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Review Article

Fecal microbiota transplantation for *Clostridium difficile* infection in Taiwan: Establishment and implementation

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Abstract *Clostridium difficile* infection (CDI) remains a major public health issue, and fecal microbiota transplantation (FMT) has become one of the standard therapies for recurrent or refractory CDI. When compared to medical therapies, such as metronidazole or vancomycin, FMT has a high rate of treatment response with acceptable safety and efficiency. Following promulgation of the amendments in September 2018 in Taiwan, FMT has been indicated for recurrent or refractory CDI. The Taiwan Microbiota Consortium contributed to the Taiwan FMT Expert Consensus, which established basic norms and stipulated essential principles, including the indications for transplantation, eligible locations and personnel, donor screening policies, fecal sample handling, and post-FMT follow-up. However, establishing an eligible FMT team in a qualified hospital remains a clinical challenge, and the requirement for facilities and well-screened donors impedes the implementation of FMT. In this review, we aim to provide domestic FMT teams with explicit instructions to facilitate realization and increase the practice of FMT. Based on the Taiwan FMT Expert Consensus and current regulations, we performed a literature review and integrated the experiences of Taiwanese multidisciplinary experts into

Abbreviations: CDI, *Clostridium difficile* infection; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; LGI, lower gastrointestinal; TFEC, Taiwan Fecal Microbiota Transplantation Expert Consensus; UGI, upper gastrointestinal.

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this article. The content intends to offer clinicians up-to-date evidence and highlight the essential points of FMT.

Introduction

In the human body, commensal microbial cells outnumber human cells by approximately 10-fold.[1] Human microbiota are defined as microbial taxa associated with the human body, including viruses, archaea, bacteria, and eukaryotes.[2] Approximately 500—1000 bacterial species, with an estimated 2,000,000 genes, which outnumber human genes by 100-fold, have been documented.[3] In recent years, gut microbiota dysbiosis has been demonstrated to provoke a systemic inflammatory response that contributes to many medical illnesses, including cardiovascular disease and certain cancers.[4] Such a "dysbiosis" is generally made up of three nonmutually exclusive components, namely, the disappearance of beneficial microbes, overgrowth of potentially detrimental organisms, and decline of overall microbial diversity.[5] Notably, gut dysbiosis plays a critical role in the development of non-alcoholic fatty liver disease, inflammatory bowel disease (IBD), and liver cirrhosis[6,7]; it is also strongly associated with extraluminal diseases, such as obesity, type 2 diabetes mellitus, chronic kidney disease, and heart failure.[8,9]

Clostridium difficile is a gram-positive, anaerobic, spore-forming bacillus.[10] *C. difficile* infection (CDI) may occur in patients with *C. difficile* colonization or who acquire the pathogen through oral intake during hospitalization or in the community; the pathogenesis is mainly attributable to toxin A (an enterotoxin), toxin B (a cytotoxin), and binary toxin.[10,11] Clinical toxigenic *C. difficile* isolates are genetically diverse and some hypervirulent ribotypes such as 027 have been reported to cause outbreaks in healthcare facilities.[12] Clinical manifestations of CDI range from diarrhea, pseudomembranous colitis, severe ileus, toxic megacolon, peritonitis, to even shock or organ failures.[10,11] In a nationwide survey of health care-associated infections in the United States, *C. difficile* was the most common pathogen.[13] CDI contributes to 453,000 cases and approximately 29,000 deaths annually in the United States,[10] and the incidence and mortality in Asia are similar to those in other continents.[14] Broad-spectrum antimicrobial therapy increases the risk of intestinal colonization of antimicrobial-resistant pathogens and contributes to the development of CDI.[10,15] The occurrence of CDI mainly involves dysbiosis and related alternations of metabolites, including increasing amounts of sialic acid and succinate, and decreasing amounts of potential inhibitors such as secondary bile acids.[16] In addition, illness and antibiotic treatment can breakdown "colonization resistance", which indicates that gut microbiota can inhibit the colonization of potentially harmful microorganisms, such as *C. difficile*.[17,18]

Approximately 10%—30% of patients suffer from at least one recurrence of CDI, and the recurrent rate increases with each successive attack.[19] CDI-attributable mortality ranges from 4.5% to 16.7% and the CDI-attributable cost of hospitalization is US$3427 to US$9960 per episode.[19] In Taiwan, the overall incidence rate in a hospital was 4.5 per 10,000 patient-days, and 79 per 10,000 patient-days in intensive care units.[14] In a medical center in southern Taiwan, the incidence was 42.6 cases per 100,000 patient-days, or 3.4 cases per 1000 discharges. The 30-day crude mortality rate of patients with CDI can reach 23.3%.[20] When compared with healthcare facility-onset or community-onset healthcare facility—associated CDI in Taiwan, community-onset CDI has a lower in-hospital mortality rate but a similar recurrence rate, which also substantially disables elderly individuals.[21] However, in the aspects of infection control and clinical diagnosis of CDI in Taiwan, there remain some gaps between clinicians' perceptions and international guidelines.[22]

Based on the clinical practice guidelines for CDI in adults and children released by the Infectious Diseases Society of America in 2017, the standard treatments for an initial episode and the first recurrence of CDI include oral vancomycin or fidaxomicin.[19] Furthermore, fecal microbiota transplantation (FMT) in addition to oral medication is an alternative therapy for the second recurrence in adult patients.[10,19] For recurrent or refractory CDI, FMT has been recommended in different international guidelines.[19,23]

Fecal microbiota transplantation

FMT refers to delivery of a solution of fecal material from a healthy donor into the gastrointestinal tract of a recipient with relative gut dysbiosis to rebuild the gut microbiota in the recipient and benefits the recipient.[24,25] Since the nineteenth century, FMT has been used formally in the treatment of refractory CDI in Western countries.[26,27] In an open-label randomized control trial, the rate of cure without relapse for recurrent CDI in patients receiving FMT through duodenal infusion was higher than that in the group receiving vancomycin (>80.0% *vs.* 30.8%).[28] Another systematic review reported that the overall success rate was 85% for recurrent CDI, and 55% for refractory CDI, in comparison with a success rate of 30—80% typically reported in patients with CDI receiving vancomycin therapy.[27] With gradual popularization, FMT has been included in many treatment guidelines regarding CDI.[23,29] The safety and outcome during long-term follow-up are satisfactory for FMT in treating refractory and recurrent CDI.[26,30] Death and

harmful adverse events seemed to be uncommon, and most could not be attributed to FMT directly.[30,31]

There are several routes for delivering donor feces, such as oral capsules, colonoscopy, or nasoduodenal (or nasojejunal) tube infusion.[32] Vital research demonstrated that the prevention of recurrent CDI was equally as effective when FMT via an oral capsule was compared with FMT via colonoscopy.[33] The major discrepancy was the patient's subjective experience; they were more comfortable with oral capsule. In addition, minor adverse effects seemed to be more common in those receiving colonoscopy.[33] Another issue is the preparation of fecal material; current evidence supports that frozen stool via an enema is as effective as fresh stool.[34,35] Most guidelines favor banked, frozen FMT for timely availability and quality control.[23,36]

In Taiwan, there have been several case series on successful FMT in both adults and children since 2017, and one FMT case series has been published.[37] The donors were the relatives of the receipts and most of the indications were recurrent or refractory CDI.[37] Since oral capsules are generally not available in Taiwan, the delivery routes include a lower gastrointestinal (LGI) route via colonoscopy or upper gastrointestinal (UGI) route through esophagogastroduodenoscopy (EGD) with nasoduodenal (or nasojejunal) tubes.[23,25] In addition, fresh stool material, rather than frozen material, has been utilized in most reported domestic cases.[37]

Regulations and norms

There are different regulations for FMT among countries, and global regulation is lacking.[24,25] In the United Kingdom, the Medicines and Healthcare Products Regulatory Agency guides FMT practices, and an institute can conduct FMT legally after gaining permission from the agency.[23] The United States Food and Drug Administration initially considered FMT a drug, but the "enforcement discretion" regarding investigational new drug applications provided a possible means for FMT in patients with unresponsive or recurrent CDI.[38] Although a regulation is necessary for safety, a government's intensive oversight could increase the trend of at-home FMT in urgent patients,[38] especially those with other indications that have not yet been approved.[24]

The Taiwan Microbiota Consortium has promoted FMT for years. The multidisciplinary experts in the Taiwan Microbiota Consortium held several consensus conferences, formulated the Taiwan FMT Expert Consensus (TFEC), and established the amendments for the regulation of FMT.[39] The TFEC included five key components, namely, the indications for transplantation, eligible centers and FMT team members, donor selection, fecal processing and delivery, and post-FMT patient monitoring.[39] In September 2018, the Department of Medical Affairs formally announced that FMT could be utilized for recurrent or refractory CDI in Taiwan. Recurrent CDI refers to CDI that recurs within eight weeks after symptoms resolution following medical therapy, and refractory CDI is defined as the continuation of clinical symptoms after CDI-targeted antibiotic therapy.[39] Accordingly, a multidisciplinary FMT team should comprise gastroenterologists, microbiologists, and infectious disease physicians.[39] Furthermore, the performance of FMT is constrained to the hospital and a dedicated laboratory for preparation is mandatory.[39] The consensus also defined the selection criteria for eligible donors.[39]

Laboratory requirements and supervision of processing

There are two major issues for laboratories: the regulation and processing of fecal material.[36,40] A biosafety level 2 laboratory, which may involve agents of moderate potential hazard to humans or the environment, is required for FMT.[25,40] Fecal processing is summarized as follows. Standard containers with labeled donor information and time of collection should be utilized for stool collection.[25] The donated feces must be processed within 1 h after defecation.[36] If fresh stool is considered for FMT, the material must be used within 6 h after the donation, and a low temperature (20°C-30 °C) for the entire process is preferred.[25] "As brief as possible" is the principle to protect anerobes.[25] Approximately 50 g of filtered stool is homogenized in 150—200 mL of sterile normal saline in a commercial blender to a final volume of approximately 250 mL.[25,36,41] To remove larger particles or undigested food, the mixed fecal material is then passed through strainers or sieves to facilitate delivery. The suspension can be centrifuged before direct infusion or stored at −80 °C, as appropriate.[25,35] For long-term storage, sterile pharmaceutical grade glycerol should be added for a final concentration of 10%.[25,35] A maximal shelf-life of frozen fecal material is approximately six months.[23] Frozen fecal material should be thawed at 37 °C on the day of FMT, and the thawed material should be infused within 6 h.[25] Traceability of FMT is of paramount important: therefore, the collection of donated fresh fecal (1—2 g) and administered preparation (1—5 mL) samples for storage before infusion is suggested.[41]

Donor: surveillance and follow-up

Source, relevant tests, and notices

Either related or unrelated donors are acceptable in Taiwan and other countries.[23,36] Physicians should obtain informed consent from the donors.[39] A potential donor must be less than 65 years old, and have a body mass index < 25 kg/m^2 in Taiwan.[39] In addition, screening for transmissible diseases or factors disturbing the gut microbiota should be conducted with a questionnaire and personal interviews.[23,36] Moreover, comprehensive blood and stool tests are both prerequisites.[23,36] Currently, the TFEC recommends that a donor should be a native Taiwanese who has lived in Taiwan at least one year before donation.[39] However, a residency restriction was not proposed in other guidelines.[23,25,36] In addition to the requisite items in the TFEC,[39] further examinations may be considered for evaluating health conditions (Table 1). The TFEC screening

Table 1 The screening questionnaire and laboratory items for donors: (A) a questionnaire; (B) blood tests and others; and (C) stool examination.

1-(A) Questionnaire	
Items[a]	Exclusion Criteria
Age	≥65 years old
Body mass index	>25 (kg/m^2)
Family history	Two or more first degree relatives with colorectal cancer
Disease	Individuals with catastrophic illness certification issued by the Taiwan NHI
	Hepatitis B virus, hepatitis C virus, HIV-1, HIV-2, syphilis, or tuberculosis
	Pseudomembranous colitis
	Autoimmune disease
	Congenital immunodeficiency disorders
	Congenital metabolic disorders
	Psychiatric conditions
	Chronic pain syndromes
	Neurodegenerative or neurological diseases
Active medical illness (or infection) in the past 3 months	Irritable bowel syndrome, hematochezia or melena, chronic diarrhea, irritable bowel disease, colonic polyposis syndrome, parasitic infection, or liver cirrhosis
Allergy	Asthma, eczema, or food allergy
Constipation	Bowel movements < 3 times per week
Bowel habit changes	Occurrence in the past one month
Travel history	Areas at high risk of transmittable gastrointestinal disease in the past 3 months
Medication in the past 3 months	Antimicrobial therapy, chemotherapy, immunosuppressants, or biological agents
Medication in the past 1 month	Proton pump inhibitors
Medication or food[a] in the past 1 month	Any medication or food known to elicit allergic reactions in the recipient
Illicit drug	Any exposure
Occupation	Working with animals
Medical exposure in the past 6 months	Needle stick accident, blood transfusion, or organ transplantation
Risk behavior in the past 6 months	Ear or body piercing, acupuncture, body tattoo, or high risk sexual activity
Negative personal events in the past 1 month	Alcoholism or imprisonment

1-(B) Blood tests and others		
Items	Cost (NTD)	Turnaround time[c]
Blood tests[b]		
Full blood count	200	1–2 h
White blood cell classification	70	1–2 h
Erythrocyte sedimentation rate	30	2 h
C-reactive protein	275	1 days
Aspartate aminotransferase	50	1–2 h
Alanine aminotransferase	50	1–2 h
Alkaline phosphatase	50	1–2 h
Albumin	40	1–2 h
Bilirubin, total/direct	90	1–2 h
Creatinine	40	1–2 h
Sodium	40	1–2 h
Potassium	40	1–2 h
Calcium	40	1–2 h
Fasting blood glucose	50	1–2 h
Antinuclear antibody	330	7 days
Entamoeba histolytica antibody	320	7 days
HIV screening test (type 1 and 2 antibody)	240	3 days
Syphilis RPR/VDRL	70	3 days
TPHA (PA)	300	7 days
Hepatitis A virus IgM	240	5 days
Hepatitis B surface antigen	160	3 days

Table 1 (*continued*)

1-(B) Blood tests and others		
Items	Cost (NTD)	Turnaround time[c]
Anti-hepatitis B surface antibody	200	3 days
Hepatitis B core antibody	250	5 days
Hepatitis C virus antibody	250	3 days
Human T-cell lymphotropic virus 1 and 2 antibody	400	7 days
Epstein Barr virus IgM	540	7 days
Cytomegalovirus IgM	700	7 days
Toxoplasma IgG	200	7 days
Optional test		
High-density lipoprotein cholesterol (serum)[d]	200	3 h
Low-density lipoprotein cholesterol (serum)[d]	250	3 h
Triglyceride (serum)[d]	120	3 h
Cholesterol, total (serum)[d]	70	3 h
Urine routine and dysmorphic erythrocytes[e]	75	1—2 h
Chest roentgenogram[e]	200	7 days
Electrocardiogram[e]	150	7 days
Abdominal sonography[e]	882	7 days

1-(C) Stool examinations		
Items[b]	Cost (NTD)	Turnaround time[c]
Occult Blood (Guaiac)	20	8 h
Amoeba	50	2 days
Parasite and ova, including *Bloastocystis hominis* and *Giardia lamblia* (microscopy)	50	2 days
Norovirus (polymerase chain reaction)	1200	4 days
Rotavirus (rapid antigen diagnosis)	280	2 days
Adenovirus type 40/41 (rapid antigen diagnosis)	600	4 days
Clostridium difficile culture/or *C. difficile* toxin gene, polymerase chain reaction	200/or 1000	10/or 4 days
Carbapenem-resistant *Enterobacteriaceae* culture	200	5 days
Vancomycin-resistant *Enterococcus* culture		
Salmonella and *Shigella* culture	200	5 days
Campylobacter culture	200	10 days
Vibrio culture	200	5 days
Listeria culture	200	5 days
Yersinia culture	200	5 days
Helicobacter pylori (stool antigen)	200	3—5 days
Optional test		
Pus and erythrocytes[f]	45	2 h

[a] Recommended by the Taiwan Fecal Microbiota Transplantation Expert Consensus,[39] except for food allergens in the recipient.[23,41].
[b] Recommended by the Taiwan Fecal Microbiota Transplantation Expert Consensus,[39] except for the optional tests.
[c] The intervals between the receipt of specimens or test performance and the result reporting is dispatched with verification in the National Cheng Kung University Hospital.
[d] To assess metabolic issues.[36]
[e] Non-invasive screening items for general health assessment.
[f] A screening item for occult gastrointestinal mucosal inflammation.
Abbreviations: HIV, human immunodeficiency virus; IgG, Immunoglobulin G; IgM, immunoglobulin M; NHI, National Health Insurance; NTD, New Taiwan Dollar; RPR/VDRL, rapid plasma regain/venereal disease research laboratory test; TPHA (PA), *Treponema pallidum* hemagglutination assay (particle agglutination assay).
Tests were priced on the basis of the Taiwan National Health Insurance system from June, 2019, except for two items that were not covered by the system (adenovirus type 40/41 and *Helicobacter pylori* stool antigen).

items need to be conducted and tested repeatedly or by alternative methods for uncertain results. Similarly, for possible latent infections, when a potential donor undergoes screening blood tests, a blood sample should be kept until six months after the FMT.

Process of donation and follow-up after donation

If the donor is considered a qualified candidate, the stool donation should be conducted within 4 weeks.[25] An interview on the day of the donation should be conducted to

check for potentially health issues with recently onset.[25] The donor's stool should be processed within 6 h of defecation.[23] Besides, the donor is asked to be interviewed again 1–2 months after the stool donation. If there are any suspicious ailments noted during follow-up, further examinations and surveillance are mandatory.[23] If the eligible donor is willing to donate stool again, the screening process shall be conducted at least every 4 months (Fig. 1).[23]

Recipient: treatment and follow-up

Indications, required records, and preparation before transplantation

In Taiwan, the current indication for FMT is recurrent or refractory CDI (Fig. 2).[39] Infectious disease physicians should be consulted for the diagnosis of recurrent or refractory CDI.[23] The decision that a patient with CDI necessitates FMT mainly depends on three factors: the number of recurrences, disease severity, and refractory to antibiotic treatment status.[24,36] All cases scheduled for FMT are requested to register online in a national registry system of the National Health Research Institute.[39] The medical records should include basic characteristics of the recipient, indication (recurrent or refractory CDI), and relevant treatment courses.[39] Regarding basic characteristics, it is necessary to record anthropometrical characteristics, past history, allergies, recent exposure to drugs affecting FMT, laboratory data, and treatment courses of CDI.[24,25]

Because it is usually difficult to distinguish FMT-related adverse events from the progression of underlying diseases,[24] physicians may consider the storage of blood and stool samples from the recipient before FMT. Furthermore, a list of health evaluations for relatively immunocompromised patients is suggested based on the discretion of the attending physician (Supplemental Table 1). More steps for recipient preparation include prior antibiotics (delivery and cessation), bowel lavage, and adjuvant medications (Fig. 3).[25,36,41]

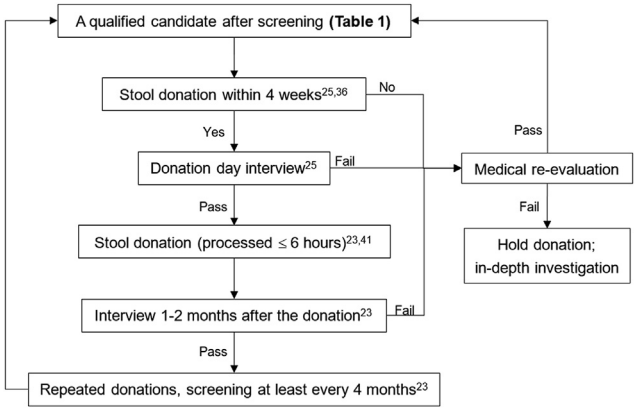

Figure 1. Process of stool donation. The optimal fecal donation time is within 4 weeks after the evaluation of an eligible donor. The recent onset of potentially harmful events must be evaluated on the same day of donation and one to two months later. If there is a concern, fecal donation or usage of the donated material should be postponed until the concern is resolved. A superscript number indicates the cited reference in the text.

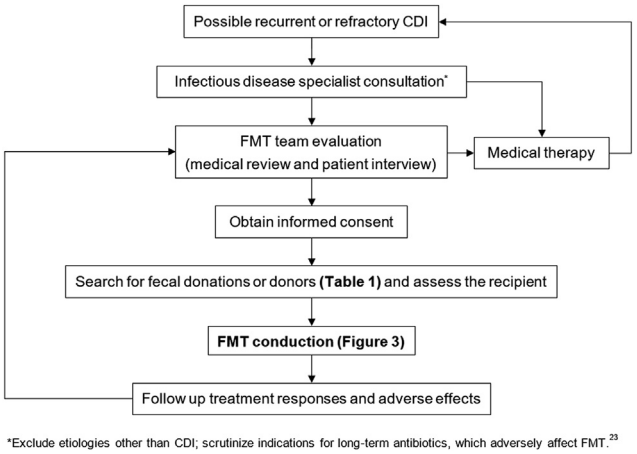

Figure 2. Fecal microbiota transplantation (FMT) for *Clostridium difficile* infection (CDI): from evaluation of recipient to post-FMT follow-up. An infectious disease physician should be consulted to confirm the indication. Once FMT is considered, the FMT team must assess the clinical condition thoroughly for the need for FMT. Informed consent is required for FMT. Post- FMT monitoring for adverse effects is mandatory. A superscript number indicates the cited reference in the text.

Follow-up after transplantation

The medical record must include the date, location, treatment schedule, working staff, colon preparation, related devices, and procedures.[39] The definition of cure, remission, failure, or recurrence of CDI has not yet been unified in the current guidelines, and should be decided individually.[23]

During the follow-up, the definitions of FMT-related events are established (Fig. 2).[25,36,41] CDI-related diarrhea was defined as ≥3 unformed stools (Bristol stool scale type 6 or 7) in 24 h with the presence of *C. difficile* toxin or toxigenic *C. difficile* in the stool, without other explanations for the diarrhea.[19,28] Rapid treatment response (initial remission) refers to the resolution of CDI-related diarrhea by day 5 after FMT.[19,23,42] Initial treatment failure is defined as unresolved diarrhea and a worsening clinical condition within five days after FMT, and repeated FMT is recommended for persistent CDI.[23] Sustained treatment response (cure) was defined as resolution of CDI related diarrhea ≥8 weeks after FMT.[28,42] If diarrhea recurs with evidence of *C. difficile* toxin or toxigenic *C. difficile* in the stool without other possible causes, recurrence (onset after >5 days but <8 weeks following FMT, whether the same *C. difficile* strain or not) is then defined. Recurrence may be due to either relapse (onset after >5 days following FMT, the same *C. difficile* strain) or reinfection (onset after >5 days following FMT, a new *C. difficile* strain).[19,28,30,42] Nevertheless, it is not always possible to clinically distinguish between CDI relapse and reinfection.[25] Repeated FMT is also considered for recurrent infections.[23] After FMT, clinicians should follow the recipients for at least one year,

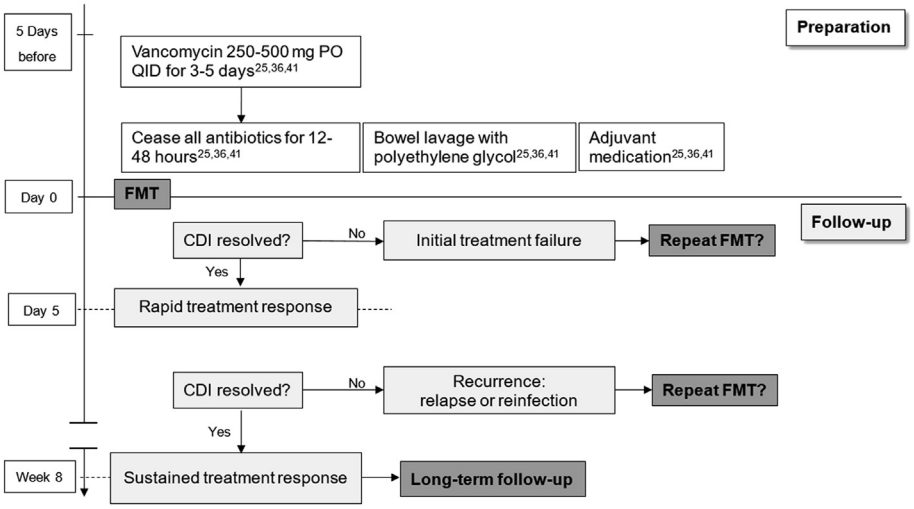

Figure 3. Fecal microbiota transplantation (FMT): from preparation of recipient to follow-up. Before FMT, antibiotic therapy for *Clostridium difficile* infection (CDI), such as oral vancomycin for at least 3 days following a half-to 2-day washout period, is suggested. Additionally, bowel lavage before FMT to reduce residual antibiotics and spores and toxins of *Clostridium difficile* in the bowel, irrespective of the delivery route, should be considered. Additionally, adjuvant medication, such as proton pump inhibitors (the evening before and the morning of FMT) and prokinetics (metoclopramide before FMT) for the upper gastrointestinal route or antimotility drugs (loperamide once after FMT) for the lower gastrointestinal route, should be considered. After the first FMT, initial treatment failure or recurrence can be managed by additional FMT(s) within three days and/or every three days until the resolution of symptoms. For those who do not respond to repeated FMT, FMT with interval vancomycin therapy is an alternative choice. A superscript number indicates the cited reference in the text.

according to the TFEC.[39] Short-term or long-term adverse events, especially severe ones, must be well documented.[25,31]

Process of transplantation and supervision and management of relevant adverse events

Process of transplantation

The administration of FMT should be guided by a qualified gastroenterologist through the LGI tract via either an anal tube or colonoscopy or the UGI tract via EGD with or without nasoduodenal (nasojejunal) tube insertion.[23,25] When endoscopy is involved, standard operation guidelines and high-level disinfection of used endoscopy equipment should be complied with.[23,25]

With variable routes of delivery, different amounts of feces and recommended retention times are introduced.[41] Up to 500 mL of fecal preparation in a disposable enema bag is suggested and the recipients have to retain the enema for least 2 h.[41] With 50 mL syringes, 300 mL fecal material can be delivered by colonoscopy, but the retention time has not yet been well defined.[23,41] Nonetheless, some articles suggest that the patient should retain the donated material for at least one to 4 h and be placed on bedrest until the next day after colonoscopy.[36,40]

For the UGI route, *i.e.*, a nasoduodenal (nasojejunal) tube, the rate of infusion is limited to 50 mL over 2 min, and the total amount of infused fecal material is 250—500 mL.[41] However, another guideline recommends no more than 100 mL be administered through the UGI route and the route should be avoided in those at risk of regurgitation or with swallowing disorders.[23] Proton pump inhibitors can be considered the night before or two to 3 h before FMT to decrease the effects of gastric acid.[41]

Adverse events: general conditions

Short-term (within 30 days) adverse events, such as nausea, belching, abdominal cramping pain or discomfort, and diarrhea, are mostly mild and self-limiting.[23,25,31,38] Major adverse events, such as aspiration in the case of EGD or bowel perforation in colonoscopy, are often related to the procedure.[23] Therefore, close monitoring after FMT is vital.

FMT-associated death mainly results from aspiration, pneumonia, and peritonitis; the mortality rate following FMT was 3.5% (38/1089).[23,31] One systematic review reported that the mortality rate was 4.1% (13/317) due to any cause and 1.3% (4/317) due to treatment conditions.[30] Similarly, in another review, three deaths (0.26%, 3/1174) were attributed to FMT itself, and 41 deaths (3.5%, 41/1174) were not attributed to FMT.[43] Therefore, most of the deaths following FMT were related to underlying diseases, such as malignancy, heart disease, or pulmonary disease.[43]

Long-term ($\leq$2 years reported by doctors and 10 years reported by patients) adverse events were seldom reported.[38] One study followed 77 post-colonoscopic FMT patients for a mean of 17 months and indicated that no adverse effect was attributable to the therapy.[26] Another study reported that 113 of 137 (82%) patients had a durable cure of CDI at a median follow-up of 22 months, and none of the 26 (19%) deaths arose from FMT itself. Additionally, the

most common cause of mortality stemmed from metastatic cancer (34.6%, 9/26), followed by heart failure, respiratory failure, or chronic kidney disease.[44]

Adverse events: supervision and management

The best solution to adverse events is prevention, including the avoidance of risky procedures in specific patients, prudent assessment of the diagnosis and severity of CDI, and preemptive screening of the donors and recipients before and after FMT.[25] Notably, there are five major issues worthy of attention: the procedure, gastrointestinal complications, infection (CDI recurrence or others), inflammation (fever of unknown cause), and IBD flare-up.[31,43]

First, of the procedural-related complications, aspiration should be monitored during sedation or with the UGI routes, especially in elderly patients or those with severe ileus.[23,43] Complications of colonoscopy, including mucosal tears or even perforation, are another issue.[31,43] The endoscopist must avoid over-inflation or consider carbon dioxide instead of ambient air during the colonoscopy. When insertion is difficult, alternative methods, such as sigmoidoscopy or an enema, must be taken into consideration.[25] Second, gastrointestinal complications, such as diarrhea within 12 h after FMT, are common but often mild and self-limiting.[45] Bloating, nausea, abdominal cramping or pain, ileus, and constipation have all been reported.[43] Because most of them subside and improve spontaneously or with medicine, good communication with the patients before FMT followed by close surveillance is essential.[25]

Third, infection after FMT should be distinguished as CDI or a non-CDI-related event, because a repeated FMT is recommended for refractory CDI.[23,45] In Taiwan, intestinal pathogens other than *C. difficile*, such as norovirus and *Campylobacter* species, are common etiologies of acute diarrhea in the community.[46] Besides, epidemiological studies regarding gastroenteritis in Taiwan also reported *Salmonella* species in young children and enterotoxigenic *Bacteroides fragilis* in senior patients.[47,48] Therefore, transmittable diseases should be actively surveyed before FMT not only in the donors but also in the recipients. Notably, the United States Food and Drug Administration in June 13, 2019 issued an alarm pertaining to FMT-related death of an immunocompromised patient because of invasive infection due to extended-spectrum beta-lactamase-producing *Escherichia coli*.[49] The agency has asked for additional testing of multi-drug resistant organisms in donors' feces and physicians must inform FMT recipients of the potential risks.[49] Healthcare personnel need to scrutinize symptoms or signs of infection and conduct proper surveys in the recipients.

Fourth, inflammation, especially fever of unknown cause, should be considered, though most patients presented febrile illness without other events.[43] Although most inflammatory events are trivial and subside spontaneously, active infectious events should be considered in those with cirrhosis or who are immunocompromised until infection can be excluded.[43] Finally, an exacerbation of IBD has been reported, but the mechanism remains unclear.[31,43] Therefore, whether a patient with IBD and CDI simultaneously can receive FMT should be considered on a case-by-case basis, and close monitoring is mandatory.[23]

Unmet needs

There are several concerns when a physician considers FMT for CDI in Taiwan. First, the TFEC does not limit FMT to adults (≥18 years old).[39] Although the majority of clinical evidence comes from adults and most guidelines have no recommendations for young people,[19,23,24] some recent evidence has supported FMT in children with CDI.[50,51] Second, the resolution rate of CDI in recurrent cases was higher and more consistent than that of refractory cases.[27] In addition, one review regarding recurrent CDI mentioned significantly lower cure rates in randomized trials (67.7%) than in open-label studies (82.7%).[52] These findings imply high heterogeneity among the recruited patients in previous studies. In some renowned randomized control trials, immunocompromised patients were excluded, such as those who underwent recent chemotherapy, those with human immunodeficiency virus infection, those with critical illness in intensive care units, those receiving long-term steroid therapy, and those undergoing treatment with antibiotics other than metronidazole, vancomycin or fidaxomicin.[28,45] Some systematic reviews also mentioned that uncontrolled case-series studies dominated, and many studies lacked eligibility criteria for donors and the details of processing.[27,53] Third, since existing evidence of the details of FMT has not been robust, current recommendations have been derived mostly from experts' opinions.[23] Further studies are warranted. Finally, long-term outcomes of altered gut microbiota, such as the effects on metabolic diseases or cancers, remain unclear. More longitudinal microbiota data in patients receiving FMT are crucial to make a convincing argument.[24]

Conclusion

In summary, FMT for recurrent or refractory CDI is effective and feasible. With the advance to an "aged society" in Taiwan, the incidence of CDI will be increasing because of advanced age and associated comorbidities. Therefore, it is time to establish multidisciplinary teams for the implementation of FMT in dedicated hospitals in Taiwan. Additionally, although FMT has been demonstrated as safe, physicians still need to be aware of adverse events after FMT. Further thorough research regarding the improvement of cure rates in aged populations with different comorbidities and active surveillance of long-term outcomes after FMT is warranted.

Compliance with ethical standards

The research was conducted according to the principles of the Declaration of Helsinki.

Statement of interests

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2019.08.009.