2013. FMT was classified as a drug and, moreover, an Investigational New Drug. The decision generally ruled out its use outside clinical trials. A few months later, after the expert community objected to this position, FDA declared the enforcement discretion for using FMT in CDI not responding to standard therapies.[28] In other indications, FMT is still perceived as the Investigational New Drug.[29]

In 2014, the European Commission declared that FMT does not fall within the scope of the EU tissues and cells legislation or any other legislation framework. This position meant EU member states were free to regulate the use of FMT on a national level.[6,16] Since then, a significant tendency to classify FMT as a medicinal product has emerged across the EU. Summary Table 2 outlines the regulatory status of FMT in different countries, as found by EMA during a recent survey.[6]

Stool donation

The selection of a stool donor is the most critical element of FMT. Candidates must be examined extensively, including medical history and laboratory testing. Their stool sample must be

Box 1. General rules for stool donation[7,8]

- Candidate screening: questionnaire, medical examinations, laboratory tests (blood, urine, and stool), interview with a healthcare professional
- Healthy donors, non-anonymous for the donation facility
- Altruism-driven donations, no direct payments for the donation
- Informed consent expressed by the donor and the recipient
- The donor's identity not to be revealed to the recipient
- Traceability of the material from the donation, through the preparation process, to the administration of the product
- Written or electronic records kept for an adequate time for vigilance reasons

free of GIT pathogens (including parasites) and drug-resistant bacteria to avoid transmission of undesirable germs or drug resistance genes. Healthcare professionals should not donate stool because they are often colonised with multidrug-resistant microbiota.[7] The microbiological safety of a stool sample is fundamental, as the transmission of antibiotic-resistant *E. coli* and subsequent serious adverse reactions to FMT were reported.[30–32] Altogether, it is easier to donate blood than stool.

Many measures typical for blood, tissues, and cells donation must be observed when performing FMT (Box 1). This similarity has led several countries to base their rules for FMT on the national tissues and cells legislation. In other countries, the classification is determined case-by-case depending on the indication, preparation process and facilities involved.[15,16]

More questions than answers

The classification influences many practical aspects of FMT use, and particularly, the drug/medicinal product status challenges clinicians, facilities, and regulators. What is the active ingredient/drug substance? How to test its potency? Is GMP necessary if the product is prepared extemporaneously in the hospital? How can batch-to-batch similarity be achieved if stool samples even from the same healthy donor vary in composition? Many other questions arise and are not yet sufficiently answered.

Better safety and availability

The role of gut microorganisms in human health is becoming evident in many other conditions besides infectious enteritides. Microbiota composition is also altered in patients with autoimmune diseases, liver pathologies, obesity, or neurological disorders.[33] As the evidence for the efficacy of FMT in these indications is not yet strong, the treatment is considered experimental and only used in the controlled environment of clinical trials. In the middle of July 2022, more than 400 academic or industry-sponsored trials registered at ClinicalTrials.gov declared the use of FMT (Figure 2).

The development of FMT rushes forward despite the regulatory ambiguity. Researchers are now hunting for microbial species responsible for the main effect in CDI, inflammatory bowel diseases, and other conditions. Companies are developing FMT-based "purified" products based on defined bacterial strains cultivated from the stool.[34,35] This approach would largely reduce safety concerns associated with administering extemporaneously prepared FMT suspension. Currently, no FMT-based medicinal product has a marketing authorisation, but several are tested in Phase III trials with encouraging preliminary results.[16,36,37]

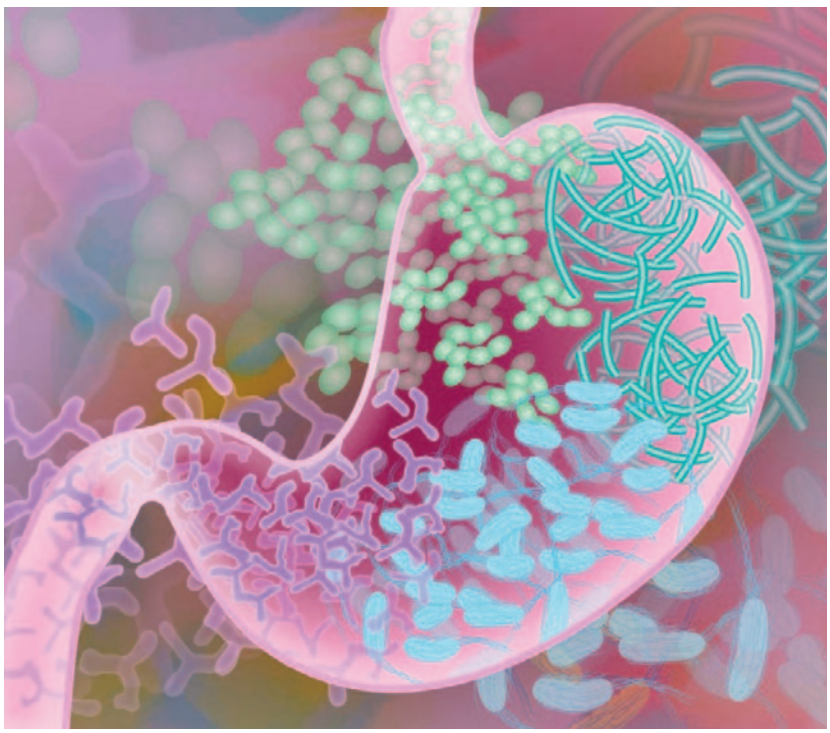
A different opinion in the expert community suggests that the effect of FMT cannot be reduced only to living bacteria. Dead bacterial cells, bacteriophages, or metabolic products of microorganisms have biological and immunological activity as well and may contribute to the clinical effect of FMT. This "whole stool" approach will benefit from continuing development of certified non-profit stool banks and efforts to internationally standardise the method.

The right place for a medical writer

As in any other clinical research and development project, the involvement of a medical writer brings advantages. Above all, it is the quality and reliability of documents and professional communication with various stakeholders.

In the clinical research of FMT, non-commercial sponsors prevail over companies. These could be universities and university hospitals, research centres, medical societies, or patients' organisations. Many non-commercial sponsors have already established a department of clinical trials handling the trials' expert administrative and communication with the regulatory authorities. And medical writers have started to appear there; however, they often had to take on more roles in the team.

When working on FMT projects, the regulatory status of FMT is important for the medical writer to choose appropriate writing guidelines and templates for the required



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regulatory documents. Consultations with the national regulatory authority are necessary and valuable, especially if there are no specific position statements regarding FMT. A medical writer well acquainted with the preparation process and facility, clinical aspects of the project, and relevant legislation can be an excellent leader in these consultations.

Last but not least, presenting FMT in a neutral, informative way to a lay audience is a challenge. It is easy to repulse potential donors and patients just by using inappropriate language or humour. The cultural differences in the approach to human waste are huge. For instance, what is acceptable for most Europeans could be totally unacceptable for the Japanese. And this is a task for a communication expert.

Conclusion

FMT is a potent tool to improve gut health and influence diseases associated with an impaired community of gut microorganisms. It is a life-saving treatment, while it can be life-threatening at the same time if not performed in a controlled way. The future should bring more profound knowledge about its mechanism of action and measures to increase the efficacy, safety, and quality of FMT as well as its availability for patients worldwide. And medical writers might take part.

Acknowledgements

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The first part of the article's title was adopted from the poem "The Riddle of Strider" by J. R. R. Tolkien.

Disclosures and conflicts of interest

The author declares no conflicts of interest.

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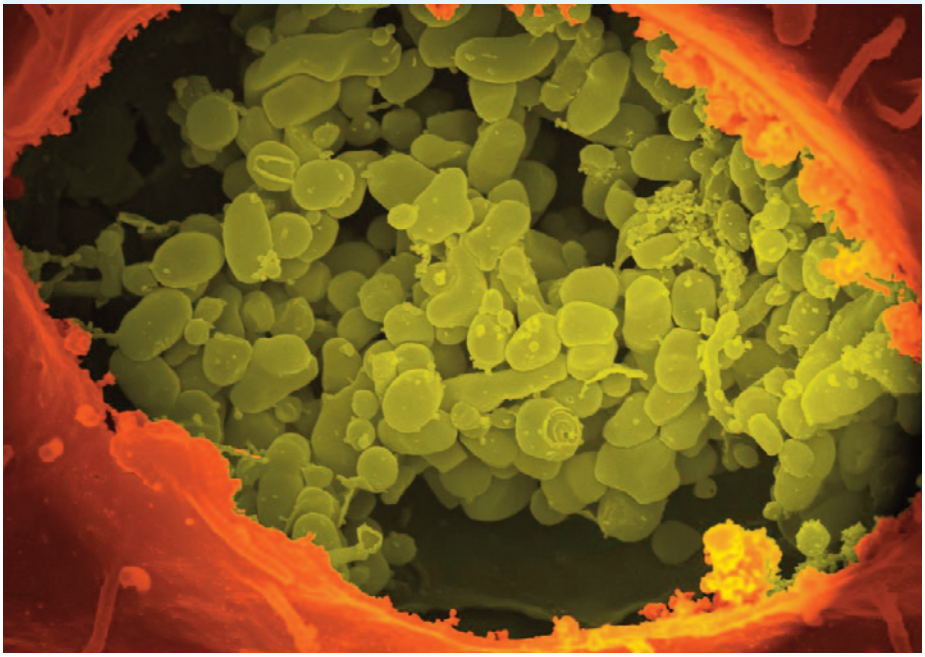

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