Review

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# Fecal Microbiota Transplantation Against Norovirus Infection: From Mechanisms to Clinical Evidence

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**Norovirus (NoV) is a leading global cause of acute gastroenteritis. Infected individuals shed virus at high concentrations in feces, and an extremely low infectious dose enables secondary transmission among household contacts, thereby expanding the scope of spread. Currently, no approved specific antiviral therapies for NoV infection are available; therefore, it is urgent to develop novel therapeutic strategies. Fecal microbiota transplantation (FMT) restores intestinal microbiota homeostasis by transplanting fecal microbiota from healthy donors, with well-proven efficacy in recurrent *Clostridioides difficile* infection. This narrative review summarizes the biological characteristics and infection mechanisms of NoV, the bidirectional interplay between intestinal microbiota and NoV, and the clinical evidence supporting FMT application in NoV infection. This review also discusses the potential therapeutic mechanisms of FMT in NoV infection, including microbiota engraftment and structural remodeling, repair of the intestinal mucosal barrier, and immune modulation, and highlights key considerations for its clinical application, such as donor screening, fecal preparation and delivery routes. Existing evidence suggests that FMT may present favorable efficacy and safety in the management of NoV infection, particularly in immunocompromised patients. Nevertheless, current studies are limited to case reports and small case series, lacking large-scale randomized controlled trials. Further high-quality studies and standardized protocols are required to validate the clinical value of FMT and facilitate its clinical translation for the management of NoV infection.**

**Keywords:** norovirus; fecal microbiota transplantation; antiviral therapies; intestinal microbiota; clinical evidence

## Introduction

Norovirus (NoV) is a major cause of gastroenteritis in people of all ages worldwide. NoV leads to around 685 million infections and over 200,000 fatalities annually, which imposes a significant disease burden [1,2]. Characterized by high infectivity, NoV is prone to inducing outbreaks in crowded or closed environments. In healthy individuals, NoV infection typically resolves without intervention within three days [3]. Nevertheless, for infants, young children, elderly people, and immunocompromised patients, the infection may become prolonged and evolve into chronic refractory gastroenteritis, which seriously impairs their quality of life and can even be life-threatening [4]. At present, no specific antiviral medications for NoV infections have been approved. Clinical management primarily focuses on symptomatic management, with the core goal of preventing dehydration and maintaining electrolyte balance [5]. Although drugs like nitazoxanide exhibit anti-NoV properties in some research, their effectiveness against NoV remains uncertain. While immunoglobulin therapy has shown positive outcomes in some cases, there is a lack of large-scale clinical evidence to support its widespread application [6]. Thus, investigating new and effective therapeutic approaches for NoV infections is of considerable clinical importance.

Fecal microbiota transplantation (FMT) is a therapeutic approach that involves transplanting fecal microbiota from healthy individuals to the intestines of patients to restore normal intestinal microbiota homeostasis. Clinical research demonstrates that FMT is both effective and safe in treating recurrent and refractory *Clostridioides difficile* infection (rCDI) [7]. Recently, FMT has been increasingly investigated and applied in areas such as inflammatory bowel disease, metabolic disorders, and neuropsychiatric disorders. More importantly, the potential value of FMT in treating viral infections has also garnered increasing attention. The complex bidirectional interaction between intestinal microbiota and intestinal viral infections provides a theoretical basis for employing FMT to treat NoV infection.

This narrative review aims to summarize the available evidence regarding the application of FMT in NoV infection treatment, and to discuss this topic from multiple perspectives, including the biological characteristics and infection mechanisms of NoV, the interaction between intestinal microecology and NoV, the clinical evidence of FMT for NoV infection, and the key considerations in FMT applica-

tion for NoV infection, thereby providing a valuable reference for clinical practice and scientific investigation.

## Biological Characteristics and Infection Mechanisms of NoV

### *Biological Characteristics of NoV*

NoV is a non-enveloped, positive-sense RNA virus, which contains three open reading frames (*ORF1–ORF3*). These three ORFs encode six non-structural proteins (NS1/2 to NS7), the major capsid protein viral protein (VP) 1, and the minor capsid protein VP2 [8]. Fig. 1 shows the human NoV genomic organization. NoV can be divided into 10 genogroups (*GI* to *GX*) based on capsid protein sequences [9]. Among these 10 genogroups, *GI* and *GII* (particularly the *GII.4* variant) are the predominant strains globally [10,11]. Moreover, NoV also exhibits extremely strong environmental resistance. NoV can tolerate both acidic and alkaline conditions with a pH of between 2 and 9, resist digestion by enzymes like trypsin and pepsin, and survive in food, water, and on object surfaces at room temperature for days to weeks [12,13,14]. It has been observed that alcohols can partly inactivate human NoV, regardless of exposure concentration or time [15]. Additionally, NoV has an extremely low infectious dose, with only a very small number of viral particles (as few as 10 virions) that can result in human infection, which is also a crucial biological basis for its easy transmission [16]. Infected individuals can shed large quantities of virus in stool (peak concentrations reaching $10^5$–$10^9$ viral copies per gram of feces), with high viral loads closely linked to increased transmission among household contacts and secondary cases occurring in approximately 32% of family members [17]. The unique biological characteristics of NoV determine its high transmissibility and difficulty in prevention and control.

### *Infection Mechanisms of NoV*

NoV infection relies on histo-blood group antigens (HBGAs) as its attachment factors [18]. HBGAs are complex carbohydrates that are widely expressed on the mucosal epithelium of the digestive system, with their synthesis regulated by the fucosyltransferase 2 (*FUT2*) gene [19,20]. The protruding domain of the NoV capsid protein specifically binds to HBGAs to accomplish initial viral attachment, which is a key determinant of differential host susceptibility to NoV infection. Individuals carrying the wild-type *FUT2* gene (approximately 80% of the population) are vulnerable to NoV infection, whereas those with a null *FUT2* allele (around 20% of the population) exhibit complete resistance to NoV infection [21]. Recent research further reveals that, besides HBGAs, certain proteins (e.g., leucine-rich repeat-containing protein 15 (LRRC15) and myelin oligodendrocyte glycoprotein (MOG)) may also act as viral attachment factors for NoV, highlighting the complexity of the viral attachment mechanism [22].

Human NoV cannot be routinely cultured *in vitro*, so the infection and pathogenic mechanisms of NoV in humans are not yet fully elucidated. Existing research suggests that NoV infection impairs brush border enzyme activity leading to osmotic diarrhea, prolongs gastric emptying time exacerbating nausea and vomiting, and downregulates tight junction proteins, thereby increasing intestinal permeability and triggering systemic innate immune responses that further contribute to diarrhea [23,24,25,26]. The host's adaptive immune response provides only temporary protection following NoV infection, and the lack of cross-protection among different genotypes of viruses results in recurrent NoV infections in humans [10]. Nevertheless, the precise pathogenic mechanisms responsible for NoV infection remain unclear to date.

## Interaction Between Intestinal Microecology and NoV

### *The Regulatory Role of Intestinal Microbiota in NoV Infection*

Recent studies reveal that the intestinal microbiota participates in NoV infection, exerting both pro-viral and antiviral effects in humans and mice. Jones et al. [27] demonstrated that depleting intestinal microbiota by oral antibiotics markedly reduced NoV replication in mice, suggesting that intestinal bacteria promoted NoV infection. Similarly, scholars reported that a single antibiotic didn't provide sustained resistance to NoV, whereas a broad-spectrum antibiotic cocktail decreased microbial abundance, indicating that multiple intestinal bacterial species were involved in promoting NoV infection. Furthermore, antibiotics did not affect NoV replication in the spleen or lymph nodes, but inhibited NoV replication in the intestine, further confirming that these antibiotics influenced NoV replication indirectly through intestinal microbiota instead of acting directly on the virus [28].

However, several studies have explored the antiviral effects of intestinal bacteria. For example, poly-γ-glutamic acid (γ-PGA), a biopolymer synthesized by *Bacillus* spp., has been recognized as a non-canonical toll-like receptor 4 (TLR4) agonist that exhibits antiviral effects against NoV infection. In *ex-vivo* cultures of mouse ileum, the oral intake of γ-PGA increased serum interferon-beta (IFN-β) content, reduced murine NoV loads in the ileal Peyer's patches and mesenteric lymph nodes [29]. Another study revealed that inoculation of murine NoV and administration of retinoic acid significantly increased the abundance of Lactobacillaceae families. The upregulation of IFN-β induced by *Lactobacillus* exerted antiviral effects against murine NoV [30]. The dual regulatory effects of intestinal microbiota on NoV infection indicate that targeting intestinal microecology is a feasible strategy for the treatment of NoV infection.

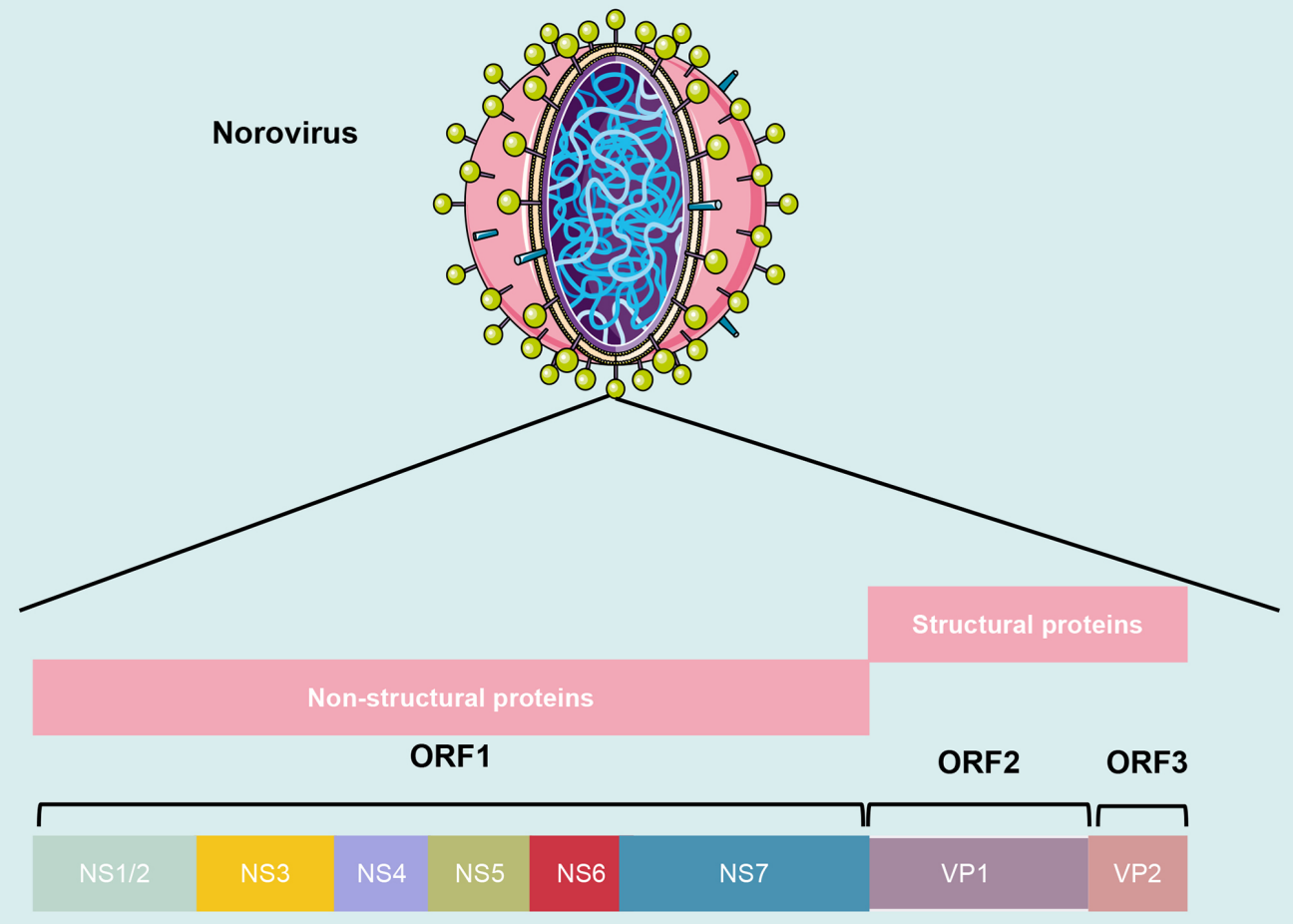


**Fig. 1. Human NoV genomic organization**. Note: NoV, norovirus; *ORF*, open reading frame; VP, viral protein; NS, non-structural protein. Image(s) provided by Servier Medical Art (https://smart.servier.com), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

### *The Regulatory Role of NoV Infection in Intestinal Microbiota*

Numerous clinical investigations revealed alterations in intestinal microbiota composition after NoV infection in both infants and adults [31]. Compared with healthy infants, those infected with human NoV exhibited higher abundances of Cyanobacteria and Fusobacteria at the phylum level, as well as increased abundance of *Enterococcus* spp., *Bacillus* spp., and *Streptococcus* spp. at the genus level [32]. The Chao1 index, a marker of microbial diversity, was obviously elevated in the human NoV-infected group, with notable differences in the abundance of potentially pathogenic bacteria [31]. Moreover, infants who tested positive for NoV in cases of diarrhea exhibited obviously higher *Enterobacter cloacae* levels than those who tested negative [33]. Another published study examined fecal samples from infants and suggested that before infection, the microbiome was primarily composed of Actinobacteria, with no significant changes during NoV infection. Nevertheless, there was a shift, with a higher proportion of Bacilli and Clostridia observed several weeks after the first episode of acute gastroenteritis ended [34]. Fecal microbiome assessments of pediatric patients with serious rotavirus or NoV infection indicated a reduced Shannon diversity index of the intestinal microbiota, along with increased abundances of Sphingomonadaceae, Campylobacteraceae, Methylobacteriaceae, Neisseriaceae, and Enterobacteriaceae when compared with healthy children [35]. Moreover, *Lactobacillus* spp. and *Bifidobacterium* spp. abundances were significantly lower in children suffering from rotavirus or NoV infection than in healthy children [36]. NoV infection induces marked structural and compositional alterations of the intestinal microbiota, creating a vicious circle with the progression of infection and further highlighting the importance of restoring intestinal microecological homeostasis.

## Clinical Evidence of FMT for NoV Infection

### *Existing Clinical Case Studies*

Accumulating clinical cases show FMT has potential for treating NoV infection, particularly among immunocompromised patients who do not benefit from conventional supportive therapies. For example, a 68-year-

**Table 1. Comparison of key clinical variables and outcomes of FMT for NoV infection.**

| Variable | Kidney transplant [37] | Four transplant recipients [38] | Good's syndrome [39] |
|---|---|---|---|
| Immune status | Renal transplant; received immunosuppressive therapy | Bilateral lung transplantation/heart-lung transplantation/allogeneic haematopoietic stem cell transplantation | Good's syndrome |
| Infection duration | 2 months | 4 months–2 years | Several years |
| FMT delivery route | Colonoscopy | Nasojejunal tube/gastrostomy | Rectal |
| The number of FMT administrations | Single | Single | Multiple (3 rounds) |
| Prior failed therapies (before FMT) | Cefixime, rifaximin, probiotics, azithromycin | Immunosuppressant tapering, Ig supply, nitazoxanide | Nitazoxanide, calcium and vitamin D supplementation, subcutaneous immunoglobulin therapy |
| Concomitant therapies (during FMT) | Not mentioned | Not mentioned | Prednisone, parenteral nutrition |
| Follow-up duration | 5 months | 6–82 months | 3 years |
| Viral clearance | Yes | 1/4 yes, 2/4 persistent shedding and 1/4 not mentioned | Yes |
| Symptom recurrence | No | No | No |

FMT, Fecal microbiota transplantation; NoV, Norovirus; Ig, Immunoglobulin.

old kidney transplant patient suffering from chronic NoV-associated diarrhea (lasting two months) achieved complete symptom resolution and viral clearance following a single FMT intervention [37]. A retrospective case series involving four immunocompromised individuals (including two with bilateral lung transplantation, one with heart-lung transplantation and one with allogeneic haematopoietic stem cell transplantation) revealed significant clinical improvements after FMT intervention, including decreased diarrhea frequency and increased weight gain, without the occurrence of serious adverse events. Of note, two patients exhibited continued viral shedding but no recurrence of gastroenteritis symptoms [38]. Additionally, a case report documented a patient with Good's syndrome who had undergone chronic NoV infection for several years. For this patient, FMT combined with parenteral nutrition achieved NoV clearance, reduced diarrhea frequency and promoted weight gain [39]. Table 1 (Ref. [37,38,39]) summarizes the key clinical variables and outcomes across the published cases described above.

While these cases collectively suggest the therapeutic potential of FMT on NoV infection, several uncertainties merit attention. First, the prior failed therapies and concomitant therapies may have independently contributed to symptom resolution and nutritional recovery. Second, the natural fluctuation of chronic NoV infection in immunocompromised hosts cannot be discounted, as the absence of control arms makes it impossible to exclude spontaneous remission. In addition, some confounders limit the interpretability of these findings. Notably, the infecting NoV genotypes were not reported in any case, yet genotypic differences in virulence and host-microbiota interactions could substantially modify FMT efficacy. The duration of infection also varied widely from two months to several years, potentially affecting the reversibility of dysbiosis and mucosal damage. Finally, some evidence gaps remain: no randomized controlled trials have been conducted, precluding causal inference of FMT efficacy over standard supportive care; and the existing data are exclusively derived from immunocompromised adults, leaving the utility of FMT in immunocompetent patients, as well as in pediatric and geriatric populations, both high-burden groups for NoV infection, entirely unexplored. Notwithstanding these concerns, these clinical case reports still preliminarily suggest the potential effectiveness of FMT in relieving refractory NoV infection symptoms and clearing the virus, providing preliminary clinical signals that warrant further investigation.

### *Efficacy and Safety of FMT in Treating NoV Infection*

FMT has emerged as a promising therapeutic option in clinical practice, with increasing evidence supporting its use in the treatment of viral infection-related diseases. Numerous case reports have indicated that FMT leads to a decrease in diarrhea frequency, an enhancement of nutritional status, and, in some instances, viral clearance, with favorable safety. For example, in a retrospective analysis involving four patients with refractory chronic NoV gastroenteritis, FMT was associated with obvious clinical improvement. All patients exhibited a significant decline in diarrhea frequency, from 6–15 times per day at baseline to 1–6 times after FMT-accompanied, along with weight gain or stabilization [38]. FMT showed favorable safety in these im-

munocompromised patients, without procedure-related infections or severe adverse events being reported in the documented NoV cases [37,38]. Mild and self-limiting symptoms, including temporary nausea, abdominal discomfort, and bloating, are occasionally observed after FMT, which aligns with the findings of a comprehensive systematic review focusing on FMT for viral disorders. A systematic review by Ebrahimi et al. [40], which included eight clinical trials with 196 participants suffering from conditions such as human immunodeficiency virus (HIV), hepatitis B, coronavirus disease 2019 (COVID-19) with *C. difficile* coinfection, and cytomegalovirus colitis, confirmed that the adverse events associated with FMT are mainly mild and transient. During treatment of NoV infection, no severe adverse events associated with FMT have been reported, suggesting an acceptable safety profile, even among patients with underlying immunocompromising conditions [37,38,39]. Overall, these preliminary findings suggest that FMT may have potential efficacy and an acceptable safety profile for the treatment of NoV infection, particularly in immunocompromised patients with refractory conditions.

### *Potential Mechanisms of FMT in the Treatment of NoV Infection*

While the mechanisms behind FMT on NoV infection remain incompletely understood, growing evidence reveals several potential mechanisms. The therapeutic effects of FMT on NoV infection are mediated through multiple synergistic pathways, mainly centered on restoring intestinal microecology, repairing the intestinal barrier and regulating the immune response. These pathways do not function independently but rather form an integrated network in which each component supports and amplifies the others.

#### Microbiota Engraftment and Structural Remodeling

The therapeutic effectiveness of FMT in treating NoV infection is closely related to microbiota engraftment and structural remodeling (Fig. 2). A study reported that, after FMT treatment, some patients with NoV infection experienced persistent viral shedding but complete symptom relief [38]. This suggests that FMT may play a key role in modulating intestinal microbiota rather than directly eliminating the virus. In addition, FMT also restores the levels of commensal bacteria that generate protective metabolites, such as short-chain fatty acids (SCFAs), in the intestines, while decreasing pathobionts associated with elevated viral loads [40,41,42]. These beneficial metabolites enhance intestinal colonization resistance and directly or indirectly inhibit pathological processes related to viral infection [43,44].

#### Repair of the Intestinal Mucosal Barrier

Furthermore, FMT repairs the integrity of the intestinal mucosal barrier by decreasing the level of intestinal fatty acid binding protein (I-FABP), a marker of intestinal barrier dysfunction. This alteration reduces intestinal permeability and bacterial translocation, thereby alleviating the systemic inflammatory response caused by viral infections [45].

#### Modulation of Host Immune Responses

Moreover, FMT influences the host's innate and adaptive immune systems by restoring the interaction between the intestinal microbiota and immunoglobulin A (IgA) and modulating cytokine release, such as promoting the secretion of the anti-inflammatory factor interleukin-10 [46,47,48].

Rather than operating in isolation, these mechanisms are functionally interconnected to achieve clinical remission of NoV infection. For example, microbiota engraftment and structural remodeling not only enhance colonization resistance but also provide the substrate for SCFA production, which in turn supports barrier integrity and modulates immune responses, thereby alleviating diarrhea in NoV infection [49,50,51]. In addition, repair of the intestinal barrier reduces bacterial translocation, thereby improving immune responses, promoting microbiota reconstitution, facilitating viral clearance and supporting recovery of nutritional status [49,52,53].

## Key Considerations in FMT Application for NoV Infection

### *Donor Screening Protocols*

Of note, donor screening is widely recognized as a critical step to ensure the safety and efficacy of FMT for the treatment of NoV infection. The standardized donor screening process involves several steps, beginning with a questionnaire, interview and clinical examination to exclude candidates with impaired intestinal microbiota homeostasis, or those who may pose potential risks to FMT recipients. Following that, the donor will undergo stool and blood testing to exclude donors with infectious diseases that have transmission potential. For candidate donors, the optimal age is generally 18 to 50 years, as individuals within this age range are more likely to have favorable overall health and a well-balanced, highly diverse intestinal microbiota [54]. Key exclusion criteria for donor eligibility include: a history of toxic substance exposure; having tattoos, piercings or infectious symptoms within the last month; exposure to blood in the last year; or a hereditary history of colorectal cancer and other gastrointestinal disorders [55]. Fig. 3 illustrates the main contraindications for FMT donors. After candidates pass the initial clinical screening, their blood samples are collected for viral testing (including HIV, hepatitis, and others), as well as for antibodies and certain serological assays. Concomitantly, matched stool specimens are subjected to standardized microbiological testing. In addition, written informed consent should be obtained from every candidate donor prior to the initiation of the screening procedure. Strict and standardized donor screening is

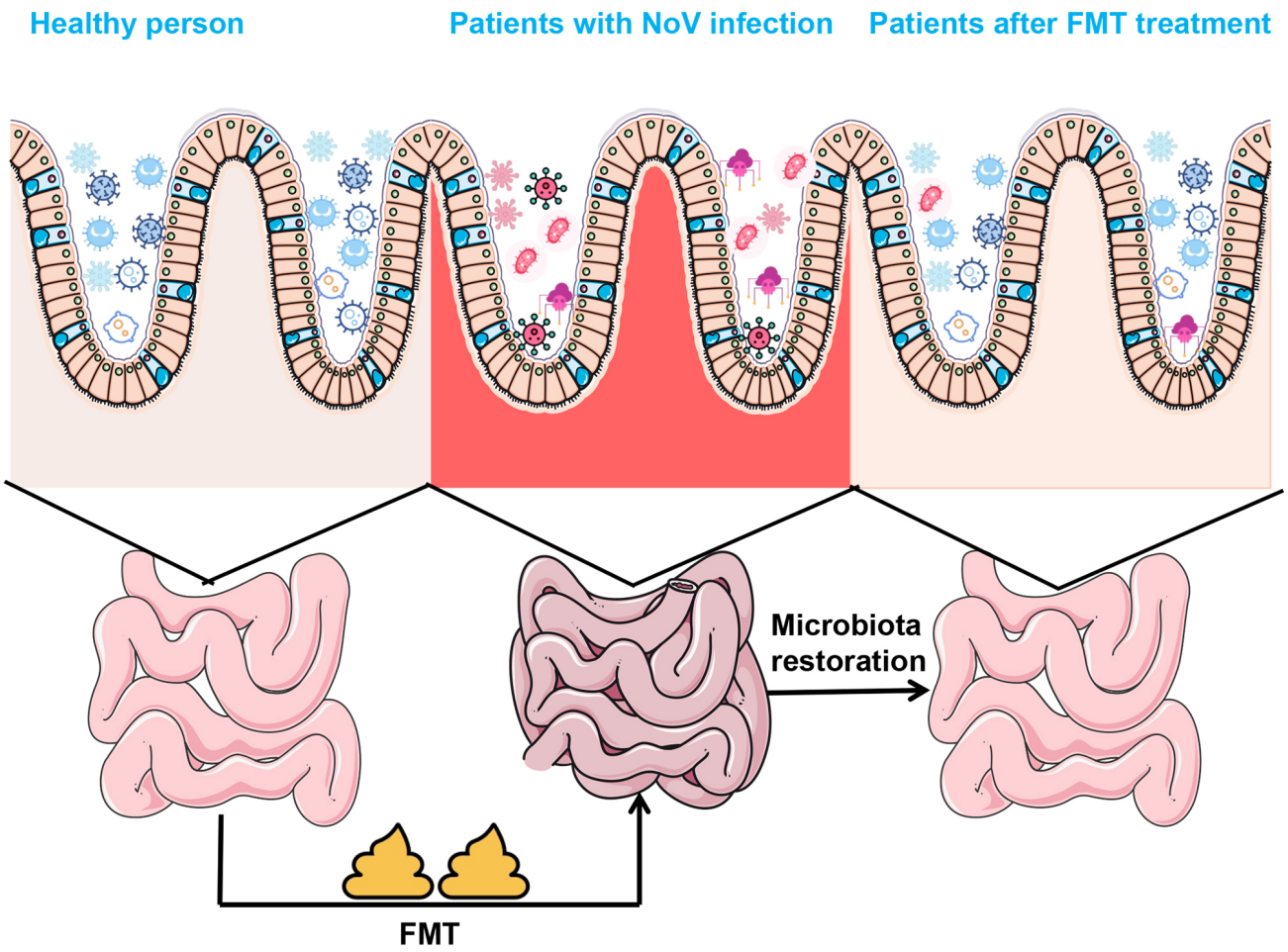


**Fig. 2. The role of FMT in treating NoV infection is closely related to microbiota restoration**. Note: FMT, fecal microbiota transplantation. Image(s) provided by Servier Medical Art (https://smart.servier.com), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

the primary prerequisite to ensure the safety and effectiveness of FMT in the treatment of NoV infection, and must be strictly implemented in clinical practice. The strength of such rigorous screening lies in minimizing the risk of transmitting infections to recipients. However, the process is time-consuming and costly, which may limit the availability of suitable donors and delay treatment. Furthermore, the lack of universally standardized criteria across different centers leads to heterogeneity in donor selection, potentially affecting the comparability of FMT outcomes across studies. Some researchers have proposed simplified screening for specific indicators, but evidence on its safety equivalence remains limited [56].

### *Fecal Preparation Strategies*

Following the completion of screening, fecal samples must be collected from individual donors within one month [57]. Common strategies for fecal sample processing involve fresh fecal preparation, frozen fecal preparation, and other similar techniques [58]. Fresh fecal transplantation is the earliest clinically established therapeutic modality in this field. The collected fecal samples should be transported to the designated institution within 6 h of collection, after which the samples are diluted with an appropriate diluent, such as normal saline, homogenized using a blender, and filtered to remove particulate material [59]. Fresh fecal transplantation is capable of maintaining the original status and activity of the microorganisms in the feces, which may, in principle, improve its therapeutic effects [58]. However, several considerations should be taken into account during fecal preparation. Using fresh fecal samples means that the collection, preparation, and transplantation of fecal samples should all be conducted on the same day as the planned FMT [60]. Nevertheless, the use of fresh fecal samples for FMT may not always be feasible due to potential delays in donor screening, as well as aesthetics and sanitation. Frozen fecal transplantation has therefore been widely adopted as an alternative method, involving simple processing for fecal samples followed by rapid freezing at low temperatures. The feces are then thawed when needed for transplantation [61]. The use of frozen fecal prepara-

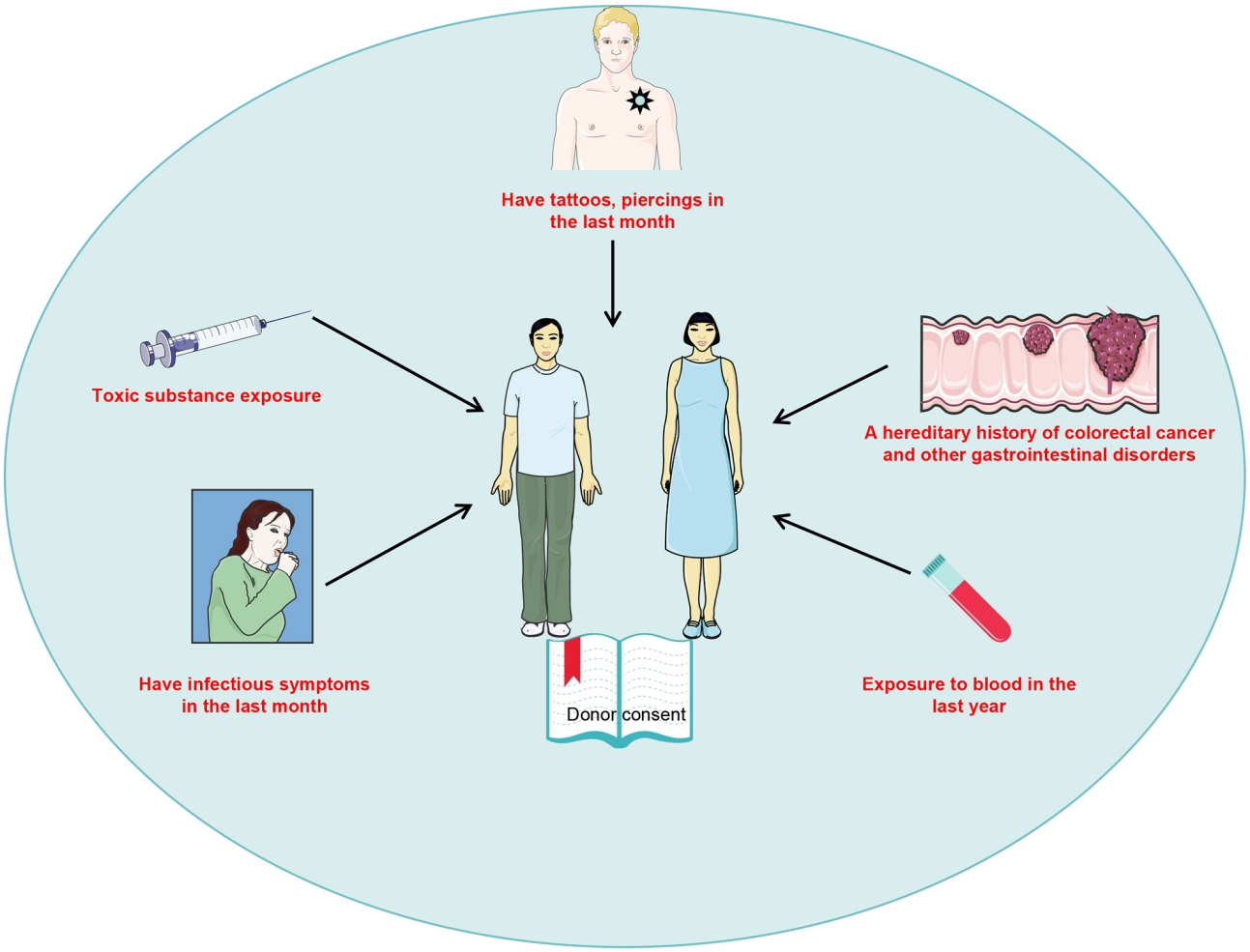


**Fig. 3. The main contraindications for FMT donors**. Note: Image(s) provided by Servier Medical Art (https://smart.servier.com), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

tions allows batch production and long-term storage, while enabling timely FMT for urgent cases. In addition, numerous studies demonstrated that frozen feces were as effective as fresh feces in treating rCDI and ulcerative colitis [62,63]. Nevertheless, certain bacteria exhibit reduced viability post-thaw, potentially diminishing the functional diversity of the transplanted consortium [64]. Recently, various studies have been exploring ways to optimize the processing techniques to enhance the survival rates and activity of microorganisms, thereby enhancing the therapeutic efficacy of frozen fecal transplantation [65]. Furthermore, it should be noted that equipment cleaning during the processing of donor stool samples is essential to minimize the risk of cross-contamination. All equipment must be thoroughly cleaned to remove any residual matter before autoclaving at 121 °C for 20 min [57]. Standardized fecal preparation can ensure the activity and stability of intestinal microbiota in the transplant, a key step to improving the success rate of FMT.

### *Delivery Routes for FMT*

FMT can be administered through various well-established methods, which are generally categorized into upper gastrointestinal (including nasogastric tube, nasoduodenal tube, nasojejunal tube, as well as capsules) and lower gastrointestinal (such as enemas and colonoscopy) approaches. The choice of delivery method is considered a crucial determinant that affects microbial colonization, patient tolerance, and clinical outcomes.

For upper gastrointestinal routes, oral capsules are a non-invasive and easily repeatable option that is more acceptable to patients. A study reveals that when equivalent volumes of donor fecal are utilized, FMT delivered via capsules is as effective as colonoscopy in treating rCDI [66]. However, a notable limitation is the potential reduction in microbial viability during the capsule preparation process, and the absence of standardized protocols may result in inconsistent therapeutic effects. Nasogastric tube delivery is technically simple and convenient, but it causes psychological discomfort for patients. Additionally, exposure to gastric acid may compromise the viability of transplanted mi-

croorganisms. Nasoduodenal and nasojejunal tubes can bypass the gastric environment and lessen gastrointestinal irritation, thereby potentially improving microbial colonization; nevertheless, nasoduodenal tubes are associated with increased risks of reflux, intestinal irritation, and catheter displacement due to the active peristalsis of the duodenum [58]. Nasojejunal tubes are technically more challenging and susceptible to luminal obstruction.

For lower gastrointestinal routes, colonoscopy allows for accurate delivery of fecal material to the target colonic region. A study compared the effects of colonoscopy and two enema methods (with and without positioning procedures) on FMT colonic distribution. The study found that colonoscopy ensures that FMT reaches the cecum in 100% of participants, and the enema with positioning procedure results in FMT reaching the cecum in 50% of participants, and the enema without positioning procedure achieves this in only 38% of participants [67]. Furthermore, a study involving 30 ulcerative colitis patients found that FMT administered through the colonic route is safer and better tolerated than the nasogastric route, and the colonic route is preferred by both patients and clinicians [68]. Moreover, research including 26 studies (1309 patients) revealed that cure rates for CDI are higher when FMT is conducted via colonoscopy than via enema or nasogastric tube, while cure rates for patients who receive FMT via colonoscopy or capsule are comparable [69]. While colonoscopy has many strengths, this technique relies on professionally trained operators, entails higher costs, and involves procedural risks; these drawbacks restrict its use in repeated therapeutic interventions. An enema is a method of drug administration in which fecal transplantation fluid is infused into the colon through the rectum. Although continuous FMT using fecal enema is less effective than colonoscopy-based FMT and is related to lower rates of sustained cure, evidence suggests that FMT via a retention enema can enhance clinical outcomes in patients unable to undergo surgery [70,71]. An enema is generally well tolerated and can significantly alleviate symptoms of rCDI in individuals with multiple underlying comorbidities. In summary, each FMT delivery method has inherent strengths and limitations that must be weighed against patient-specific factors, disease characteristics, and clinical goals. Furthermore, dosing intervals are important for treatment outcomes. For example, a study reported that in patients with CDI, the cure rate of two-dose FMT (72%) is higher than that of single-dose FMT (54%) [72]. A preclinical study demonstrated that intrarectal FMT at low dosing intervals better maintains the donor's intestinal bacterial community [73]. An animal study also reported that multiple FMTs are more effective at sustaining microbial recovery than a single FMT [74]. Notably, the existing evidence on FMT delivery routes and administration intervals is derived from clinical studies of CDI infection, ulcerative colitis, and preclinical animal models, rather than from NoV-specific comparative data; thus, these findings should be considered indirect evidence for NoV infection. Accordingly, it can only be hypothesized that for patients with NoV infection, receiving FMT via colonoscopy at low dosing intervals may be an effective strategy to improve viral clearance rates.

## Challenges, Mechanistic Exploration and Future Directions

### *Limitations of Current Research*

It must be acknowledged that the application of FMT in NoV infection is still in the early stage, with several important challenges remaining. The primary limitation is the low level of clinical evidence. Available clinical studies are limited to case reports and small case series, lacking robust evidence from large-scale, multicenter, randomized controlled trials. This impedes an accurate evaluation of the true therapeutic efficacy of FMT in treating NoV infection. Furthermore, the scope of study populations is relatively narrow, with most research focusing on immunocompromised patients with chronic NoV infection. Data on NoV infection in immunocompetent individuals, as well as in children and the elderly, are severely lacking, making it challenging to ascertain the practical value of FMT for these groups. Additionally, at present, no standardized protocols have been established for donor screening, fecal processing, or delivery route, which restricts the comparability among results and severely hinders clinical standardization and scalability. Moreover, basic research investigating the relationship between intestinal microbiota and NoV largely relies on animal models such as mice, whose intestinal microbial composition and host receptor characteristics differ greatly from those in humans. Thus, findings are not readily translatable to clinical practice. Taken together, these challenges pose major barriers to progress in this field.

### *Unresolved Mysteries at the Mechanistic Level*

Although the bidirectional relationship between intestinal microbiota and NoV has been proposed, and FMT provides therapeutic benefits by restoring the balance of intestinal microbiota homeostasis, many mechanistic questions are still unresolved. Currently, evidence indicates that intestinal commensals exert synergistic antiviral effects against NoV. Nevertheless, the specific bacterial strains responsible for this activity have not yet been identified, along with their targets and the molecular mechanisms involved, which hampers the development of targeted probiotic formulations. Furthermore, although metabolites derived from microbiota, such as SCFAs and secondary bile acids, have been demonstrated to inhibit NoV infection, the exact molecular pathways through which they interact with host cells and NoV remain unclear, and the optimal concentrations and timing of their antiviral effects have not yet been established. The intricate network of interactions among intestinal microbiota, NoV, and host immunity is

also not fully understood. Specifically, it remains unclear how the healthy microbiota restored by FMT precisely influences host immune responses to achieve effective viral clearance. In addition, given the considerable diversity of NoV genotypes in terms of antigenicity and host susceptibility, whether genotype-specific interactions exist between NoV and the intestinal microbiota remains largely unexplored. These mechanistic gaps substantially hinder a more comprehensive understanding and further optimization of FMT in treating NoV infection.

### *Future Research Directions*

To specifically tackle the limitations of current research (e.g., low-level clinical evidence, narrow study populations, and lack of standardization for donor screening, fecal processing and FMT delivery route) and the mechanistic gaps (e.g., unidentified antiviral bacterial strains, unclear molecular pathways of intestinal microbiota and their metabolites, the intricate microbiota-NoV-host immune network, and genotype-specific interactions), the following future research directions are proposed. Firstly, there is an urgent requirement for large-scale, multicenter randomized controlled trials to confirm the efficacy and safety of FMT in diverse populations, including immunocompetent individuals, children, and elderly people with NoV infection, and to standardize FMT protocols encompassing donor screening, fecal preparation, and delivery routes for clinical application. Secondly, multi-omics technologies should be used to investigate core antiviral bacterial strains and their molecular targets, elucidate the interaction pathways of microbial metabolites (e.g., SCFAs) with host immune cells and NoV, and clarify genotype-specific crosstalk between NoV and intestinal microbiota. Lastly, translational research should focus on developing targeted probiotics and optimizing personalized FMT strategies based on host microbiota profiles and NoV genotypes to enhance therapeutic effects. Conducting targeted research in the above directions will accelerate the clinical translation of FMT and provide more effective solutions for treating NoV infection.

## Conclusion

NoV is a primary cause of acute gastroenteritis worldwide, and there are no approved specific antivirals at present. FMT shows preliminary promise as a therapeutic option for alleviating NoV infection, particularly in immunocompromised patients, and may have the potential to indirectly reduce intra-familial transmission by alleviating clinical symptoms such as diarrhea, thereby decreasing fecal contamination and exposure risk. This narrative review summarizes the available evidence of FMT against NoV infection, thereby providing new therapeutic approaches for NoV infection. Large-scale randomized controlled trials and standardized protocols are urgently needed to clarify the definitive role of FMT on NoV infection and promote wider clinical translation of FMT.

## Availability of Data and Materials

Not applicable.

## Author Contributions

Conceptualization, ZW, WT and SY; investigation, ZW, CL, WT and SY; visualization, ZW and CL. ZW and CL has been involved in drafting the manuscript and all authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest.

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