Donor screening for fecal microbiota transplantation in China: Evaluation of 8,483 candidates

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Therapeutic application of fecal material has been described as early as 4th century China\(^1\). Subsequently, the intervention has evolved and fecal microbiota transplantation (FMT) has become one of the recommended treatment from ACG guideline for a second recurrent *Clostridioides difficile* infection (CDI)\(^2\) and has emerged as a promising intervention to address dysbiosis linked to a number of diseases\(^3\). A robust donor screening program is an important element of safe FMT; however, there are limited data with variable screening rates\(^4,5\). Recently, a large FMT program in the United States reported data that suggest a qualification rate of approximately 2.5\(^%\); however, the qualification rate for donors in Asia has been only described in literature review analysis\(^7\). There are limited real-world data reporting if candidate donors in Asia have a distinct health and risk factor profile for the donation of biological material to be processed for FMT. Accordingly, we outline the eligibility rate and etiology of exclusion for the largest FMT center in China (10th People’s Hospital, Tongji University, Shanghai, China) where over 60,000 FMTs across more than 5,000 patients have been conducted since 2012 for various gastrointestinal diseases (e.g., recurrent CDI, inflammatory bowel disease, irritable bowel syndrome) and extraintestinal diseases (e.g., autism spectrum disorder, Parkinson disease).

The standardized donor screening program nowadays is based on the Chinese Expert Consensus FMT guideline, which recommends evaluation of donor screening across the following six dimensions: physiology, psychology, personal history, stability, persistence, and tolerance to dietary restriction\(^8\), while the clinical protocol of recruiting the FMT donor evolves depending from different phrases of period. Starting from 2012, a 3-step protocol is employed, while from 2015 to 2019 a fourth step of evaluating candidates’ life style was adjoined. Until now, enrollment of candidate donors was extended prospectively into a 5-step protocol (Fig. 1). In the first step, candidate donors are excluded based on age, body mass index (BMI), and high-risk sexual behaviors and personal history. In the second step, a more detailed clinical evaluation is conducted for microbiome-mediated diseases and risk factors for transmissible infection. This step also excludes candidates with a history of chronic diseases and mental health conditions as per assessment by both a trained physician and senior psychiatrist. In the third step, candidate donors undergo stool testing including 16S sequencing to evaluate dysbiosis (Shannon’s diversity index lower than 50% normal population excluded) and a full panel test of infectious pathogens, and in the fourth step they undergo hematologic and serologic testing to exclude blood-borne pathogens and systemic organ dysfunction (Appendix 1). In the fifth step, donors are evaluated for diet restriction if material is for a recipient with significant food allergies, as well as logistical and quality control factors.

Initially when we started the screening project of FMT donors in 2012(phase I), a simple 3-step protocol based on age limitation, BMI restriction, clinical and laboratory assessment are used, leading to a rate of 8.38\(^%\) to screen out the standard donors. After 2015 we started to incorporate an life style evaluation (phase II) to exclude our candidates without sufficient amount of exercise (walk less than 6000 steps/d), and unqualified eating habit (including consuming irritant spicy food ,
saturated fatty acid food, not enough fresh fruits nor vegetables (<300g/d), which turn out that the success rate of obtaining the donors are decreased to 3.93%, however, the overall FMT efficiency is increased from 42.8% to 58.6%. Retrospectively, dated to December 2020, a total of 8,483 donor candidates were evaluated (Figure 1). Most common exclusion criteria at each step included: age (n=1,364) or non-optimal BMI (n=1,383) at step 1, history of chronic disease (n=461) at step 2, intestinal dysbiosis (n=280) at step 3, abnormal liver panel (n=104) at step 4 and unqualified amount of exercise (n=193) at step 5. Overall, 145 candidate donors qualified resulting in a 1.7% qualification rate, leading to an even higher efficiency (68.7%) but a lower adverse effect (20.1%).

When we started the donor screening projects within phase I protocol, few laboratory assessments are utilized due to the limitation of technology. After 2015, during phase II protocol, 16sRNA sequencing are wildly applied which greatly increase the overall efficiency and lower the adverse effects. In phase III protocol we differentiated the fecal assessment and peripheral blood assessment, but in both level we use 16S RNA sequencing to screen out the possible infectious disease including Covid-19 and rule out dysbiosis. The donor screening qualification rate in China is in keeping with that from a large US stool bank. However, stricter criteria including narrower age and BMI range, assessment of intestinal dysbiosis by 16S RNA sequencing, and the addition of additional screening dimensions (e.g. exercise, restricted eating habits) may contribute to the lower qualification rate reported here. Different regimes of oriental and occidental country might greatly impact human intestinal microbiota, which should be taken into account when applying similar protocol to other ethnics groups.

Figure 1. Evolvement of the protocol of the FMT donors screening strategy

Three phases of FMT donors screening strategy are summarized in the above figure. In phase I (2012-2015) only 3 steps are employed, leading to an overall efficiency of 42.8%, adverse effects of 30.7% (only minor adverse effects: abdominal distention, nausea, vomiting, diarrhea, abdominal pain, sore throat or fever, none major adverse effects like GI bleeding or enterogenous infection); in phase II (2015-2019) another step of evaluating donors’ life style is added, leading to an overall efficiency of 58.6%, adverse effects of 26.3%; in phase III (after 2019 Covid-19 pandemic) screening for Covid-19 in both peripheral blood and feces are wildly applied among candidates. Therefore, enrollment of candidate donors was conducted prospectively in a 5-step protocol: step 1, candidate donors are excluded based on age, BMI, high-risk sexual behaviors and personal history; step 2, detailed clinical evaluation is conducted for microbiome-mediated diseases and risk factors for transmissible infection, excluding candidates with history of chronic and mental disease; step 3, 16S sequencing screening strategy to evaluate dysbiosis and infectious pathogens; step 4, hematologic and serologic testing to exclude blood-borne pathogens and systemic organ dysfunction; step 5, diet restriction eligibility, logistical and quality control. The overall efficiency of FMT donors is increased to 68.7%, while the adverse effects are decreased to 20.1%.
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