REVIEW 10.1111/1469-0691.12796

Practical implementation of faecal transplantation

N. Kapel[1], M. Thomas[2], O. Corcos[3], C. Mayeur[2], L. Barbot-Trystram[1], Y. Bouhnik[3] and F. Joly[3,4]

1) *Laboratoire de Coprologie Fonctionnelle, APHP, GH Pitié-Salpêtrière Charles Foix, Université Paris Descartes, Paris,* 2) *Commensal and Probiotics-Host interactions Laboratory, INRA, UMR1319 MICALIS, Jouy-en-Josas,* 3) *Department of Gastroenterology and Nutrition Support, Beaujon Hospital, Assistance Publique – Hôpitaux de Paris, Université Paris VII, Clichy, and* 4) *Gastrointestinal and Metabolic Dysfunctions in Nutritional Pathologies, Inserm UMR 1149, Centre de Recherche sur l'Inflammation Paris Montmartre – UFR de Médecine Paris Diderot, Paris, France*

Abstract

Clostridium difficile infection is a leading cause of antibiotic-related and healthcare-related diarrhoea. In the past decade, faecal microbiota transplantation or transfer has attracted increasing interest as an effective treatment strategy for severe recurrent *C. difficile* infection, with a global success rate of >80%. However, experience with this procedure is limited by a lack of randomized trials supporting its efficacy and the lack of standardization of the procedure. This review will address the practical aspects of the protocol.

Keywords: *Clostridium difficile*, donor faeces infusion, faecal transplantation, microbiota, recurrent infection
Article published online: 1 October 2014
Clin Microbiol Infect 2014; **20**: 1098–1105

Corresponding author: F. Joly, Pôle des maladies de l'appareil digestif (PMAD), Gastroentérologie, MICI et Assistance Nutritive, Hôpital Beaujon, 100 bd du général Leclerc, 92110 Clichy, France
E-mail: francisca.joly@bjn.aphp.fr

Introduction

The goal of faecal microbiota transplantation or transfer (FMT) is to restore the physiological balance by transferring gut microbiota from a healthy donor. In the past decade, this technique has attracted increasing interest as an effective treatment strategy for severe recurrent *Clostridium difficile* infection (CDI) [1–3]. It has been recently shown that FMT has an immediate and long-lasting reparative effect on the intestinal microbiota of CDI patients, with a decrease in the level of *C. difficile* after transplantation [4]. The FMT leads to a shift from an ecosystem dominated by potentially harmful bacteria to a healthy-like microbial profile. In March 2014, the European Society of Clinical Microbiology and Infectious Diseases published the 'Update of the Treatment Guidance Document for *Clostridium difficile* Infection', which strongly recommended (A-I) faecal transplantation in combination with oral antibiotic treatment for the treatment of multiple recurrent CDIs unresponsive to repeated antibiotic treatment [5]. However, practical aspects regarding the donors, recipients and physicians were not mentioned.

Furthermore, FMT appears to be a promising treatment in the setting of other diseases associated with microbial dysbiosis and whose aetiologies are unknown or uncertain (e.g. inflammatory bowel disease, irritable bowel syndrome, metabolic syndrome, and neurodevelopmental disorders) [6] or against extended-spectrum β-lactamase-producing *Enterobacteriaceae* residing in the large intestine, as recently shown [7].

In general practice, experience with this procedure is limited by a lack of randomized trials supporting its efficacy, the lack of standardization of the procedure, and the unappealing nature of the treatment. This review will address the practical aspects of the protocol.

Regulatory Aspects of FMT

Defining the status of FMT is actually a challenging regulatory issue. The Food and Drug Administration considers FMT to be a drug, and released a new guidance for public consultation in February 2014 [8]. In Europe, the UK's National Institute of Health and Care Excellence has stated that it does not

consider FMT to involve the transplantation of body tissue [9], and in March 2014 the French regulatory agency (ANSM) expressly declared it to be a drug [10]. The European Medicines Agency has not yet promulgated its position. In contrast, Smith *et al.* [11] argue that, for medical uses, the human stool should be considered a tissue, and not a drug. Classic definitions are of limited value, as neither 'tissue' of human origin nor 'conventional drug' seems to be a relevant classification for a therapy intended for microbiome modulation. Recently, Megerlin *et al.* suggested that FMT should be regulated as a *sui generis* biological drug for the treatment of severe recurrent CDI without any possible biosimilarity between lots [12,13].

Practical Aspects of FMT

Although patient perceptions of FMT are positive, navigating the known and unknown risks remains a major issue for the clinician managing patients with CDI. Up to now, there has been no clear consensus on the optimal protocol for faeces preparation before FMT, even if the donor microbiota is determinant for the outcome of FMT [4]. Studies have differed in terms of types of donors and the protocol for their screening, sample handling and preparation, recipient preparation, administered quantity, and mode of infusion. However, the overall reported success rate is >80% [2,3].

Donor selection

Once FMT candidates have been identified, they are generally asked to identify a healthy, related faeces donor, as they share the same environment and life habit, thus limiting the risk of pathogen transmission [1,2]. Most patients will identify their spouse or another close family member as a potential donor. Those who have ineligible family members may suggest a friend. Unrelated healthy screened donors can also be selected to facilitate the availability of a faecal sample [3,14,15]. Not only could the availability of a healthy pre-screened unrelated donor allow prompt treatment, as it can take up to 2 weeks to obtain screening laboratory results, but it could also reduce overall laboratory screening costs and provide more standardized treatment to patients. One systematic review provided data to suggest that FMT with faeces from a related donor (spouse or intimate partner) yields a somewhat higher rate (93.3%) of CDI resolution than FMT with faeces from an unrelated donor (84%) [16]. The work of Fuentes *et al.* [4] is a first step towards better identification of microbial signatures from donor and patients, which could improve FMT outcome. Recently, ANSM strongly encouraged the selection of anonymous donors with regard to French legislation concerning organ donation [10].

Although absolute and relative exclusion criteria can be identified for the donor by the use of a questionnaire (Table 1), transmission of communicable disease remains an inevitable risk, despite rigorous donor screening for infectious disease. These risks are well defined in blood transfusion practice, but they are less clear in FMT, especially as donor screening protocols vary, widely despite calls for standardization [1]. However, it is critically important to give primary consideration to the severity of the patient's illness.

Some centres initially screen potential donors either in person at the patient/recipient visit or via phone interview with, sometimes, a specific FMT coordinator using a standard screening questionnaire. The interview with potential donors should determine the potential risk of the donor harbouring a transmissible blood-borne or enteric pathogen. Donors with a history of high-risk behaviours, incarceration, recent tattooing or body piercing, illicit drug use or multiple sexual partners are excluded. Persons with recent international travel to areas at high risk for enteric infections or multiple drug-resistant bacteria are excluded. Potential donors with chronic gastrointestinal illnesses (Crohn's disease, ulcerative colitis, irritable bowel syndrome, and coeliac disease), malignancy or autoimmune disorders are also excluded. Some additional aspects could be considered, such as recent ingestion of a potential allergen in persons with past allergic reactions to this (these) allergen(s), diseases potentially associated with or attributable to microbiota changes, such as major gastrointestinal surgery (e.g. gastric bypass and short bowel syndrome), metabolic syndrome, morbid obesity, atopic diseases, including asthma and eczema, eosinophilic disorders of the gastrointestinal tract, and chronic pain syndromes (e.g. chronic fatigue syndrome and fibromyalgia) [1,16,18,19]. Furthermore, potential donors must not have received antibiotics or chemotherapy, or have been hospitalized, within 3 months before donation. Different centres did not specify whether a physical examination was performed, aside from the questionnaire and biological testing.

Theoretically, sexually intimate contacts would have previously shared body fluids and exposure to relevant communicable diseases, so some centres allowed intimate partners to opt out of testing for blood-borne pathogens, to save costs and facilitate more rapid performance of FMT.

Screening for pathogens

Regardless of the relationship between the donor and the recipient, screening for potential blood or faecal pathogens is always performed. New guidelines have been published in the last few years [1,10,18]. The precautionary principle stipulates