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Faecal microbiota transplantation associated adverse events

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ABSTRACT

Faecal microbiota transplantation (FMT) aims to restore intestinal microbiota balance with the objective of normalising its composition and achieve therapeutic benefits. The procedure involves the administration of fresh or frozen faecal microbes from a healthy donor into the recipient's gastrointestinal tract with the intent to restore the proper structure and functionality of the recipient's intestinal microbial community. Evidence showing the positive effects of FMT is abundant, however, less attention has been devoted to FMT-associated adverse events, especially in relation to liver diseases.

Based on literature review, studies and reports regarding FMT-associated adverse events since the beginning of FMT use, have been analysed. The review covering the period 2010-2022 was undertaken in accordance with the PRISMA guidelines.

Studies conducted on the patient population suffering from various types and forms of liver disease have proven the possible effectiveness of the FMT method and reported moderate adverse events (nausea, constipation, flatulence). Severe adverse events occurring in relation to FMT were also noted. No safety issues or infection signals associated with FMT were observed in studies performed within the population suffering from cirrhosis.

The present review of scientific reports, publications and literature reviews describes the adverse events reported in the literature. Faecal microbiota transplants are associated with adverse events classified as mild, moderate and severe, among others, diarrhoea, fever, infections or death. There is a need to implement a donor screening programme and personalised transplantation methods. Further research is recommended to assess and monitor FMT efficacy, benefits and risks.

INTRODUCTION

According to literature data, the first stool transplant was described by the Chinese physician Ge Hong (4th century). The faeces were called "yellow soup" and were used in patients with diarrhoea. Until the 16th century, fresh or fermented faecal suspensions were administered to patients with gastrointestinal (GI) diseases, including diarrhoea, constipation and abdominal pain [1,2]. At present, the method, first described in 1958 by Eiseman B. *et al.* for administering faecal enemas to re-populate the intestines with beneficial bacteria, is used [3].

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In practice, faecal microbiota transplantation (FMT) was initiated in 1983 to treat a patient with *Clostridioides difficile* (*C. difficile*) infection (CDI) resulting in immediate symptoms reduction during 9 months' observation [4]. The first FMT description used for non-infectious diseases treatment was published in 1989; a recipient with refractory ulcerative colitis (UC) underwent FMT, the outcome being clinical improvement [5]. Likewise, the first case of an UC patient treated with FMT was also reported in 1989 [6].

FMT efficacy studies have been carried out that resulted in reports regarding various groups of patients, case reports and few randomised trials. It was noticed that modifying intestinal microbiota composition through FMT leads to a significant decrease in the alanine aminotransferase

concentration and liver image improvement in elastography. In relation to the treatment of encephalopathy caused by hepatic insufficiency, this method was associated with improved mental health and cognitive abilities. Nowadays, FMT is used more frequently as a treatment option for liver diseases [7,8].

FMT aims to restore intestinal microbiome balance with the intent to normalise its composition and achieve therapeutic benefits [9]. The metabolic capabilities of the altered microbiome can significantly differ from those of the resident strains, which is likely to improve physiological functionality [10]. Remodelling the composition of the intestinal microbiome can lead to new strategies for treating many diseases [11,12]. FMT can effectively maintain microbiological homeostasis and antagonise pathogenic microorganisms; therefore, it is considered an effective therapy for intestinal failure, regardless of the causative factors, especially in cases of antibiotic overuse and drug resistance [13].

From a technical perspective, the transplantation of natural intestinal microbiota from donor faeces consists of the preparation of the "transplant material", i.e. dissolution in a solvent (water or NaCl), dispersion and homogenization, followed by filtration to separate insoluble particles. A commonly used method for sample extraction is the Amsterdam protocol, where the sample is frozen until its transplantation [14]. Once the recipient's intestines have been cleansed of resident bacterial colonies, the donor's microbiome is transplanted [15,16]. Sub-analyses have suggested that the rate of clinical remission in the case of FMT with fresh faeces was higher, as compared to frozen faeces.

This study aims to analyse the reported FMT associated adverse events (AE), with special attention paid to the use of the transplantation in populations with liver diseases.

MATERIALS AND METHODS

Based on literature review, studies and reports regarding FMT-associated adverse events since the beginning of FMT use have been analysed. To review the FMT-associated adverse events, studies and reports regarding such events were searched for and the content of provided information was analysed in detail. The FMT adverse events were already described in 2010 in the literature and, from the analysed studies, we extracted information on the type, severity and location of adverse events during FMT therapy, including events related to liver diseases. The classification of an adverse reaction is determined by its severity, i.e. the reaction may be mild, moderate or severe.

According to the different identified publications, serious adverse event is defined as an adverse event that results in death, is life-threatening, or requires hospitalization. In terms of intensity, the event might be also classified as mild when it does not interfere with routine activities or moderate when it interferes with routine activities [17]. In line with the Common Terminology Criteria for Adverse Events (CTCAE), a mild adverse event occurs when it is asymptomatic or symptoms are mild, requires clinical or diagnostic observations only and there is no need of an intervention. A moderate grade indicates that a minimal, local or non-invasive intervention is indicated and the event is mildly limiting age-appropriate instrumental daily activities.

In this work, the identified FMT treatment related adverse events within the performed literature review were classified taking only their severity into account and were grouped accordingly as mild, moderate or severe as the original researchers classified the events within their respective studies. The reported adverse reactions were not analysed by route of FMT administration or by the time of adverse reaction occurrence from the time of administration.

This literature review was conducted in accordance with the systematic reviews and meta-analyses PRISMA guidelines. The review period was January 2010-August 2022, and PubMed and Google Scholar search included scientific reports, publications and literature reviews. The search term used in all databases was: "adverse events in FMT". Manuscripts describing empirical studies that contain basic data (qualitative or quantitative) and review studies were selected for the analysis. The identified articles were assessed for eligibility by title and abstract. All the duplicated and overlapping records were removed and final selection of full manuscripts was reviewed and analysed by two independent researchers.

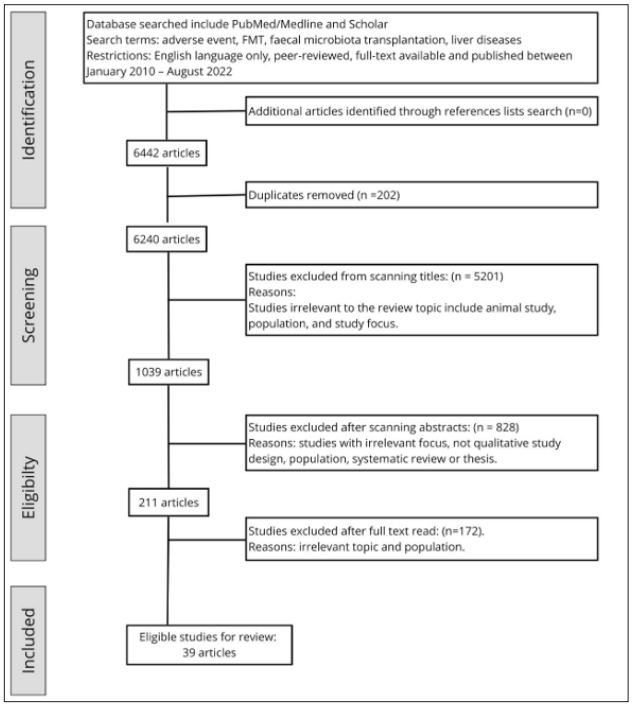

Figure 1. PRISMA diagram for study search and selection for literature review

RESULTS

The total identified number of records was 6442 in PubMed and the Scholar Google database. The inclusion criterion for the collected publications' analysis was related to the single-arm studies qualified data which were presenting the practical effectiveness of FMT, i.e. studies conducted in real clinical practice. As a result of the search and selection, 39 articles were qualified for this review.

Studies conducted on the patient population suffering from various types and forms of liver disease also have proven the possible effectiveness of the FMT method and

Table 1. FMT – associated adverse events

FMT administration route	Adverse events		
	Mild	Moderate	Severe
• nasogastric or nasoduodenal probe, • colonoscopy, • enema, • capsule	1. constipation [24] abdominal pain [24-26,28,31,32,35] 2. vomiting [28,30-32] 3. abdominal discomfort [23,26,28,29,34] 4. breathing discomfort [30] 5. herpes zoster [32]	1. fever [23,26,28,29,34] 2. increased concentration of C-reactive protein [28] 3. bleeding [28] 4. recurrent non-specific inflammatory bowel diseases [30] 5. diarrhoea [23,26,28,30,31,34-36]	1. deaths [27,29,34] 2. bacteraemia [27] 3. perforation [27,28] 4. infections [29,34] 5. *Clostridium difficile* infections [33] 6. Inflammatory Bowel Disease (IBD) [36] 7. SARS-CoV-2 [37]

reported moderate adverse events (nausea, constipation, flatulence). However, research is still ongoing concerning the options of applying this method in treating liver diseases.

The reported side effects within the identified manuscripts were mostly related to the digestive system, such as diarrhea, constipation, cramps, fullness, bloating, nausea, belching, fever, hyperventilation and anesthesia related symptoms. It should be noted that severe adverse events occurring in relation to FMT were also reported, e.g. death, as well as other life-threatening events, e.g. bacteraemia or perforation.

There was, no safety issues or infection signals associated with FMT in studies performed within the population of patients with cirrhosis. Moreover, the abundance of antibiotic resistance genes (ARGs) was found to be significantly reduced after FMT, compared to the baseline pre-FMT groups and non-FMT groups with diagnosed decompensated cirrhosis [18].

FMT is also expected to play a role in alcoholic liver disease treatment, in particular, by correcting the intestinal microbial balance. Initial studies also confirmed that FMT benefits in terms of improved disease severity and survival rate, with minor adverse events reported [19]. FMT, as a method of treating diseases by changing the intestinal microbial flora, is also qualified for complications after TIPS, when hepatic encephalopathy (HE) develops and FMT improves liver function without serious adverse events being observed [20].

Faecal microbiota transplantation may also be a potential immunomodulatory therapy in patients with chronic hepatitis B. In one study, despite an antiviral treatment, the patients underwent well tolerated FMT at 4-week intervals through the nasoduodenal route, and 42.8% (6/14) of the patients reported only one or more minor adverse reactions [21]. Concerning the use of FMT in hepatic myelopathy (HM), which is a rare neurological complication in patients with chronic liver disease, reversible HM occurred after three FMT transplants. As a result of the treatment, the muscle strength of patient's both legs increased to varying degrees, and the patient's condition improved from HM2 to HM1, with no adverse events observed [22].

According to literature, the majority of reported adverse events associated with the gastrointestinal tract, e.g. diarrhoea, bloating and belching, usually subside after 2-3 days [23]. The reported cases include mostly mild and moderate events, among others, diarrhoea, constipation, fever and abdominal pain, lasting for about one week. Serious adverse events (SAEs), *e.g*. deaths, are far less numerous and result from comorbidities with unrelated disease processes [24]. Such side effects have been reported in a study on 6 patients with chronic active UC treated with FMT administered via colonoscopy. According to the study results, all patients experienced short-term clinical improvement in the first 2 weeks following FMT, however, none achieved clinical remission [25]. The first pilot study conducted, involving 10 patients aged 7-21 years who were receiving faecal infusions for 5 days, reported acceptable and resolved several mild adverse events, e.g. cramps, fullness, bloating, diarrhoea and one moderate adverse event (fever) [26].

The first FMT studies review identified 109 publications describing FMT use in 1555 people. The data consisted of a limited number of randomised controlled trials, studies and case reports. Therein, AEs were rare, often mild, self-limiting and, for the most part, only affected the GI tract. SAEs, however, included bacteraemia, perforation and death [27]. Another report has identified short-term side effects that were consistent with those described in the published case reports, and included mild fever, bloating, constipation, diarrhoea, vomiting and abdominal discomfort, all of which subsided within a few weeks. FMT administration through nasointestinal tube was correlated with high fever and increased C-reactive protein concentrations. In cases of colonoscopic FMT administration perforation, bleeding and anaesthesia-related symptoms have been observed [28].

Another study identified 7562 original articles (the analysis included 50) and according to the determined percentage of AE, the incidence rate of mild events was 28.5% (the most common was abdominal discomfort), SAEs incidence, in contrast, was 2.0%. 44 kinds of SAEs occurred in 9.2% of all study participants, including death (3.5%), infection (2.5%), recurrent non-specific bowel disease (0.6%). The above findings indicate that adverse events are not uncommon and should be monitored [29].

A retrospective clinical data analysis of 406 patients undergoing FMT (2014-2016) demonstrated that no SAEs occurred during the follow-up. The most common mild adverse events were breathing discomfort and increased ventilation in the nasogastric transplant group. Similar events occurred in the capsule group, and, additionally, nausea was observed. The most common complication in the colonoscopy group was diarrhoea [30].

Another retrospective study conducted on 49 patients who underwent 114 FMT procedures, reported short-term AEs. Accordingly, 26.32% of the study population endured abdominal pain, diarrhoea, fever and vomiting. These afflictions resolved spontaneously, without symptoms within 48 hours, however, one death occurred in post-FMT week 4. Although FMT has been demonstrated to be tolerated by children, caution should be taken in cases of immunocompromised patients since FMT impact on long-term health is unpredictable [31]. At post-FMT month 1, 13.6% of the patients with CD enrolled in the study experienced mild

AEs, such as increased bowel movements, fever, abdominal pain, bloating, vomiting, flatulence and zoster [32].

In 2019, the cases of two immunocompromised adults who received FMT and developed invasive infections with ESBL-producing *E. coli* were described [33]. Based on an analysis of 129 studies involving 4241 patients, 19% of all FMT procedures reported adverse events (diarrhoea and abdominal discomfort/cramps), while 1.4% were SAEs, including infections and deaths. Four of the five FMT-related deaths were reported in patients receiving FMT via the upper gastrointestinal tract route. The reported FMT-related SAEs developed in patients with mucosal barrier injury. Most AEs were mild-to-moderate and self-limiting [34].

Subsequent studies were selected based on pre-specified exclusion criteria and were assessed in terms of quality. Out of 334 peer-reviewed papers from prospective, randomized, controlled, high-quality studies, 9 were selected. Herein, the total incidence rate of AEs was 39.3% and were reported by 112 patients. The most common AEs encountered were abdominal pain and diarrhoea. The later was mild and self-limiting. The incidence rate of SAEs was 5.3% (diarrhoea) [35].

The analysis of studies describing FMT administration due to recurrent CDI during 2012-2018, used logistic regression models for adverse events, showing higher risk of diarrhoea and a lower risk of IBD after FMT [36]. A SAE related to its preparation has been reported. This did not include screening for multidrug-resistant organisms. In such a case, SARS-CoV-2 is a potential pathogen and can be transmitted by FMT [37].

DISCUSSION

Alterations of the intestinal microbiota contribute to pathogenesis of inflammatory bowel diseases, irritable bowel syndrome, metabolic, cardiovascular and autoimmune diseases, anorexia nervosa, multiple sclerosis, cancer and neuropsychiatric disorders [38]. Indeed, In 2014, a study was conducted, and clinical data of 2010 patients who had successfully underwent FMT for intestinal dysfunction treatment, were collected [5]. Interest in the FMT method has grown since 2000, with the emergence of epidemic strains of *C. difficile* and with significant advances in microbial sequencing. FMT, has, therefore, been restored as a novel approach to the treatment of recurrent CDI [39-41]. Of note, FMT use in CDI research reports date back to 2003 [42,43].

Faecal suspension can be administered by a nasogastric or nasoduodenal probe, colonoscope, sigmoidoscope, enema or orally (capsules) [44]. According to Kao D. *et al.,* 96.2% of all participants suffering from recurrent CDI were cured with the "faecal pill" [45]. The efficacy of FMT is most likely dependent on the donor's ability to provide the necessary taxon capable of restoring the recipient's metabolic deficits that contribute to the disease. Hence, the term of 'super-donors of faeces' is used [46]. For this purpose and to ensure samples of the highest quality, faecal samples are collected continuously for 60 days and quarantined in a bank until all assessments have been completed [47].

Remodelling the composition of the gut microbiome through faecal microbiota transplantation can lead to new treatment strategies for treating many common diseases. Therefore, FMT is considered an effective strategy for reconstructing the intestinal microbiota [48,49]. The results of the first two double-blind, randomized, controlled trials regarding FMT in UC were published in 2015 [50]. The most common indications for FMT are gastric diseases: pseudomembranous enterocolitis caused by *C. difficile*, non-specific colitis, irritable bowel syndrome, chronic diarrhoea, rectal ulceration, chronic constipation and non-alcoholic fatty liver disease [50-58].

Moreover, the efficacy of FMT increases to 90% when multiple transplants are performed [60]. Subsequent studies have reported the effects of FMT on weight gain and on treatment of neurological, gastrointestinal and cancer diseases [61].

FMT efficacy is proven in liver diseases, such as hepatitis B, liver damage resulting from alcoholic hepatopathy, and cirrhosis with recurrent hepatic encephalopathy (HE). Intestinal microbiota changes can alleviate metabolic disorders in the course of liver diseases. Thus, based on innovative studies results, FMT intervention may be justified [62]. In patients with chronic hepatitis B, experience with FMT therapy has shown that it can induce HBeAg clearance in patients who remain HBeAg positive after long-term antiviral treatment.

Despite the promising benefits of modulating the gut microbiota in CHB treatment, further research with a larger sample is needed [63]. In a 3-month follow-up study, patients with alcoholic hepatitis were treated with: FMT (n=16), pentoxifylline (n=10), corticosteroids (n=8) and nutritional therapy consisting of a special diet (n=17). Favourable intestinal microbiological changes were found in the group of patients after FMT treatment, and three-month survival was the highest within this group [64]. A study among men with cirrhosis and recurrent HE found that donor-selected FMT for hospitalization improved cognitive function and dysbiosis in cirrhosis recurrent HE [65,66].

The review by Kao D. *et al*. presented eight studies that met the inclusion criteria, including two randomized clinical trials, three case reports and three studies in rodents (results not included into the analysis). In one such case report, 39 HE patients were treated with the FMT technique, leading to improved neurocognitive test scores [67].

FMT has been also used for the treatment of alopecia areata [68], Tourette's syndrome [69] and asthma [70]. Studies determining the relationship between the intestinal flora and the brain are increasingly common [71]. In this case, the mechanism of the disease is analysed by focusing on the gut-brain-microbiome axis, and such work has inspired novel treatment options by remodelling the intestinal microbiota [72]. Furthermore, attention has been paid to the relationship between specific patterns of gut bacteria and genital diseases, such as polycystic ovary syndrome (PCOS), endometriosis and bacterial vaginosis (BV). In such cases, FMT can be a treatment option [73]. Several case reports have also revealed the likely therapeutic effects of FMT in patients with autism [74]. FMT therapy can be a new and improved treatment strategy option for patients with radiation enteritis [75]. Moreover, FMT is used to treat membranous nephropathy and chronic diarrhoea [76]. In Crohn's disease, FMT has been found effective and safe

as it increases the overall diversity of the gut microbiome [77]. FMT can also be used to eliminate multi-drug resistant microorganisms (MDR) colonisation and to prevent recurrent infections [78,79]. In the studies mentioned above, the need for comprehensive research has been postulated, preferably in the form of randomised trials with large control groups.

The performed literature search was focused on the safety of FMT, with special interest on the observed adverse events. It was not the aim of the literature search to reassess the events classification, only to analyse the identified. However it is worth to mention that the adverse events definitions are regulated e.g. by the Pharmaceutical Law Act, and, according to that legal Act, adverse event occurs when the intervention causes, regardless of the dose used. These include, among others: patient's death, the intervention is life-threatening or results in necessity or an extension of hospitalization or permanent or significant health detriment [80]. In determining the severity of the reaction, a severe serious adverse drug reaction must be distinguished from a severe adverse drug reaction [81].

The FMT-associated adverse events can be divided into short-term and long-term; short-term events can, in turn, be subdivided into those related to the method of administration and those related to the FMT itself [82]. According to literature, FMT provides a high recovery rate with several SAEs [83].

Two studies performed in 2013, identified obstacles for FMT adoption as treatment method. These are donors, identification and logistical challenges [84,85]. In another study, patients with inflammatory bowel disease (IBD) undergoing FMT due to CDI have been found to be at increased risk of IBD exacerbation [86]. A study with 21 IBD patients resistant to conservative therapy reported mild, moderate and self-limiting events. Based on literature data, a single FMT is relatively safe and may result in a short-term response in young patients with active IBD [87]. Studies on public understanding of FMT as key obstacle for its acceptance identified procedure-associated repulsion, however, there exists evidence that the procedure "aesthetics" have surmounted this barrier [88,89].

Out of 742 citations identified, 7 were considering potentially relevant. Of these, 4 regarded studies encompassing 254 participants. Research evidence does not suggest an overall clinical benefit of FMT for global IBS symptoms and further evaluation in high-quality controlled clinical trials is needed [90]. To date, it has been difficult to draw reliable conclusions about FMT efficacy and safety for IBD due to non-uniformity of the therapeutic protocols and methods across studies [91]. Cases of, bacteraemia, demonstrating a potential risk of FMT infection regardless of the pre-treatment screening protocol were observed [92]. AEs including perforation/tear, death and Gram-negative bacteraemia may occur in CDI patients receiving FMT. Despite these of being of not high incidence, that these occurred should be considered important due to health risks associated with adverse reactions [93].

The FDA issued a warning about the risks of FMT and the need for a thorough donor examination using various microbiological and molecular tests [94]. Considering the adverse events variety, the transplant method should be personalized [95]. The potential risk of transmission of the SARS-CoV-2 by using faecal microbiota from infected donors should also be considered [96]. FMT can be adapted to the scenario related to the SARS-CoV-2 pandemic or similar pandemic situations, provided that appropriate safety measures are implemented; such as obligatory rigorous screening and testing of donors [97]. This was confirmed through a study on 26 patients (treated for recurrent CDI) when after following a special protocol with specific safety measures for FMT procedures, no SAE was reported [98]. During the pandemic, stool banks were obliged to maintain safety and apply high-quality procedures, i.e. appropriate selection of patients and donors, testing of faeces and post-FMT follow up [99].

A challenge worth mentioning and related to FMT is the reliability of the donor screening performed in order to obtain safe material for the recipient. This may include risks related to *C. difficile* infection, irritable bowel syndrome, inflammatory bowel disease or metabolic disorders [100]. One of the studies determined that only 10% of all respondents qualified as stool donors. For example, most healthy, asymptomatic donors failed stool testing, primarily because of being positively tested for parasite infection. Therefore, high donor exclusion rates generate high costs of such tests [101]. Consequently, developing an effective stool donor screening strategy must take into account emerging disease trends and detailed blood and stool testing procedures [102].

CONCLUSIONS

Due to FMT high effectiveness and safety, it can be a treatment option recommended for *C. difficile* infections after failure of drug therapy. However, FMT-associated adverse events should be considered, hence, personalised methods of transplantation should be recommended.

FMT can be a treatment option for other diseases and conditions, e.g. patients with hepatic encephalopathy and other such liver diseases.

FMT is associated with adverse events classified as mild, moderate and severe, and there is a need to implement a programme of donor screening, while personalised transplantation methods should be recommended.

Further research is recommended to assess and monitor FMT efficacy, benefits and risks.

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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