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CLINICAL PRACTICE GUIDELINES

Donor selection for faecal microbiota transplantation. Consensus document of the Catalan Society of Gastroenterology and the Catalan Society of Infectious Diseases and Clinical Microbiology☆

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KEYWORDS
Faecal microbiota transplantation;
Faecal microbiota donor selection;
Faecal microbiota donor screening

Abstract Faecal microbiota transplantation (FMT) is an effective and safe treatment of recurrent *Clostridioides difficile* infection. It is essential to make every effort to perform FMT rigorously and based on scientific knowledge. Selection of the faecal microbiota donor is a key part of the process to ensure recipient safety. Protocols of action must be implemented that allow clinicians to act with the maximum guarantees and to minimise the risks of the procedure. In this regard, a multidisciplinary working group has been set up with the aim of establishing recommendations for selecting the faecal microbiota donor.

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◊ The members of the Catalan Group for the Study and Development of Fecal Microbiota Transfer are presented in Appendix A.

PALABRAS CLAVE
Trasplante de microbiota fecal;
Selección del donante de microbiota fecal;
Cribado del donante de microbiota fecal

Selección del donante para la transferencia de microbiota fecal. Documento de posicionamiento de la Societat Catalana de Digestologia y de la Societat Catalana de Malalties Infeccioses i Microbiologia Clínica

Resumen La transferencia de microbiota fecal (TMF) es un tratamiento eficaz y seguro para tratar la infección recurrente por *Clostridioides difficile*. Es esencial extremar esfuerzos para que la TMF se realice con rigor y en base a los conocimientos científicos. La selección del donante de microbiota fecal es un punto clave del proceso para garantizar la seguridad del receptor. Es necesario disponer de protocolos de actuación que permitan a los clínicos actuar con las máximas garantías y minimizar los riesgos del procedimiento. Por este motivo se ha constituido un grupo de trabajo multidisciplinario con el objetivo de establecer unas recomendaciones para la selección del donante de microbiota fecal.

Introduction

Faecal microbiota transplantation (FMT) has emerged in recent years as the treatment of choice for recurrent *Clostridioides difficile* infection, with overall cure rates of 85–90%.[1] The efficacy of FMT has been widely demonstrated in multiple uncontrolled studies and in several clinical trials.[2–5] Consequently, the main clinical practice guidelines and medical associations recommend FMT as the first treatment option in recurrent *C. difficile* infection.[6–10]

Continuing advances in our understanding of the human gut microbiome have shown that there is an association between altered gut microbiota and a broad spectrum of disorders and diseases. These data have aroused growing interest in the scientific community to establish the role of FMT in conditions other than recurrent *C. difficile* infection, such as inflammatory bowel disease, metabolic syndrome, intestinal colonisation by multi-resistant microorganisms, irritable bowel syndrome, etc.

FMT is considered a safe, well-tolerated procedure with virtually no short-term adverse effects if performed correctly. However, the evidence available on long-term safety is limited. It is therefore essential to establish action protocols which allow clinicians to work with the maximum guarantees and minimise the risks of the procedure.

The pandemic caused by the SARS-CoV-2 virus which causes COVID-19 forces professionals to take additional control measures in the selection of faecal microbiota donors. Several studies have documented the presence of SARS-CoV-2 virus RNA in faeces,[11,12] meaning there is a potential risk of faecal-oral transmission of SARS-CoV-2. This consensus document establishes a series of recommendations to mitigate the risk of contagion of COVID-19 through FMT which without doubt will be subject to refinement as scientific knowledge in this field advances.

A multidisciplinary working group has been set up in Catalonia with specialists in gastroenterology, infectious diseases, microbiology and endocrinology with the aim of establishing recommendations which serve to ensure this treatment is performed according to strict standards and, at the same time, offer a practical aid for the methodology to follow. These recommendations will be reviewed and updated on a planned and periodic basis.

Donor selection

The selection of the donor must be rigorous to guarantee the safety of the procedure. Donor screening is vital to prevent the transmission of infectious diseases. There is also a theoretical risk of FMT modulating susceptibility for developing conditions or diseases related to the intestinal microbiota. To minimise these risks, prior to donation, each potential candidate will have a personal interview and laboratory tests, including a blood study and a stool study.

Donor information sheet

Everyone who enters the donor selection process will be informed about how the process works and about the purpose of their contribution. They will be given an information document which guarantees the confidentiality and protection of personal data. They will then be asked to sign an informed consent form. An example of a donor information sheet is attached in Appendix B.

Personal interview

In the personal interview, stress should be placed on the importance of the donor being honest when answering the questions, making sure the donor fully understands this. The interview must be conducted without witnesses, to protect the privacy of the donor. The safety of the recipient is the main concern. Therefore, the donor will be turned down if the personal interview reveals relevant medical history or behaviours associated with an increased risk of contracting communicable diseases. Donors must have the contact details of those responsible for the faecal microbiota transplant programme so they can immediately notify of any change in their symptoms or other relevant changes that may occur during the selection and donation period. An example questionnaire to be used in the personal interview is attached in Appendix B.

Laboratory tests

After conducting the personal interview, laboratory tests must be performed. A list of those considered essential is shown in Table 1. Depending on the clinical context of the recipient, for example in the case of immunosuppression, other pathogens may be tested for if deemed appropriate. Donors who are immigrants may be subject to additional serology tests according to the risk factors or diseases specific to the region they come from (e.g. Chagas disease, schistosomiasis, etc.).

Donor exclusion criteria

Donors should be turned down if risk factors are detected for the transmission of infectious agents or other characteristics we anticipate could affect the health of the recipient or affect the composition of the intestinal microbiota.

At present, we do not know the ideal composition of the donor's gut microbiota for FMT to be effective, so donors are selected by a principle of exclusion rather than inclusion. It has to be taken into account that if the screening is carried out properly, in the end only a minority will be able to act as donors.[13,14]

Donor exclusion criteria

- Under 18 or over 50 years of age.
- Having taken antimicrobials (antibiotics, antivirals, antifungals) or probiotics in the 6 months prior to donation.
- Positive result for any pathogen determined in laboratory tests during the screening period (Table 1).
- Smoker (> 10 cigarettes/day).
- Having a fever or gastrointestinal symptoms (diarrhoea, nausea, vomiting, constipation, abdominal pain, etc.).
- Relevant medical history (cancer, communicable diseases, etc.) and, specifically, history of gastrointestinal disorders, including inflammatory bowel disease, coeliac disease, irritable bowel syndrome, chronic constipation, chronic diarrhoea, previous history of *C. difficile* infection or gastrointestinal bleeding.
- History of autoimmune diseases (e.g. multiple sclerosis, connective tissue disorders, type 1 diabetes mellitus), atopy-related diseases, asthma, other types of diabetes mellitus, current treatment with immunomodulatory agents, history of chronic pain syndromes (e.g. fibromyalgia, chronic fatigue), neurological or neurodevelopmental disorders, psychiatric disorders, metabolic syndrome (NCEP-ATP III criteria), obesity (body mass index > 30 kg/m^2) or malnutrition (body mass index < 18.5 kg/m^2).
- Family history of colorectal cancer, polyposis syndrome, inflammatory bowel disease, coeliac disease or autoimmune diseases.
- Substance abuse.
- Taking medication that may be excreted in the faeces, that may pose a risk to the recipient or that may cause changes in the intestinal microbiota or dysbiosis (proton pump inhibitors, etc.).
- History of behaviours associated with increased risk of contracting communicable diseases:
  - Risky sexual behaviour: sexual relations in the last 6 months with anonymous partners, with multiple partners, with HIV carriers, with people who have taken drugs intravenously, with people who practice or have practiced prostitution.
  - Having a tattoo, body piercing or acupuncture in the last 6 months.
  - Recent or previous history of time spent in prison
  - Recent travel (6 months) to tropical countries, countries with endemic diarrhoeal diseases or high risk of traveller's diarrhoea (Africa, Southeast Asia, Mexico, Central America, South America, Caribbean).
  - Recent needle-stick injury.
  - Having received blood products in the last 6 months.
  - Having received live or attenuated vaccines in the last 6 months.
  - Individuals who work with animals (risk of zoonosis transmission).
- Having risk factors for colonisation by multi-resistant microorganisms:
  - Healthcare workers.
  - People in contact with the healthcare system defined as: recent hospitalisation, recent admission to long-stay centres, regular attendance at day hospitals or outpatient surgery.
- Major gastrointestinal surgery.
- Major non-gastrointestinal surgery in the last 4 months (e.g. pneumonectomy, cardiac intervention or thoracic surgery, severe fracture (femur, pelvis, etc.), joint replacement (hip, knee, etc.).
- Having risk factors for Creutzfeldt-Jakob disease (spongiform encephalopathy).
- Having SARS-CoV-2 infection (confirmed or suspected):
  - Typical symptoms: fever, fatigue, dry cough, myalgia, dyspnoea, headache, diarrhoea, anosmia, dysgeusia or skin rashes; with or without diagnostic test.
  - Test with positive result for SARS-CoV-2 with or without symptoms of the disease.
- Contact with SARS-CoV-2 infection (confirmed or probable) in the last 4 weeks.

COVID-19 and donor selection

Several studies have documented the presence of SARS-CoV-2 virus RNA in faeces, and it can continue to be detected even when the results in respiratory samples are negative,[11,12] meaning there is a potential risk of faecal-oral transmission of SARS-CoV-2. To mitigate the risk of contagion of COVID-19 through the FMT, the following measures are recommended:

- Rule out SARS-CoV-2 infection in all donors by nasopharyngeal PCR + serological test + PCR in stool or rectal swab.
- It is advisable to leave the sample in quarantine for 4 weeks until the study has been repeated to rule out SARS-CoV-2 infection (Fig. 1).
- Any positive test result for SARS-CoV-2 or the presence of symptoms are exclusion criteria for donation of faecal microbiota.
- Asymptomatic donors with positive IgG for SARS-CoV-2, but with all other parameters negative (nasopharyngeal

Table 1 Laboratory tests.

Blood	Glomerular filtration rate, liver profile, C-reactive protein, thyrotropin (TSH) and thyroxine (T4), anti-transglutaminase antibodies, lipid profile
Viruses	Cytomegalovirus IgG Ab and Epstein-Barr virus IgG Ab[a]
	Herpes simplex 1 + 2 IgG Ab[a]
	Hepatotropic viruses: HBsAg, HBcAb, HCV Ab, HAV IgM, HEV IgM
	Human immunodeficiency virus (HIV-1, HIV-2)
	HTLV (human T-lymphotropic virus) type I + II (Ab)
	Serology for SARS-CoV-2 (IgM Ab + IgG Ab)
Bacteria	Serology for *Treponema pallidum*
Parasites	*Strongyloides stercoralis* IgG Ab (ELISA)
	Toxoplasma gondii IgG Ab
Stool	
Bacteria	Standard stool culture (*Campylobacter*, *Salmonella*, *Shigella* and *Yersinia*)
	Study for toxigenic *Clostridioides difficile*
	Real-time PCR of gastrointestinal pathogens or available technique: *Campylobacter* spp., *Salmonella* spp., *Shigella* spp., *Yersinia* spp., *Vibrio cholerae*, detection of *Escherichia coli* pathogens (enterotoxigenic, enteroaggregative, enterohaemorrhagic, enteropathogenic, enteroinvasive)
	Tests to detect carriers of multidrug-resistant bacteria (rectal swab or sample of donated stool): extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, vancomycin-resistant enterococcus, carbapenem-resistant Enterobacteriaceae, and methicillin-resistant *Staphylococcus aureus* (MRSA)
	Helicobacter pylori in stool
Viruses	Real-time PCR for norovirus, rotavirus, adenovirus
	PCR in stool or rectal swab for detection of SARS-CoV-2
Parasites	Conventional parasite test
	Real-time PCR study or available technique (EIA, etc.) for *Giardia lamblia*, *Cryptosporidium* spp., *Entamoeba histolytica*, *Blastocystis hominis*, *Dientamoeba fragilis*
Other determinations	Faecal calprotectin
	Faecal occult blood
Other	Nasopharyngeal PCR for detection of SARS-CoV-2
	Nasal swab for the detection of methicillin-resistant *Staphylococcus aureus* (MRSA)

[a] It is recommended to reject donors with positive IgG for cytomegalovirus, for Epstein-Barr virus and for herpes simplex virus in the case of immunocompromised recipients with negative serology.

PCR, stool PCR, IgM) are not considered as meeting the exclusion criteria.

- If a donor develops symptoms of COVID-19 or has a positive test for SARS-CoV-2, all samples they have given in the last 4 weeks must be destroyed.
- A donor who has had COVID-19 (confirmed or suspected) cannot be assessed as a possible donor until 12 weeks after the resolution of the infection.
- A donor who has had contact with COVID-19 (confirmed or suspected) cannot be assessed as a possible donor until 4 weeks after the contact.

Validity of the selection process

Donors who do not show any exclusion criteria either in the personal interview or in the laboratory test results will be eligible for donation. However, it is highly recommended not to use any sample until after further testing to rule out infection by the SARS-CoV-2 virus (nasopharyngeal PCR + serological test + PCR in faeces) 4 weeks after donation (Fig. 1).

As an additional measure, it is advisable to keep the donation in quarantine for 60 days until the donor passes the full set of laboratory tests again (regardless of whether the donor wishes to continue providing samples or is making a single donation).[15] This measure would detect infections which were in the window period or were not detected in the initial study. Samples in the quarantine period should be stored at −80 °C until use. Another equally valid option is to keep the sample dried after the freeze-drying process. Also, as a safety measure, it is recommended to keep an aliquot of the donor's faeces so that it can be analysed in the future, if necessary.

After the first donation, if the donor is eligible and wishes to continue providing samples, the following tests must be performed:

- Detect any changes in the questionnaire at each donation.
- Rule out the presence of symptoms suggestive of COVID-19 at each donation.
- PCR in stool or rectal swab for SARS-CoV-2 at each donation.
- Complete stool analysis at least every 1–2 weeks.

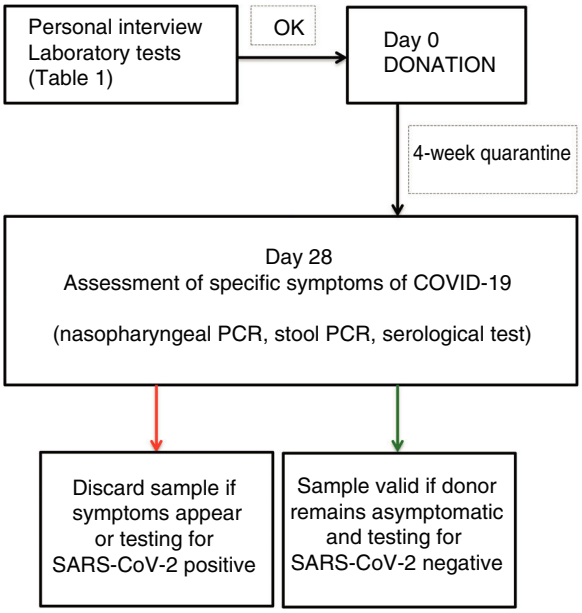

Figure 1 COVID-19 and donor selection.

- Nasopharyngeal PCR for SARS-CoV-2 at least every 4 weeks.
- Serological test for SARS-CoV-2 every 4 weeks.
- Complete blood analysis at least every 2 months.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.gastre.2020.07.005.

References

1. Kelly CR, Kahn S, Kashyap P, Laine L, Rubin D, Atreja A, et al. Update on fecal microbiota transplantation 2015: indications, methodologies, mechanisms and outlook. Gastroenterology. 2015;149:223–37.
2. Van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med. 2013;368:407–15.
3. Cammarota G, Masucci L, Ianiro G, Bibbò S, Dinoi G, Costamagna G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs vancomycin for the treatment of recurrent *Clostridium difficile* infection. Aliment Pharmacol Ther. 2015;41:835–43.
4. Kelly CR, Khoruts A, Staley C, Sadowsky MJ, Abd M, Alani M, et al. Effect of fecal microbiota transplantation on recurrence in multiply recurrent *Clostridium difficile* infection: a randomized trial. Ann Intern Med. 2016;165:609–16.

5. Hvas CL, Dahl Jorgensen SM, Jorgensen SP, Storgaard M, Lemming L, Hansen MM, et al. Fecal microbiota transplantation is superior to fidaxomicin for treatment of recurrent *Clostridium difficile* infection. Gastroenterology. 2019;156:1324–32.
6. Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. Am J Gastroenterol. 2013;108:478–98.
7. Mc Donald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66:987–94.
8. Cammarota G, Ianiro G, Tilg H, Rajilic-Stojanovic M, Kump P, Satokari R, et al. European consensus conference on fecal microbiota transplantation in clinical practice. Gut. 2017;66:569–80.
9. Mullish BH, Quraishi MN, Segal JP, McCune VL, Baxter M, Marsden GL, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. Gut. 2018;67:1920–41.
10. Sokol H, Galperine T, Kapel N, Bourlioux P, Seksik P, Barbut F, et al. Faecal microbiota transplantation in recurrent *Clostridium difficile* infection: recommendations from the French Group of faecal microbiota transplantation. Dig Liver Dis. 2016;48:242–7.
11. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2 [published online ahead of print, 2020 Mar 3]. Gastroenterology. 2020, http://dx.doi.org/10.1053/j.gastro.2020.02.055.
12. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in different types of clinical specimens [published online ahead of print, 2020 Mar 11]. JAMA. 2020, http://dx.doi.org/10.1001/jama.2020.3786.
13. Paramsothy S, Borody TJ, Lin E, Finlayson S, Walsh AJ, Samuel D, et al. Donor recruitment for fecal microbiota transplantation. Inflamm Bowel Dis. 2015;21:1600–6.
14. Kassam Z, Dubois N, Ramakrishna B, Ling K, Qazi T, Smith M, et al. Donor screening for fecal microbiota transplantation. N Engl J Med. 2019;381:2070–2.
15. Cammarota G, Ianiro G, Kelly CR, Mullish BH, Allegretti JR, Kassam Z, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. Gut. 2019;68:2111–21.