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Advancing Access to Intestinal Microbiota Transplant: Bridging the Gap Between National Practices and the European Strategy

Facilitar o Acesso ao Transplante de Microbiota Intestinal: Alinhar as Práticas Nacionais com a Estratégia Europeia

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ABSTRACT

Clostridioides difficile is an opportunistic pathogen that can cause a range of conditions, from asymptomatic carriage to severe illness, posing a significant public health threat due to its high mortality rates and substantial healthcare costs. Traditional treatment options, including antibiotics, often fail to eradicate the infection, leading to recurrent cases that severely impact patients' lives. Intestinal microbiota transplant (IMT) has emerged as an effective strategy for decolonizing pathogenic agents, demonstrating safety and efficacy, particularly in treating recurrent *Clostridioides difficile* infection (rCDI). Despite its potential, access to IMT is limited due to safety concerns, logistical challenges, and a lack of proper guidance, underscoring the urgent need for structured intestinal microbiota banks (IMBs). These organized facilities are crucial for the collection, screening, processing, and distribution of intestinal microbiota preparations, thereby facilitating the clinical application of IMT. In this narrative review, we discuss the relevance of applying IMT for the treatment of rCDI in Europe, with a focus on Portugal. We highlight the existence and distribution of IMBs across Europe and their importance in improving access to IMT. This review also addresses the challenges in creating an IMB and the development of such a structure in Portugal as a centralized repository for high-quality, standardized microbiota preparations, making IMT accessible for national hospitals. Additionally, it emphasizes the need to raise awareness among healthcare providers and the public to support the broader adoption of IMT.
Keywords: Clostridioides difficile; Clostridium Infections; Europe; Fecal Microbiota Transplantation; Gastrointestinal Microbiome

RESUMO

Clostridioides difficile é um agente patogénico oportunista capaz de causar desde condições assintomáticas até doenças clínicas graves, representando uma significativa ameaça à saúde pública devido às suas elevadas taxas de mortalidade e aos substanciais custos associados aos cuidados de saúde. Os tratamentos tradicionais, incluindo antibióticos, muitas vezes falham em erradicar a infeção, o que leva a recorrências que afetam de forma significativa a qualidade de vida dos pacientes. O transplante de microbiota intestinal (TMI) surgiu como uma estratégia eficaz para a descolonização de agentes patogénicos, demonstrando segurança e eficácia, especialmente no tratamento de infeções recorrentes por *Clostridioides difficile*. Apesar do seu grande potencial, o acesso ao TMI é limitado devido a questões de segurança, desafios logísticos e à ausência de diretrizes claras, o que destaca a necessidade urgente de bancos de microbiota intestinal (BMI). Estas estruturas são essenciais para a recolha, rastreio, processamento e distribuição das preparações de microbiota intestinal, facilitando, assim, a implementação clínica do TMI. Nesta revisão narrativa, discutimos a relevância da aplicação do TMI no tratamento de infeções recorrentes por *C. difficile* na Europa, com especial enfoque em Portugal. Destacamos a existência e distribuição dos BMI na Europa e a sua importância na melhoria do acesso ao TMI. Esta revisão aborda também os desafios da criação de um BMI em Portugal, destacando a importância de um repositório centralizado de preparações de microbiota padronizadas e de alta qualidade, tornando o TMI acessível aos hospitais nacionais. Adicionalmente, sublinha a necessidade de sensibilizar os profissionais de saúde e o público em geral para apoiar a adoção mais ampla do TMI.
Palavras-chave: Clostridioides difficile; Europa; Infecções por Clostridium; Microbioma Intestinal; Transplante de Microbiota Fecal

INTRODUCTION

Over the past decade, intestinal microbiota transplantation (IMT), also known as fecal microbiota transplantation, has become a key area of biomedical research. It is based on restoring the disrupted gut microbiota of the patient by transferring processed fecal material and its microbiota from a healthy donor to the patient.[1] Robust scientific evidence has demonstrated the safety[2] and efficiency of this procedure, particularly for the treatment of recurrent *Clostridioides difficile* infection (rCDI).[3]

Clostridioides difficile is an opportunistic pathogen responsible for infections that can range from asymptomatic carriage to severe conditions, posing a significant public health concern due to its high mortality rates and associated healthcare costs.[4]

Numerous questions arise regarding IMT application in clinical practice, particularly concerning the perceptions and acceptance among physicians and patients, as well as operational and logistical challenges related to donor selection, material preparation, distribution, and delivery of IMT, along with the absence of oversight support and dedicated centres.[5]

This narrative review aims to critically evaluate the

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pertinence of IMT application in the context of rCDI in Europe and Portugal, identify best practices for the provision of IMT material, and underscore the importance of establishing sustainable infrastructures for the continuous supply of IMT, ensuring its ongoing availability in clinical practice.

METHODS

This narrative review follows a systematic approach to literature selection, with relevant studies identified through a comprehensive PubMed search using key terms like "fecal microbiota transplant", "Clostridioides difficile infection", and "microbiota banks". To ensure thoroughness, the search was supplemented by manually screening reference lists from pertinent studies. In alignment with the upcoming European Union new rules on substances of human origin (SoHO legislation), the term 'Intestinal Microbiota Transplantation' will be used instead of 'Fecal Microbiota Transplantation' since the "intestinal microbiota" is the substance of human origin that is regulated by the European Commission.

Intestinal microbiota transplant for recurrent *Clostridioides difficile* infection in Europe and Portugal

Clostridioides difficile is a Gram-positive anaerobic bacterium. *Clostridioides difficile* infection (CDI), has been recognized as a leading cause of healthcare-associated infections and imposes a substantial burden to public health and health-related costs globally.[6] However, it is acknowledged that CDI can also be acquired in the community by young, healthy individuals without prior exposure to antibiotics or hospitals.[7] The main factors increasing the risk of CDI include age, immunosuppression, hospitalization, and the use of antibiotics.[8,9]

The burden of healthcare-associated CDIs in acute care hospitals in the European Union and European Economic Area (EU/EEA) was estimated at 123 997 cases annually according to the European Center for Disease Prevention and Control (ECDC) surveillance report.[10] The direct attributable costs were estimated to be between €5798 - €11 202/episode,[11] with a total estimated burden of €3 billion per year in the EU.[12] Moreover, recurrent CDI has a particularly significant impact, both economically and in terms of strain on healthcare resources, underscoring the importance of identifying the most cost-effective strategy for its prevention and treatment.[13]

Antibiotic therapy is considered the standard treatment for CDI, although other therapies, such as IMT may be considered depending on disease severity and recurrence.[14] Substantial evidence in real-world practice,[15] supported by large-scale clinical trials and long-term follow-up studies[16,17] emphasize the efficacy and safety of IMT in rCDI, with clinical resolution rates approaching 90% across multiple studies,[18,19] and demonstrated effectiveness in preventing further relapses.[20] Moreover, in a network meta-analysis, Rokkas *et al* identified IMT as the most effective treatment for rCDI, outperforming other interventions, including standard antibiotics like vancomycin and fidaxomicin.[21] Thus, IMT not only demonstrates superior clinical resolution but also offers additional benefits by reducing the reliance on antibiotics, thereby minimizing the risk of development of antimicrobial resistance.[22] Additionally, IMT contributes to the restoration of a healthy gut microbiome, enhancing gut microbial balance and functionality.

From an economic perspective, data from a well-established IMT program in Denmark suggests that the average cost of an IMT procedure in a public hospital – whether administered via colonoscopy or nasojejunal tube – was €3095. This investment yielded a 42% reduction in hospital costs related to rCDI within the first year, primarily driven by fewer hospital admissions and shorter lengths of stay.[23] Moreover, in comparison to standard care for first or second episodes of CDI, the hospital observed €1645 lower costs over a 26-week period for patients treated with IMT, due to fewer admissions, reduced hospital contacts, and decreased medication use.[24]

Nevertheless, a Europe-wide survey conducted in 2019, across 31 IMT centers, in 17 countries, reported that only 1077 IMT procedures were performed for treating CDI, covering just 10% of the approximately 12 400 patients estimated to be eligible for this treatment each year. The authors concluded that there is a significant gap in IMT coverage, suggesting "the need to increase the IMT activity in Europe by at least 10-fold to meet the true, indicated need".[25]

In Portugal, the epidemiology of CDI has been documented.[26] Most patients are over 70 years old, 49.1% of the cases are classified as healthcare associated and 44% of primary episodes were community-associated. The primary risk factor for developing CDI was antibiotic exposure, affecting 86.0% of patients. These findings are consistent with reports from other European countries.[27] The study by Nazareth *et al* identified 385 cases of primary CDI across six public hospital centers in Portugal, revealing that 2.6% of these patients experienced multiple recurrences, providing a national framework of potential candidates for IMT. However, it was acknowledged that the rate of recurrent episodes is likely underestimated, as only hospitalized patients within the participating hospitals were included in the surveillance.

Data on IMT performed in Portuguese healthcare institutions is currently unavailable, and there is no national documentation regarding the number of transplants conducted in Portugal. Our literature review identified only a limited number of published studies on this subject, all of which involved hospital-based treatments with IMT prepared

on-site. In a single-case study, IMT was performed as a decolonization strategy in a patient infected with multidrug-resistant bacteria. In this case the donor was a relative.[28] In an observational study that included 28 patients treated with IMT between June 2014 and January 2017, to assess the safety and efficacy of IMT for the management of refractory and recurrent CDI, donors were unrelated volunteers selected and screened based on medical history and laboratory testing.[29] The same hospital team conducted a retrospective analysis to investigate intestinal decolonization of carbapenamase-producing Enterobacteriaceae in patients screened as positive for these resistant bacteria and undergoing IMT between 2014 and 2019.[30] Nonetheless, it is important to consider that additional patients in Portugal may have been treated with IMT and those cases may not be documented. However, it is reasonable to assume that the national results regarding the use of this microbiota-based therapy are significantly lower compared to those in other European countries.[25] The absence of an easy access to intestinal microbiota preparations could be one of the reasons that limits the use of IMT.

Additionally, limited awareness among healthcare providers and insufficient guidance from local regulatory authorities on procedure regulation[31] could also be limiting patient access to this life-saving therapy.

Intestinal microbiota transplant for microbiome related diseases

Beyond CDI, repairing the gut microbiota through IMT has opened novel therapeutic avenues for a number of potentially dysbiosis-related diseases.[32,33] Dysbiosis can be defined as an alteration in the composition or function of the gut microbiome[34] and it can be driven by several host and environmental factors.[35] Dysbiosis has been strongly associated with inflammatory bowel diseases (Ulcerative colitis and Crohn's disease),[36] but also with antibiotic-associated diarrhea,[37] metabolic disorders,[38] autoimmune diseases[39] and neurological disorders.[40]

While IMT has demonstrated effectiveness in treating rCDI, its potential in other clinical contexts remains uncertain. Data are limited to small, heterogeneous clinical trials, lacking the consistency needed to identify specific microbiome-derived therapeutic agents and the underlying mechanisms of action.[41,42] The human gut microbiota is a complex and diverse community of microorganisms that interact through metabolic, immune, and neuroendocrine pathways, making it difficult to pinpoint causal relationships between specific microbes and health outcomes.[43,44] Achieving consistent, long-term success with IMT is also challenging due to the gut microbiota's resilience. Donor's bacteria often fail to establish permanently, with recipients' microbes frequently returning to baseline after a few weeks.[45-47] Additionally, environmental factors like diet and medication can rapidly alter gut microbiota, adding potential confounding. Individual microbial signatures, shaped by unique environmental experiences, further contribute to varied responses among patients with similar diagnoses.[48,49]

Despite these challenges, several clinical trials have expanded our understanding of human microbial communities, underscoring new directions for research in this field. De Groot *et al* have shown that the donor's microbiota profile can affect metabolic outcomes after IMT.[50] In turn, Kootte *et al* concluded that the recipient's microbiota profile at baseline was decisive in defining the success of the engraftment.[45] In turn, Li *et al* suggested that donor-host interactions do not depend on the taxonomic affiliation of species nor on differences in relative abundance between donor and recipient species, but rather on an immune-based compatibility, with specific strains showing superior dominance over native species while others exhibit a resistance capacity.[51] While preliminary, these findings are promising and are encouraging further research across Europe (Table 1).[52]

Intestinal microbiota banks

The use of IMT in routine clinical practice requires a robust infrastructure reliant on voluntary donors, which has led to the emergence of intestinal microbiota banks (IMBs) as a model for scaling access to this treatment.[53] These banks have been fundamental in advancing IMT procedures, shifting from fresh stool preparations sourced from relatives, handled in basic laboratory settings, to frozen preparations or capsules containing carefully selected processed feces from anonymous, healthy donors.[54] Additionally, published guidelines from scientific consensus reports on donor identification, screening, and IMT-optimized protocols have been crucial in establishing best practices and defining a standardized model for IMBs.[55-57]

Intestinal microbiota banks are centralized facilities that provide ready-to-use donor intestinal microbiota preparations (IMP), minimizing the challenges regarding IMT production, distribution, and application.[58] They may operate at an institutional (e.g., university, hospital-based), national, or international level and are currently settled in several European countries.[56] Ideally, an IMB ensures that the IMT can be delivered safely, at scale, guaranteeing its wide access. This is possible through the centralization of donor selection, material processing and safety monitoring, functioning in a similar way to a blood bank.[59] The centralization of donors makes it possible to adopt systematic measures for donor identification and data protection, rigorous screening for transmittable diseases and pathogens, anonymization, long-term traceability of the product/raw material and the possibility of linking the patient to the specific administered

Table 1 – (section 1 of 2) Active clinical trials related to intestinal microbiota transplant (searched terms: "microbiota transplant | Not yet recruiting; Recruiting studies | Interventional studies) | Europe | Registered on clinicaltrials.gov"). In all studies, intestinal microbiota is the substance derived from human donors, reinforcing the need of microbiota banks for advancing the knowledge in the field of other diseases. Some studies were registered using the term "FMT", but in accordance with the new terminology adopted in this review, the intervention in the table is named as "IMT".

Country	Intervention	Condition	Identifier
Austria	IMT	Obesity	NCT06268990
	IMT	Acute graft-versus-host-disease after allogeneic hematopoetic stem cell transplantation	NCT03819803
	IMT combined with Atezolizumab plus Bevacizumab	Patients who failed to respond to prior immunotherapy for advanced hepatocellular carcinoma	NCT05750030
Belgium	IMT	Decolonization of Gram-negative multi-resistant organisms	NCT04188743
Denmark	IMT	Chronic diarrhea in patients with systemic sclerosis	NCT06333795
	IMT	Treatment-naïve patients with newly diagnosed chronic inflammatory diseases	NCT04924270
	IMT	Liver cirrhosis	NCT04932577
	IMT	Eradication of multidrug resistant organisms in the intestine	NCT05742074
	IMT	Anorexia nervosa	NCT05834010
	IMT	Microscopic colitis	NCT05998174
	IMT capsules	Checkpoint Inhibitor-mediated diarrhea and colitis	NCT06206707
	IMT and FVT	Restoration of the gut microbiome after cesarean section	NCT06264219
Finland	Lyophilized capsulated autological IMT	Gut microbiome restauration after treatment with antibiotics	NCT06250413
	IMT	Postoperative Crohn's disease	NCT04637438
	IMT	Initial clostridioides difficile enteritis	NCT05257538
	IMT	Irritable bowel syndrome associated food intolerance	NCT05361785
	IMT	Optimal route of IMT for irritable bowel syndrome	NCT05874830
	IMT	Prevention of recurrent urinary tract infections caused either by sensitive *E. coli* or ESBL-*E. coli*	NCT06050148
	IMT (maternal fecal transplant)	Preterm infant intestinal microbiota development	NCT06227845
France	IMT capsules	Severe irritable bowel syndrome	NCT06433180
	IMT	Prophylaxis of recurrent pouchitis after IMT in ulcerative colitis with ileo-anal anastomosis	NCT03524352
	IMT	Prevention of allogeneic hematopoietic stem cell transplantation complications and particularly draft-versus-host disease	NCT04935684
	IMT capsules	Eradicate colonizing emergent superbugs (multi-drug and extensive-drug resistant Gram negative bacteria)	NCT05035342
	IMT	IMT as a maintenance treatment following anti-TNF agent withdrawal in Crohn's disease patients	NCT04997733
	IMT capsules (MaaT033®)	Axial spondyloarthritis patients resistant to conventional treatment	NCT05654753

IM: intestinal microbiota; IMT: Intestinal microbiota transplant; CDI: clostridioides difficile infection; FVT: fecal virome transplantat; ESBL-*E. coli*: extended-spectrum beta-lactamase *escherichia coli*

product, active recruitment and donor loyalty program.[58] Material processing must be described in standard operating procedures, under a quality control program, including good manufacturing/laboratory practices, ensuring that the IMTs administered are consistent, safe, and traceable.[60] Moreover, with standardized preparation and storage methods, the risk of contamination and variability can be drastically reduced, leading to more predictable and effective treatments. At the same time, safety monitoring, one of the main concerns in IMT practice, requires the development of a suitable risk management system with all the critical steps along the process properly characterized, capable of

Table 1 – (section 2 of 2) Active clinical trials related to intestinal microbiota transplant (searched terms: "microbiota transplant | Not yet recruiting; Recruiting studies | Interventional studies) | Europe | Registered on clinicaltrials.gov"). In all studies, intestinal microbiota is the substance derived from human donors, reinforcing the need of microbiota banks for advancing the knowledge in the field of other diseases. Some studies were registered using the term "FMT", but in accordance with the new terminology adopted in this review, the intervention in the table is named as "IMT".

Country	Intervention	Condition	Identifier
Germany	Fecal filtrate transplantation *VS* IMT	Mild to moderate active ulcerative colitis	NCT03843385
Hungary	Fecal filtrate transplantation *VS* IMT	Multiple recurrent CDI	NCT04960306
Italy	IMT capsules	Hepatic encephalopathy	NCT06368895
	IMT	Patients with mild-to-moderate ulcerative colitis	NCT05739864
	Autologous IMT	Ameliorate nintedanib-induced diarrhea in patients with idiopathic pulmonary fibrosis	NCT05755308
	IMT	Eradicate intestinal colonization by carbapenem-resistant enterobacteriaceae	NCT05791396
	IMT	Relieve symptoms of irritable bowel syndrome without constipation	NCT05803980
	IMT	Relieve symptoms of irritable bowel syndrome with constipation	NCT05803993
	IMT	Recurrent CDI and ulcerative colitis: single infusion *versus* sequential approach	NCT06071312
Netherlands	IMT	Ulcerative colitis	NCT05998213
	IMT	Convert the response to immunotherapy in immune checkpoint inhibitors refractory metastatic melanoma patients	NCT05251389
	Lyophilized IMT capsules in combination with pre- and probiotics	Non-alcoholic steatohepatitis	NCT05821010
Norway	IMT	Axial spondyloarthritis	NCT06451588
	IMT derived from feces of clinical responders	Cancer patients who have failed immunotherapy	NCT05286294
Poland	IMT	Prophylaxis of necrotizing enterocolitis (premature infants)	NCT06333405
	IMT	Decolonize antibiotic - resistant bacteria	NCT06156956
Romania	IMT	Liver cirrhosis	NCT06478602
Spain	IM capsules	Recurrent diverticulitis	NCT06687382
Switzerland	IMT capsules	CDI first episode and first recurrence	NCT05266807
United Kingdom	IMT capsules	Cirrhosis	NCT06461208
	IMT	Primary sclerosing cholangitis	NCT06286709
	IMT	Intestinal microbiota transplant prior to allogeneic stem cell transplant	NCT06355583

IM: intestinal microbiota; IMT: Intestinal microbiota transplant; CDI: clostridioides difficile infection; FVT: fecal virome transplantat; ESBL-*E. coli*: extended-spectrum beta-lactamase *escherichia coli*

addressing risk identification, prevention, and minimization.[61]

A number of well-established IMBs in Europe have already published reports of their experience as IMT providers. Lacking a product-specific regulatory support, most IMBs, relying on formal or informal guidance from their health authorities, reported finding support in the National Tissues Act and the EU Tissues and Cells Directive (2004/23/EC), and in expert consensus reports when planning the most appropriate framework for assessing the quality, safety and traceability of donor feces.[59,62–65] It is also implied in most published reports that donor recruitment programs are challenging, especially due to the low eligibility rate and excessive costs of screening.[64] Nevertheless, following strict donor selection criteria, standardized processing and storage of IM suspensions, and consultation by a multidisciplinary team of IMT experts, results in safe and effective application of IMT, as reported by the Netherlands Donor Feces

Bank.[65] Intestinal Microbiota banking has proven to be cost-effective for two main reasons. First, one donor can serve for multiple IM donations, eliminating the restriction of having on-demand single-donation IMT procedures, resulting in better profitability of donor screening processes.[66] Secondly, laboratory costs can be significantly reduced due to the large amounts of samples collected from donor blood and feces.

Universal intestinal microbiota banking has emerged in Europe as a reliable source for IMT, and the best strategy to suppress the need for the product, both in clinical practice and in research. These banks are funded through a combination of national and European funds, grants, private investments, and donations. However, some of the western countries that face a high burden of microbiome-related diseases (e.g., intestinal bowel disease, obesity, and antibiotic-resistant infections), such as Portugal, are underrepresented in translational microbiome research. The Europe-wide survey conducted by Baunwall *et al* revealed that IMBs are concentrated in central axis countries,[25] showing a clear imbalance in the access to IMT, compromising both its use as therapy and in clinical research.

Establishing Portugal's first intestinal microbiota bank

Recognizing the absence of a national IMB and its crucial role in addressing public health issues, a multidisciplinary team initiated the establishment of the first Portugal IMB in 2020. Based at NOVA Medical School (NMS|FCM, UNL) and in partnership with YourBiome®, a spin-off of NOVA University, the project aims to support physicians and advance scientific knowledge by providing high-quality donor IMP. The working group, comprised of translational microbiome experts, research scientists, and specialists in infectious diseases and gastroenterology, is committed to improving education and awareness among physicians and patients. The goal is to foster greater confidence and willingness to perform the procedure while consistently prioritizing ethical standards and patient safety.

Following the European model, the Portuguese IMB draws on the experiences of existing IMBs and expert consensus reports, while adhering to the latest guidelines to establish a standardized biobanking process. The Portuguese IMB ensures the availability of high-quality, standardized IMP and enhances patient safety through rigorous screening protocols. These protocols are designed to minimize the risk of transmitting microbiome-related conditions and improve microbiota quality, leading to more predictable and effective treatment outcomes. This was possible by harnessing the extensive expertise and knowledge of the multidisciplinary team of collaborators, many of whom are leading experts with published, high-impact contributions in the field of microbiota research.[67-69] The Portuguese IMB is currently recruiting donors and is also providing IMP for distribution across several national hospitals. This initiative aims to improve access to IMT for patients with recurrent or refractory CDI and ensure equitable distribution among those clinically indicated for treatment.

Regulation

Products of human origin, as complex as feces, have a high potential risk of infecting the recipient. A careful and substance-specific regulatory approach especially targeted for the critical steps in the process is necessary. The European Union's Competent Authorities for Tissues and Cells have recognized that intestinal microbiota falls outside the scope of the Human Tissue Directive 2004/23/EC,[70] prompting discussions on revising the legislation to address new substances of human origin. In 2022, the European Commission (EC) adopted the proposal for a regulation on quality and safety standards for substances of human origin (SoHO)[71] intended for human application, and in April 2024 the regulation was approved by the European Parliament. This new regulation, to be effective from 2027, in which the IM is included, intends to implement the conditions for harmonization across Member States. The new regulation for SoHO, which reflects the experience of regulatory networks for blood products and/or tissues and cells, provides specific regulatory standards to ensure adequate quality and safety for intestinal microbiota transplantation, particularly in the context of regulation and inspection of IMBs, for donor protection and management, and for the implementation of a robust bio-surveillance system. Furthermore, the European Centre for Disease Prevention and Control has been tasked with developing technical guidelines for donor testing and deferral strategies, standardizing safety measures across member states and facilitating cross-border procedures to narrow gaps in availability.

It is expected that at some point, microbiota-derived drugs may supplant the complete donor intestinal ecosystem, but for now, conventional IMT remains the most suitable treatment, particularly for those with rCDI. Intestinal microbiota banks will remain a vital source of microbiota-based preparations for IMT, while analyzing long-term data on gut microbiome manipulation will shed light on the effects of IMT developments and policy changes.[72]

Final considerations and perspectives

Recognition of the beneficial therapeutic effect of IMT, particularly for the treatment of rCDI, has prompted scientific societies to issue recommendations and guidelines endorsing this life-saving therapy. Despite these advancements, its broader potential remains unclear. The medical and scientific community should support the establishment of IMBs, ideally staffed by multidisciplinary teams

responsible for clinical protocols, ongoing oversight, and dissemination of best practices, thereby enhancing both knowledge and confidence among practitioners. Intestinal microbiota banks must stay up to date with emerging scientific evidence, addressing technical, safety, and ethical considerations. Special emphasis should be placed on IM interactions within organ axes and other ecological niches in the human body to proactively prevent undesirable microbiota-mediated responses. Additionally, to support the establishment of IMBs and strengthen their structure, it is crucial to develop a regulatory and strategic framework at the national level, that promotes broad and equitable therapeutic access in line with established standards. Even though the adoption of the SoHO Regulation will harmonize guidelines for donor screening , each country still needs to develop specific guidelines and establish its own screening panel based on its unique social, cultural and epidemiological context, in addition to the general recommendations.

A significant challenge in establishing an IMB relies in raising public awareness about the critical role of the human microbiota in health and disease. The transfer of knowledge between the scientific and medical communities and the general public is therefore essential to enhance donor recruitment efforts. Also, the healthcare and scientific communities must come together to properly define relevant terms, rather than perpetuating the use of concepts and words that can lead to misinterpretation. For example, terms like “feces” or “stool” should not be routinely associated with the therapeutic use of the IM, as they may convey a misleading or trivialized understanding to the general public.

There has been a paradigm shift in global public health strategy for the treatment of *Clostridioides difficile*, transitioning from the traditional reliance on antibiotics to the use of IMTs. To ensure optimal care, it is crucial to stay aligned with this evolving approach and the development of new microbiota-based therapies, avoiding delays in adopting modern treatment advancements. As awareness of IMT as a therapeutic option grows, denying patients access due to unfamiliarity to the procedure or logistical constraints may increase unsupervised, ‘home-made’ procedures using unscreened feces from friends or relatives, raising the risk of inadvertently transplanting harmful pathobionts. It is crucial to raise awareness, improve education, and increase familiarity with IMT among healthcare practitioners, especially regarding its technical aspects, encouraging clinicians to critically review the literature, ensuring evidence-based clinical decisions. Simultaneously, managing patient perceptions and expectations is essential for the broader acceptance of IMT.

Understanding microbiome-mediated health and disease mechanisms is essential for developing new clinical microbiome-based interventions. While alternative approaches like defined consortia and IMT-like products are under development, donor-derived IMT currently remains unmatched. Dedicated structures for Intestinal Microbiota Banking are essential for addressing urgent public health challenges related to gastrointestinal disorders and beyond, while also contributing to the development of robust scientific evidence. Looking ahead, gut microbiota-based therapy is expected to evolve toward more accessible and standardized treatments, including oral formulations with well-defined ingredients, clear mechanisms of action, and proven safety profiles. Future advancements may emphasize personalized microbiome restoration, tailoring treatments to individual patient needs based on clinical assessments.

AUTHOR CONTRIBUTIONS

LD, DP, CM: Writing and critical review of the manuscript.

HP, PP, CC: Critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients’ data publication.

COMPETING INTERESTS

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