Revisiting the donor screening protocol of faecal microbiota transplantation (FMT): a systematic review

We read with interest the recent work by Haifer *et al*,[1] which highlighted the importance of donor selection in determining the clinical efficacy of treating ulcerative colitis (UC) using faecal microbiota transplantation (FMT), with one donor having 100% efficacy compared with a second donor (36% efficacy). Considering the impact of COVID-19 pandemic on FMT, updated guidance including patient selection, donor recruitment and selection, FMT procedures and stool manufacturing was provided by worldwide FMT experts in international guideline by Ianiro *et al*.[2] The US Food and Drug Administration (FDA) has recommended that FMT donor screening must include a questionnaire specifically addressing risk factors for colonisation with multidrug-resistant organisms (MDROs) and stool testing for MDROs, including extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, vancomycin-resistant enterococci (VRE), carbapenem-resistant Enterobacteriaceae (CRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) at minimum.[3] The evolution of FMT and the introduction of essential donor screening requirements by the FDA are listed in figure 1A. However, little is known on the differences in donor screening protocols in different FMT centres. Therefore, we aim to provide an update on the screening strategy for faecal donors based on emerging trends in diseases as well as to propose a set of blood and stool tests to ensure safety of the FMT procedure via systematically reviewing the existing data and with our own experience in the centre of FMT at The Chinese University of Hong Kong.

We thus systematically reviewed (INPLASY2021120063)[4] the published literature (Embase and MEDLINE through PubMed and Web of Science) and consensus documents on donor screening procedures from FMT units worldwide. Thirty-three (n=33) clinical studies (Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart, figure 1B) and 11 (n=11) consensus documents in different WHO regions (figure 1C) were compared along with our local donor screening procedure (see online supplemental appendix)

The consensus documents and national guidelines published in all WHO regions supported screening of MDROs, including ESBL, VRE, CRE and MRSAs, in potential stool donors, except the Austrian[5] and Taiwan guidelines.[6] There was one European study testing for other MDROs, MDR *Acinetobacter baumannii*.[7] Considering the high prevalence of MDROs in Hong Kong, with ESBL and MRSA being 52.8% and 2.5%, respectively,[8] our FMT centre is currently screening ESBL, VRE, CRE, MRSA and MDR *A. baumannii*. Equally, a controversy is to what limits detecting ESBL–Enterobacteriaceae in the donor, for example, in India, where >70% of the population is already colonised.[9]

Different practices of SARS-CoV-2 testing for potential stool donors were adopted by different stool bank centres

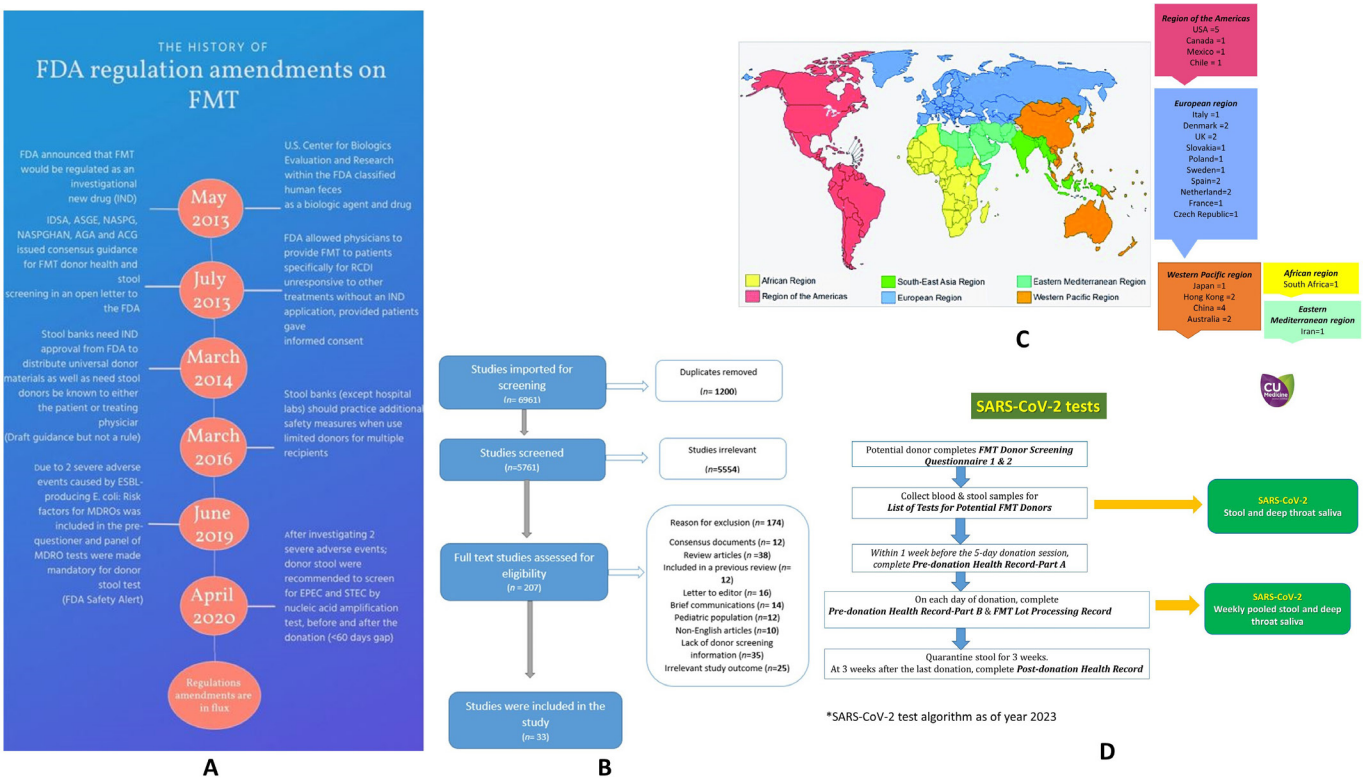

Figure 1 (A) FDA regulation amendments and safety alerts on FMT. (B) PRISMA flow diagram for the study selection. (C) Included study stratification according to the WHO regions. (D) SARS-CoV-2 testing time points. ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; ASGE, American Society for Gastrointestinal Endoscopy; EPEC, enteropathogenic *Escherichia coli*; ESBL, extended-spectrum β-lactamase; FDA, Food and Drug Administration; FMT, faecal microbiota transplantation; IDSA, Infectious Disease Society of America; IND, investigational new drug; MDRO, multidrug-resistant organism; RNASPG, North American Society for Paediatric Gastroenterology; NASPGHAN, North American Society For Paediatric Gastroenterology, Hepatology & Nutrition; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCDI, Recurrent Clostridiodes difficile infections; STEC, Shiga toxin-producing *Escherichia coli*.

since the COVID-19 pandemic. Currently, our biobank is following a stepwise procedure to detect SARS-CoV-2 in donors (figure 1D).

The repertoire of the optimal testing methods for infective agents is rapidly changing due to the advancement of technology and our increased understanding of the risks associated with FMTs. For example, increasingly more national consensus guidelines, including the American guideline,[10] recommend the detection of Shiga toxin in *Escherichia coli* with PCR, which is a more sensitive method as compared with enzyme immunoassays (EIA), but with a higher cost. In addition, the detection of specific MDROs in stool samples of potential donors depends on their local prevalence and risk assessment. With the rapidly increasing numbers of FMT biobanks established worldwide, there is a need for a working consensus perhaps of a minimal set of screening questionnaire and laboratory test requirements. Here we propose (table 1) a minimum but essential set of screening questionnaire and laboratory tests in donor selection. Additional consideration made to specific conditions and tests will be based, according to a risk-based assessment, depending on the geographical prevalence of disease and other cultural and medicine licensing requirements and risk–benefit factors in their region.

Table 1 Recommended minimum list of questionnaire, blood and stool test for rigorous FMT donor screening procedure

Prescreening data	Test method
Risk of infectious agents	
Known HIV, hepatitis B or C infections	Questionnaire
High-risk sexual behaviours	Questionnaire
Use of illicit drugs	Questionnaire
Travel (within the last 6 months) to high-risk countries with travellers' diarrhoea	Questionnaire
Recent needle stick accident	Questionnaire
GI comorbidities	
History of IBD	Questionnaire
History of IBS, idiopathic chronic constipation or chronic diarrhoea	Questionnaire
History of GI malignancy or known polyposis	Questionnaire
Factors that could affect the composition of gut microbiota	
Antibiotics within the preceding 3 months	Questionnaire
Major immunosuppressive medications	Questionnaire
Other factors	
History of major GI surgery	Questionnaire
Metabolic syndrome	Questionnaire
Systemic autoimmunity (multiple sclerosis and connective tissue disease)	Questionnaire
Atopic conditions (asthma, atopic dermatitis and eczema)	Questionnaire
Obesity	Questionnaire
Depression	Questionnaire
Schizophrenia or delusion disorder	Questionnaire
Blood tests	Test method
Testing for viruses	
Hepatitis A (HAV)	HAV-IgM
Hepatitis B	Hepatitis B surface antigen (HBsAg), anti-Hbc
Hepatitis C (HCV)	Anti-HCV
Hepatitis E (HEV)	Anti-HEV IgM
HIV I and II	Anti-HIV
Human T-cell lymphotropic virus	Anti-HTLV
Testing for bacteria	
Treponema pallidum	Screening test (eg, Rapid Plasma Reagin (RPR), Venereal Disease Research Laborotory test (VDRL) and EIA)
Other tests	
Complete blood count	NA
C reactive protein	NA
Renal function test	NA
Liver function test	NA
Stool tests	Test method
Testing for viruses	
Rotavirus	EIA
Norovirus	PCR
Testing for bacteria	
Salmonella sp	Culture±PCR
Shigella sp	Culture±PCR
Campylobacter sp	Culture±PCR
Vibrio sp	Culture±PCR
Clostridium difficile	PCR
Helicobacter pylori	Stool antigen
MDR bacteria	
ESBL-producing Enterobacteriaceae	Culture
VRE	Culture
CRE (KPC, NDM and OXA 48)	Culture

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Table 1 Continued

Prescreening data	Test method
MRSA	Culture
Testing for parasites	
Cyclospora sp	Microscopy±antigen
Isospora sp	Microscopy±antigen
Giardia sp	Microscopy±antigen
Cryptosporidium sp	Microscopy±antigen
Entamoeba histolytica	Microscopy±antigen
Light microscopy for ova and cysts	Microscopy

CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase; FMT, faecal microbiota transplantation; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable; NA, not available; VRE, vancomycin-resistant enterococci .

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