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Factors Associated with FMT Failure in *Clostridioides difficile* Infection and Age-Related Considerations: A Review

Khaeru Irgi*, Ahsanal Kasasiah, Agustina Rusmayanti

Department of Pharmacy, Faculty of Health Sciences, University of Singaperbangsa Karawang, Karawang, Indonesia
*e-mail: 2310631210034@student.unsika.ac.id

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Abstract: *Clostridioides difficile* infection (CDI) is a major cause of nosocomial diarrhea worldwide, and limitations of standard antibiotic therapy have driven the adoption of fecal microbiota transplantation (FMT) as an alternative therapeutic approach. Although FMT achieves clinical success in most patients, treatment failure still occurs in a considerable proportion of cases. Existing literature has examined overall FMT efficacy, yet no review has comprehensively synthesized the multifactorial determinants of FMT failure while incorporating age-related considerations. This narrative review provides an integrative overview of factors contributing to FMT failure in adults with CDI. A literature search of PubMed and Google Scholar identified original research articles published between 2015 and 2025. Evidence indicates that FMT failure is influenced by host-related factors such as comorbidities, immune function, and nutritional status; disease-related characteristics, including CDI severity and recurrence history; technical aspects, such as bowel preparation, donor type, and route of administration; and pharmacological factors, including antibiotic exposure before or after the procedure. These factors collectively affect donor microbiota engraftment and increase the risk of therapeutic failure. Age-related physiological and microbiome changes may additionally modify treatment responses. This review highlights the need for comprehensive patient assessment, standardized procedural protocols, and careful post-FMT monitoring. Addressing current evidence gaps and improving clinical guidance will be essential for optimizing the safety and effectiveness of FMT across different adult age groups.

Keywords: Aged; *Clostridioides difficile* Infection; Fecal Microbiota Transplant; Risk Factors.

Introduction

Clostridioides difficile infection (CDI) is a leading cause of nosocomial diarrhea, with particularly high incidence among the adult population in worldwide. According to the Global Burden of Disease (GBD) analysis, in 2021 CDI accounted for approximately 15,598 deaths and 284,051 disability-adjusted life years (DALYs), with the greatest burden observed in older adults, especially those aged ≥80 years, and this trend is projected to continue rising through 2040. These data underscore CDI as a major global public health concern, with the heaviest burden in high-income countries and among the aging population [1].

In Asia, awareness and surveillance of CDI have remained poor, and epidemiological data across the region are still limited. Although limited studies over the past decade suggest that CDI represents a significant cause of nosocomial diarrhea in several Asian healthcare settings, systematic testing and reporting remain inconsistent. Consequently, the actual burden and distribution of CDI in many Asian countries are still uncertain, and its true prevalence remains largely unknown [2].

It is similar to the data from Indonesia, which remains very limited. A study conducted in several hospitals in Central Java reported that, among 340 patients with diarrhea, 15% were GDH-positive/toxin-negative, with 5.6% confirmed as toxin-positive. These findings indicate a considerable burden of CDI, although the majority of patients were colonized without developing clinical symptoms. Limited diagnostic facilities and the lack of routine testing for toxins A/B in diarrheal patients are likely major contributors to the underreporting phenomenon in Indonesia [3].

Cases of CDI among the older adults in developing countries, including Indonesia, are rarely reported compared to those from developed countries. This can be explained by the phenomenon of underreporting in developing countries, which is influenced by several factors. First, there are diagnostic limitations, like toxin assays or PCR testing for CDI have not yet been implemented as routine examinations in many hospitals [4]. Second, low clinical awareness remains a major barrier to CDI recognition; many episodes go undiagnosed because clinicians often fail to suspect the infection in patients with diarrhea [5]. Clinical judgment, therefore, plays a crucial role in determining when to test patients with diarrhea to avoid missed cases. Low clinical awareness means that in older adult, diarrhea is often attributed to chronic comorbidities or medication use (such as antibiotics and proton-pump inhibitors), rather than prompting consideration of CDI [6]. The combination of these factors suggests that the true incidence of CDI among the elderly in Indonesia is likely higher than currently reported. Although national data remain limited, studies from neighbouring Southeast Asian countries have shown that low clinical awareness often leads to misattribution of diarrhea in older adults to comorbidities or medication use rather than recognizing it as a manifestation of CDI [7].

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In the elderly population, gut microbiota diversity declines with advancing age. Aging is associated with reduced diversity and stability of the gut microbial community (age-related dysbiosis), which weakens colonization resistance against pathogens, including CDI [8]. In cohort studies of older adults with recurrent CDI (rCDI) receiving Fecal Microbiota Transplantation (FMT), clinical effectiveness remained high; however, the recovery of microbiota composition and diversity after FMT appeared less robust compared to younger populations, suggesting that age-related changes may influence donor microbiota engraftment [9].

Common factors such as polypharmacy (e.g., antibiotics, PPIs), comorbidities, and recurrent hospitalizations further exacerbate dysbiosis and impair engraftment following FMT in older adults. This is consistent with findings from several studies on predictors of FMT failure, where CDI severity, inpatient status, and prior hospitalization were shown to increase the risk of therapeutic failure in elderly patients with chronic dysbiosis [10], [11], [12], [13].

Another important factor contributing to FMT failure is prior or concomitant antibiotic exposure, which has been observed in several cases to be associated with reduced treatment success and higher recurrence rates [14]. Studies have shown that FMT failure is prior or concomitant antibiotic exposure, which, although intended to reduce *C. difficile* burden, can simultaneously disrupt donor microbial engraftment and host protective microbiota, thereby increasing the risk of recurrence [15].

Conventional antibiotic therapy for CDI is often insufficient in older adults, particularly in cases refractory to standard regimens. The limited efficacy of such treatment and moderate cure rate highlight the urgent need for alternative approaches such as FMT [16]. In this context, FMT has emerged as an innovative treatment. In the United States, the Food and Drug Administration (FDA) has approved standardized microbiota-based products REBYOTA (2022) and VOWST (2023) for the prevention of CDI recurrence following completion of antibiotic therapy. These approvals represent a significant milestone in promoting the standardization of FMT procedures, including donor screening, product quality, and patient safety [17], [18].

In terms of effectiveness, clinical evidence from multiple studies has demonstrated that FMT achieves a success rate of 80–90% in patients with CDI, including those in elderly populations. Nevertheless, approximately 10–31% of patients experience treatment failure. Factors contributing to such failure include CDI severity, inpatient status during the procedure, history of recurrent hospitalizations, comorbidity burden, quality of bowel preparation, post-FMT antibiotic exposure, and donor source [10], [11], [13], [19].

Although FMT has been recognized as an effective therapy with cure rates of 80–90% in patients with CDI, evidence from multiple studies indicates that approximately 20% of patients experience treatment failure. This proportion of failure cannot be overlooked, particularly among elderly populations who are more vulnerable due to age-related alterations in the gut microbiota, a high burden of comorbidities, and repeated exposure to antibiotics and hospitalizations [9], [11], [13].

However, despite several reviews on FMT efficacy, none have specifically synthesized the multifactorial causes of treatment failure in patients with CDI while incorporating age-related considerations. This review aims to address this research gap by examining factors that may influence FMT outcomes across adults with CDI and considering how age-related characteristics may modify these associations. These factors are reviewed from several perspectives, including clinical aspects such as CDI severity, comorbidity burden, and history of hospitalization, technical factors such as the route of administration, bowel preparation, and donor source, and pharmacological considerations such as antibiotic use before or after the procedure. By examining the current limitations of available evidence, this review aims to provide guidance for future research and the development of more targeted clinical guidelines, thereby facilitating the optimal use of FMT in managing CDI.

Research Methods

The narrative review approach in this article follows the method used by Phenwan et al. [20] with modifications. The PEO framework was applied to structure the review question and guide the selection of eligible studies. A PRISMA-style flow diagram (Figure 1) was used to present the screening process in a transparent manner. A narrative design was considered appropriate because the determinants of FMT failure involve heterogeneous clinical and methodological characteristics that cannot be examined adequately through a strictly systematic approach.

A comprehensive literature search was conducted in reputable international databases, including PubMed and Google Scholar, covering publications from 2015 to 2025. The search strategy incorporated combinations of the following keywords: fecal microbiota transplantation, *Clostridioides difficile* infection, elderly, risk factors, and treatment failure. All retrieved records underwent title and abstract screening, followed by full-text evaluation when required. The inclusion criteria consisted of original research articles published in English that investigated the effectiveness or failure of FMT in patients with CDI. Commentaries, editorials, and review articles were excluded. Duplicate removal, staged screening, and predefined PEO criteria were applied to enhance the robustness of the selection process. No formal risk of bias assessment was performed due to the heterogeneity of study designs.

The initial search identified 373 articles. After title screening, exclusion of duplicates, abstract evaluation, and final assessment using the PEO criteria, 10 studies met the eligibility requirements and were included in the final synthesis. These articles were then evaluated for consistency with the PEO framework. The outcomes of this evaluation are summarised in Table 1.

Table 1. Inclusion criteria based on PEO elements

Parameter	Inclusion	Exclusion
Population	Articles that investigate patients with CDI who receive FMT therapy.	Articles that do not involve patients with CDI or patients who did not receive FMT therapy.

Exposure	Articles that examine factors related to FMT failure in adult CDI patients.	Articles that do not assess risk factors or factors associated with FMT failure.
Outcome	Articles that report data on FMT failure in adult CDI patients and provide information regarding predictors of failure.	Articles that do not report FMT failure or only assess success without information related to failure.
Language	Articles written in English.	Articles written in languages other than English.
Publication Year	Articles published between 2015 and 2025.	Articles published before 2015.

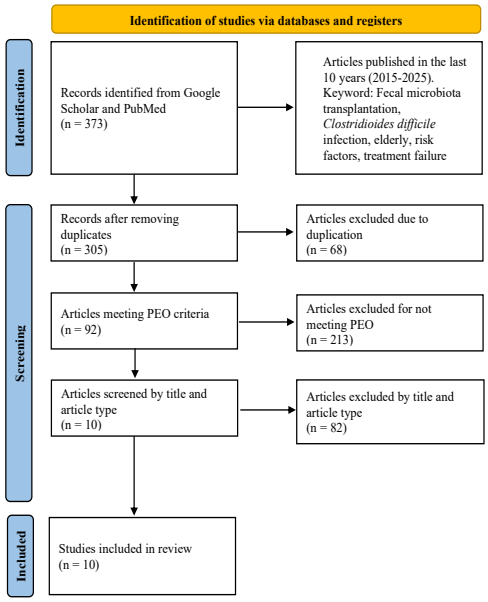

Figure 1. PRISMA diagram

Results and Discussion

Results from several studies that summarizes the failure rates of FMT reported across various clinical studies, along with predictive factors particularly relevant to patients with CDI (Table 2). The data indicate that while FMT demonstrates overall high effectiveness, a substantial proportion of patients, ranging from approximately 12% to over 31% experience treatment failure. Factors consistently associated with these failures include advanced age, comorbidity burden, hospitalization status, poor bowel preparation, antibiotic exposure, and donor source. These findings underscore the multifaceted nature of FMT outcomes and the importance of meticulous patient stratification in elderly populations.

Overall, these factors indicate that FMT can fail for various reasons. Failure is not typically caused by a single problem, but rather by a combination of issues related to the patient, the disease, the procedure itself, and even the use of antibiotics. This means that treating patients, especially the elderly, requires careful planning, good preparation, and close follow-up to make sure the treatment works as well as possible [12], [15].

FMT is generally effective for treating CDI, and many patients show clear clinical improvement after the procedure. However, treatment failure still occurs in a notable number of cases across adult populations [13]. These failures are rarely due to a single cause but often result from a combination of patient-related, disease-related, and procedural factors. Advanced age, comorbidities such as diabetes, and the use of antibiotics around the time of transplantation have all been identified as major contributors to reduced engraftment of donor microbiota [16]. These factors highlight that successful FMT depends on patient, adequate preparation, and careful post-procedure monitoring to prevent recurrence and maximize therapeutic success [15].

Table 2. Reported FMT Failure Rates and Associated Factors in Elderly Populations

Source	FMT Failure Rate	Predictive Factors Relevant to the Elderly
Ianiro et al. [13].	31% failure	Severe CDI, suboptimal bowel preparation
Fischer et al. [11].	18.6% failure	Severe/complicated CDI, hospitalization, history of prior hospitalization
Meighani et al. [21].	12.4% failure	Female sex, prior hospitalization, and surgery before FMT
Peri et al. [19].	20.2% failure at Day 30 21.9% at Day 90	Older age with comorbidity
Kachlíková et al. [10].	25% failure	Charlson Comorbidity Index (CCI) ≥7, low albumin
Watts et al. [22].	12.7% failure	Family donors are associated with a higher risk than stool bank donors
Park et al. [23].	32.3% failure	Antibiotic use post-FMT, advanced age, high CCI
Warraich et al. [12].	27% failure	Active malignancy, repeated hospitalizations, and non-CDI antibiotics
Allegretti et al. [24].	25% failed after a single FMT 4.8% failed after the second FMT (evaluated within 8 weeks)	Inpatient status at first FMT, pseudomembranes, and immunocompromised state
Nguyen et al. [15].	24.6% failure within 1 year	Age ≥70,4 ≥ CDI episodes, diabetes mellitus

Compared to younger adult patients, elderly individuals show similar clinical outcomes in terms of improvement of primary symptoms such as diarrhea, abdominal pain, and bloating [9]. However, their response to therapy appears more gradual, and the restoration of gut microbiota composition after FMT shows a slower and less

stable pattern than in younger hosts. Experimental evidence indicates that although microbiota transfer from young to aged recipients can reverse several age-associated features, microbial reconstitution in older hosts remains partial and shaped by age-related gut conditions [25]. In terms of safety, FMT is generally well tolerated in older adults. In high-risk elderly populations, it has been shown to be a safe and effective option for treating CDI [26]. Even during long-term follow-up, recurrence of CDI or severe complications was not observed, indicating that the procedure remains safe even in this more vulnerable population [9].

The effectiveness of FMT in treating CDI depends on more than the technical success of the procedure itself. Host-related factors also play a decisive role, particularly in older adults, where multiple comorbidities, immune decline, and nutritional limitations can reduce treatment response [9]. These underlying conditions help explain why, despite FMT's generally high success rate, a portion of patients still experience therapeutic failure [26]. One contributing aspect involves the following interrelated factors that influence treatment outcomes.

Age-Related Determinants of FMT Failure

Advanced age is a strong predictor of FMT failure. Several studies have shown that the older the patient, the higher the risk of treatment failure. Some studies report that each additional year of age is associated with an increased risk of FMT failure (OR 1.06; p=0.001) [19]. Similar results were found in another study that found that patients aged ≥70 years had a 2.66 times higher risk of failure compared to younger patients [15].

Biologically, this association can be explained by the phenomenon of age-related dysbiosis, characterized by a progressive decline in gut microbiota diversity and compositional stability with advancing age. As individuals grow older, both chronological and biological aging are associated with reduced microbial richness and loss of beneficial commensal species, which may impair gut resilience and increase susceptibility to treatment failure in elderly patients [27]. Although donor age influences the composition of the gut microbiota, particularly with a reduction in beneficial taxa such as *Bifidobacteriaceae* among older donors [28]. Elderly patients tend to show an increased relative abundance of *Proteobacteria* and a reduction in *Firmicutes*, reflecting an age-related dysbiosis in gut microbial composition [8]. This suggests that donor microbiota engraftment is less robust in older adults, making them more vulnerable to long-term failure after FMT [9].

In addition, elderly patients are more frequently exposed to antibiotics, are more likely to reside in long-term care facilities, and often undergo repeated hospitalizations. These factors further disrupt the gut microbial community and reduce the body's ability to maintain colonization resistance against *C. difficile*. Therefore, advanced age should not be viewed merely as a numerical variable, but rather as a reflection of complex biological and clinical conditions that increase the likelihood of FMT failure [23].

The Role of Comorbidities in FMT Failure

Comorbidities represent another important host-related factor associated with FMT failure. The Charlson Comorbidity Index (CCI) is commonly used to evaluate the overall impact of chronic diseases. Patients with a CCI score of ≥7 are at a significantly higher risk of failure after FMT, with reported failure rates reaching up to 25% in this group. This is largely because higher CCI scores indicate more severe chronic conditions that may weaken immune function, increase the need for antibiotics, or disrupt the intestinal environment [10].

Among these comorbidities, diabetes mellitus is one of the most prominent. Diabetes has been shown to nearly triple the risk of FMT failure (OR 2.82) [15]. The underlying mechanisms are thought to involve chronic hyperglycemia, which shifts gut microbiota composition toward a pro-inflammatory state and increases intestinal permeability [29], [30]. In other words, diabetes creates a biological environment that does not support the successful engraftment of donor microbiota [15].

In addition to diabetes, several other comorbidities have also been reported to contribute to FMT failure. Patients with active malignancies exhibit a higher risk of treatment failure (RR 2.56), as do those with a history of repeated hospitalizations due to CDI (RR 2.42) [12]. Furthermore, patients who have undergone prior surgery are more vulnerable to FMT failure, possibly due to alterations in gut anatomy and microbial colonization following surgical procedures [21].

Impact of Immune Status on FMT Efficacy

In patients with immunosuppression, donor microbiota engraftment encounters significant barriers [31]. Elderly individuals frequently experience age-related immune decline, a phenomenon known as immunosenescence. This condition is characterized by weakened T-cell responses, reduced phagocytic function, and decreased mucosal immunoglobulin A production [32], [33]. Immunosenescence creates a state in which the host can no longer effectively regulate microbial community balance, preventing donor microbiota introduced via FMT from establishing and stabilizing. This phenomenon partly explains why the rate of FMT failure is higher among older patients [31].

Beyond natural age-related changes, immunosuppression may also be pathological or iatrogenic. The success of FMT in humans relies heavily on the integrity of adaptive immune responses that regulate microbial colonization and mucosal homeostasis. Clinical and translational evidence suggests that when adaptive immunity, particularly regulatory T-cell activity, is compromised, donor microbiota fail to establish durable colonization, leading to persistent dysbiosis and intestinal inflammation [31]. In immunocompromised patients, such as hematopoietic stem-cell transplant recipients, FMT initially induces a donor-like microbiota profile, but this similarity declines over time, indicating that host immune dysregulation and post-transplant inflammatory environments impede long-term microbial stability [34]. In such individuals, immune suppression, prior antibiotic exposure, and chronic inflammation reduce microbial resilience, resulting in incomplete engraftment and limited clinical improvement [35].

Patients undergoing immunosuppressive therapy face similar risks. Long-term corticosteroid use, chemotherapy

agents, and biologic therapies such as anti-TNF suppress immune activity and increase susceptibility to opportunistic infections [36]. In immunocompromised patients, the use of immunosuppressive agents such as long-term corticosteroids, chemotherapy, and anti-TNF biologics suppresses adaptive immune activity, leaving the body more vulnerable to opportunistic infections. This heightened susceptibility often necessitates the use of non-CDI antibiotics to manage secondary infections. However, such additional antibiotic exposure can hinder the success of FMT by disrupting the engraftment and stability of the newly transplanted donor microbial community [37]. For these reasons, strict control of antibiotic use in this vulnerable population represents a key strategy for improving the long-term success of FMT [12].

Nutritional Deficiency and Its Impact on FMT Outcomes

Beyond immune status, nutritional condition has a significant influence on the outcomes of FMT. Malnutrition, particularly among the elderly, is a common condition that leads to structural and functional deterioration of the intestinal mucosa. In older adults, reduced mesenteric perfusion and atherosclerosis contribute to compromised intestinal integrity, impairing nutrient absorption and barrier function [38]. Experimental studies confirm that protein-energy malnutrition induces villous atrophy, loosens tight junctions, and reduces intestinal mucus, weakening mucosal defence [39]. In murine models, protein-energy deficiency was found to markedly decrease mucosal immunoglobulin A secretion by suppressing polymeric IgA receptor expression, thereby weakening the first line of mucosal defence [40]. Consequently, this diminished mucosal barrier integrity may hinder the engraftment and persistence of donor microbiota following FMT. Serum albumin level is a key biomarker of nutritional and systemic health, and hypoalbuminemia has been associated with poorer FMT outcomes, reflecting both malnutrition and chronic inflammation that impair host immune and intestinal resilience [41]. In addition, clinical data demonstrate that low serum albumin is a strong, independent predictor of infection recurrence, complications, and one-year mortality in CDI, a condition closely linked to the indication for FMT. In that cohort study, patients with serum albumin <33.1 g/L had a 56% sensitivity and 80% specificity for predicting 90-day recurrence of infection, while levels <29.2 g/L predicted one-year mortality, underscoring the role of albumin as both a nutritional and inflammatory marker. Under such conditions, hypoalbuminemia has been associated with poorer FMT outcomes. Hypoalbuminemia is a known risk factor for developing rCDI after treatment with standard antibiotic therapy [42].

From a metabolic perspective, malnutrition also reduces the availability of substrates essential for the growth of healthy microbes. For example, elderly individuals with low dietary fiber intake produce limited amounts of short-chain fatty acids (SCFA). SCFAs, such as butyrate, are critical for colonic health because they provide the main energy source for colonocytes and help maintain an anaerobic environment that favors protective bacteria. A deficiency of SCFA disrupts the engraftment of donor microbiota [43], [44]. The combination of these nutritional factors creates conditions in the intestine that are unfavorable for long-term donor microbiota engraftment. As a result, elderly patients with multiple comorbidities and poor nutritional status often require repeated FMT procedures, and in some cases may fail to respond at all, even when the procedure is performed under optimal standards.

The Role of Disease Severity as a Factor in FMT Outcomes

Several studies have confirmed that severe or fulminant CDI is associated with a significantly increased risk of FMT failure. Patients presenting with fulminant disease and extensive pseudomembranes often exhibit poor response to a single FMT and require multiple sequential procedures to achieve cure, indicating that disease severity substantially reduces initial FMT efficacy [45]. Furthermore, cohort data indicate that disease severity strongly influences FMT outcomes, with cure rates decreasing from 100% in severe CDI to 87% in severe-complicated or fulminant cases, underscoring that fulminant infection is an independent predictor of FMT failure [46].

Fulminant CDI presents major therapeutic challenges, as many patients fail to respond adequately to a single FMT [13]. In clinical observations, approximately one-third of fulminant cases required subsequent colectomy because of inadequate response after the first FMT, even though the overall 30 day mortality in the FMT-only group was notably lower than in those treated with colectomy or combined therapy. The median number of FMTs administered among fulminant cases was two, emphasizing that repeated administration is often necessary to achieve clinical resolution, since single-dose treatment is frequently insufficient to prevent recurrence [47].

Prior Infection as a Contributing Factor

rCDI history is among the strongest predictors of FMT efficacy. The greater the number of recurrence episodes a patient has experienced, the higher the risk of FMT failure [11], [24]. Patients with multiple recurrences are more likely to fail after FMT compared to those undergoing the procedure at their first or second recurrence [11].

Patients with ≥4 episodes of rCDI exhibit higher failure rates than those with fewer recurrences. This suggests that the more frequent the relapses, the more severe the damage to the diversity and stability of the gut microbiota, making healthy flora transplantation increasingly difficult. Several studies reinforce this evidence, reporting that patients with ≥4 recurrences have nearly double the failure rate compared to those with fewer relapses [15].

rCDI is characterized by progressive disruption of intestinal microbial homeostasis. Each relapse following antibiotic therapy further decreases microbial diversity and colonization resistance. The cumulative effect of repeated antibiotic exposure is a chronically dysbiotic gut environment that undermines donor microbiota engraftment during FMT. In a clinical cohort, the recurrence rate after FMT increased from 5.25 to 27.3 percent across successive infection episodes, indicating that recurrent disease diminishes FMT efficacy [48]. In addition to recurrence-driven dysbiosis, other microbial perturbations can also compromise FMT outcomes. Gut fungal overgrowth,

particularly of *Candida albicans*, has been shown to correlate with reduced donor engraftment and lower cure rates in both humans and experimental models of CDI. A high fungal burden in either the donor or recipient stool decreases FMT efficacy, whereas antifungal intervention restores the response, supporting a causal role for fungal dysbiosis in treatment failure [49].

Antibiotic exposure profoundly alters intestinal microbial metabolism, leading to functional impairment of bile acid transformation and SCFA synthesis that normally sustain mucosal integrity and immune regulation. The disruption of bile acid deconjugation and 7α-dehydroxylation pathways, while the decline in secondary bile acids diminishes inhibitory signalling against vegetative growth. Concurrently, reduced SCFA production weakens epithelial barrier function and promotes a pro-inflammatory luminal environment [50].

A history of CDI is an important factor influencing the outcomes of FMT. Prior CDI-related hospitalizations and recent antibiotic exposure have been associated with higher rates of FMT failure, reflecting the cumulative disease burden and microbial disruption preceding treatment [11]. Patients with repeated hospital admissions for CDI are more likely to have persistent dysbiosis and impaired intestinal recovery, while recurrent antibiotic therapy further depletes microbial diversity and delays donor microbiota engraftment. These indicate that hospitalization history and antimicrobial exposure serve as indirect markers of prior infection severity and may adversely affect the likelihood of successful FMT outcomes [24].

Bowel Preparation Prior to FMT

One of the most influential technical aspects determining the success of FMT is the quality of bowel preparation. This process plays a critical role in preparing the recipient's colon to become more receptive to donor microbiota colonization. Several studies have demonstrated that inadequate bowel preparation is an independent predictor of FMT failure. In a prospective study evaluating factors contributing to the success of single fecal infusion (SFI), bowel preparation quality was assessed using the Ottawa Bowel Preparation Scale (OBPS). Patients with scores ≥7, indicating suboptimal cleansing, had a significantly higher risk of failure, with an odds ratio (OR) of 11.53 (95% CI 1.71–115.51; p = 0.019) [13].

Further clinical data indicate that the quality of bowel preparation has a direct impact on both early and late treatment outcomes. In an analysis of patients with rCDI, lower bowel preparation quality was significantly associated with early FMT failure (p = 0.034) and late recurrence (p = 0.050) [51].

In other words, although host-related variables strongly influence clinical outcomes, technical parameters such as bowel preparation remain equally critical for ensuring successful engraftment and preventing recurrence. Although bowel preparation is intended to facilitate donor microbiota engraftment, improper cleansing strategies may actually limit FMT effectiveness. Experimental evidence suggests that bowel cleansing reduces the bacterial load by approximately one log, indicating that many endogenous microbes remain and may compete with donor strains during engraftment. While this reduction is sufficient to allow initial engraftment of donor species, residual native bacteria and the altered spatial organization of the intestinal microbiome can affect the long-term stability of the newly formed microbial ecosystem. In addition, overly frequent FMT administration has been shown to disturb ecosystem stability, resulting in microbiota shifts over time that may compromise sustained donor colonization [52].

Donor Source as a Determinant of FMT Outcomes

The selection of a donor source is one of the important technical considerations that may influence the clinical success of FMT, as differences in donor characteristics and microbial composition have been associated with variable treatment outcomes [53]. Donors for FMT can be sourced either from family members or close relatives (family-related donors) or from standardized stool banks. Clinical observations indicate that the choice of donor source may influence treatment outcomes. In a retrospective cohort study, family stool donation was associated with higher odds of FMT failure compared with stool bank donation (OR 4.13; 95% CI 1.00–7.01; P = .049), suggesting that standardized donor banks may provide more consistent efficacy [22]. Family or friend donors are often viewed as more acceptable and accessible options for patients. However, the use of self-identified or family donors can present challenges in screening rigor and safety, reinforcing the need for standardized, prescreened stool banks [54]. Stool banks operate as centralized and highly regulated facilities that systematically manage every stage of FMT, from donor recruitment and screening to material storage and quality assurance, thereby addressing the variability and logistical limitations of patient-selected donation models [55]. Within these institutions, each prospective donor is required to complete an extensive, multilayered evaluation involving comprehensive health questionnaires, clinical and lifestyle assessments, and microbiological as well as virological examinations to ensure that only healthy individuals with optimal gut microbiota profiles are selected, a process so stringent that it typically yields an acceptance rate of less than 5 % [56]. To maintain both safety and operational efficiency, public stool banks have implemented standardized protocols and recurring re-screening cycles often every 60 days or less, supported by mathematical modelling and donor-specific monitoring, which together minimize infection risk, control costs, and guarantee the consistent supply of clinically reliable FMT material for large healthcare centers [57]. Stool banks enable faster and more efficient access to FMT material by eliminating the delays often encountered when identifying and screening family donors, a process that can critically impact patients with severe or fulminant CDI. By maintaining frozen, pre-screened donor samples that are readily available on demand, stool banks standardize the FMT process and ensure timely treatment, reducing the risk of complications associated with delayed therapy and gradually establishing themselves as the preferred model of care in many advanced healthcare systems [58].

Variability in FMT Outcomes Across Delivery Routes

The route of administration is considered one of the procedural aspects that can determine whether FMT

succeeds or fails. Clinical data indicate that variations in delivery pathways may influence bacterial engraftment and the overall treatment outcome, as each route exposes donor microbes to distinct environments within the gastrointestinal tract [59]. Such physiological differences may partly explain why upper gastrointestinal administration, such as through a nasogastric tube, produces slightly lower cure rates, particularly among patients with more advanced or complicated infections. These results indicate that incomplete microbial delivery to the colon may hinder full bacterial restoration and lead to FMT failure [60]. The choice of administration route should therefore be carefully aligned with the patient's condition [61].

Commonly applied routes for FMT include colonoscopy and rectal enema, each offering procedural advantages and practical limitations that can influence therapeutic outcomes. Colonoscopic delivery remains the preferred approach in many clinical settings because it ensures targeted infusion of donor material directly into the colon, which is the primary site of CDI [61]. Differences in the route and technique of FMT can influence how effectively donor material reaches the colon. Imaging data have shown that enema procedures vary in how far the infused material travels through the colon, while colonoscopy ensures full delivery to the cecum, indicating that incomplete colonic coverage may reduce treatment efficiency. Rectal enema provides a simpler and less invasive route for FMT, but the infused donor material tends to remain in the distal colon, which may limit proximal microbial distribution and potentially reduce therapeutic success [62].

Adverse Impact of Antibiotic Exposure Prior to FMT

Antibiotic exposure is a critical determinant that strongly influences the success or failure of FMT. Post-procedural antibiotic use, particularly when unrelated to CDI, has been shown to significantly increase the risk of recurrence by disrupting donor microbiota engraftment and altering the intestinal environment necessary for long-term stability [37]. While antibiotics are essential for eradicating the initial infection, they also exert a destructive effect on the gut microbiota ecosystem, thereby hindering the engraftment and colonization of donor microbiota following FMT [23].

Several studies have reported that post-FMT antibiotic use is among the most consistent predictors of therapeutic failure. Non-CDI antibiotic exposure after FMT represents one of the most critical drivers of treatment failure, as it interrupts the process of microbiota restoration required for durable protection against *C. difficile.* Antibiotic administration within the first eight weeks post-FMT can destabilize the recovering gut ecosystem, reducing colonization resistance and enabling recurrent infection. Patients who received additional non-CDI antibiotics within two months of FMT were more likely to experience CDI recurrence compared with those who avoided further antibiotic therapy, emphasizing that strict avoidance of unnecessary antibiotics is essential to maintain FMT treatment effectiveness [37].

Early antibiotic administration during the first 8 weeks after FMT remains a common occurrence in clinical practice. Antibiotic exposure in this vulnerable post-transplantation phase disrupts the early stabilization of donor microbiota, leading to a significantly higher likelihood of FMT failure. Even after controlling for other relevant recurrence risks, antibiotic use during this period remains the strongest independent predictor of unsuccessful treatment outcomes [14]. Broad-spectrum agents such as fluoroquinolones, third-generation cephalosporins, and carbapenems can cause profound damage to the newly established gut microbial community. These antibiotics rapidly reduce microbial diversity and deplete key anaerobic taxa, leading to ecological instability that compromises the recovery and persistence of donor microbiota after FMT [63]. As a result, the likelihood of *C. difficile* regrowth and domination increases, even after successful FMT, since exposure to non-*C. difficile* antibiotics shortly after transplantation have been shown to significantly reduce treatment success by disrupting donor microbiota engraftment and promoting recurrence [64].

This phenomenon underscores the importance of antibiotic stewardship in maintaining the long-term success of FMT [37]. Stewardship strategies include minimizing unnecessary antibiotic prescriptions and carefully evaluating the need for antimicrobial therapy to prevent disruption of donor microbiota and recurrence of infection in post-FMT patients. With stricter antibiotic control, the durability of FMT outcomes can be improved and the risk of relapse substantially reduced [23]. Therefore, clinicians are encouraged to apply careful antibiotic stewardship, ensuring that prescriptions are well-indicated and favor narrow-spectrum agents when possible. Consultation with FMT or infectious disease specialists is recommended to guide safe decision-making during this critical recovery window [14].

Future Direction for Indonesia

To improve FMT outcomes in Indonesia, it is crucial to address the multifactorial causes contributing to its failure. But despite that, FMT implementation in Indonesia remains very limited due to procedural challenges but also to the lack of diagnostic capacity, absence of standardized stool banks, and low clinician awareness of CDI and FMT. With the growing elderly population and high antibiotic consumption in hospitals, the burden of rCDI and treatment failure may continue to rise [3], [5], [6].

To address the shortage of diagnostic facilities in Indonesia, it is recommended that national laboratory networks and research collaborations be strengthened. Improving access to microbiome sequencing, donor screening, and CDI analysis would enhance the accuracy of detection and clinical monitoring.

Conclusion

FMT is an effective treatment option for CDI, but some patients still experience treatment failure. This occurs because numerous factors influence the outcome. These include patient-related factors such as comorbidities, immune status, and nutritional condition; disease-related factors, including CDI severity and previous recurrences; technical aspects, including bowel preparation, donor selection, and the route of administration; and antibiotic use after FMT. These factors show that successful FMT requires careful patient evaluation, standardization of procedural protocols, and strict post-procedural monitoring to reduce

recurrence risk. Looking ahead, future research should focus on prospective studies with more representative populations, the development of predictive biomarkers, the strengthening of national stool bank infrastructures, and the exploration of biological mechanisms of engraftment and microbiota-derived metabolites as key directions to further enhance the efficacy and safety of FMT.

Author's Contribution

K. Irgi: Conducted literature search, selected and analyzed articles, synthesized findings, and wrote manuscript. A. Kasasiah: Provided academic supervision, guided the writing process, contributed to the conceptual scope of the review, added substantive content, reviewed the methodology, and ensured the overall quality of the manuscript. A. Rusmayanti: Provided constructive input to refine the writing.

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