



Case report

Washed microbiota transplantation in an elderly patient with lymphocytic leukemia and *Clostridioides difficile* infection: A case report illustrating a triumph over complexity

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ABSTRACT

Background: Fecal microbiota transplantation (FMT) is recommended for treating patients with recurrent *Clostridioides difficile* infection (CDI). However, the therapeutic efficacy of FMT in elderly patients with complex medical conditions remains uncertain. The new method of FMT, washed microbiota transplantation (WMT) has been widely used in China to improve the safety of transplantation.

Case report: A 94-year-old man with chronic lymphocytic leukemia (CLL) was admitted to our hospital due to recurrent diarrhea persisting for eight months. The patient had experienced multiple relapses of CDI despite receiving standard therapies. He underwent colonic transendoscopic enteral tubing (TET) and subsequently received WMT during the procedure. Following the treatment, no episodes of diarrhea or adverse events were observed, and the patient remained stable over a three-month follow-up period.

Conclusion: This case demonstrates the efficacy and safety of WMT in treating elderly patients with CLL. The successful management of this case offers valuable clinical insights into the use of WMT for elderly CDI patients with complex medical conditions. Moreover, this report contributes practical experience regarding the administration of WMT through the colonic TET.

1. Introduction

Recurrent *Clostridioides difficile* infection (rCDI) is characterized by severe symptoms, including refractory diarrhea, hematochezia, toxic megacolon, and pseudomembranous colitis, all of which significantly reduce the patient's quality of life. Currently, no specific antibiotics are tailored for the treatment of *Clostridioides difficile* infection (CDI), and each antibiotic used can induce varying levels of dysbiosis within the host's microbiome [1]. Moreover, the efficacy of most antibiotics is limited [2].

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Fecal microbiota transplantation (FMT) has proven to be an effective and safe treatment option for rCDI, demonstrating an overall efficiency of 90 % [3]. Nonetheless, evaluating FMT in the treatment of complex medical conditions remains challenging, and the precise indications for its use require further definition. We report a case of an elderly patient with rCDI complicated with chronic lymphocytic leukemia (CLL) who was successfully treated with newly improved FMT administered via colonic transendoscopic enteral tubing (TET).

2. Case presentation

A 94-year-old man presented with recurrent diarrhea, which had persisted for eight months following antibiotic treatment for aspiration pneumonia. He experienced more than 10 times of diarrhea, sometimes accompanied by blood and mucus. The patient tested positive for CDI via a fecal polymerase chain reaction (PCR) test and initially received oral metronidazole at a local hospital. His symptoms subsided after the treatment, with the negative test of *Clostridioides difficile* toxin. However, fifteen days later, his diarrhea reoccurred with the positive test of CDI, confirming a recurrence of CDI. He was then treated with a 10-day course of vancomycin, after which the fecal test was negative. Despite this, the patient's diarrhea recurred repeatedly over the next eight months, during which treatments of vancomycin, rifaximin, and probiotics provided temporary relief. Eventually, he experienced further episodes of diarrhea, characterized by unformed stools and mucus, occurring 5–6 times daily. After starting another course of vancomycin, the patient voluntarily discontinued the treatment on the 11th day with a positive stool test of CDI by PCR and sought further management at our hospital. A schematic diagram of the disease timeline is shown in Fig. 1. The patient suffered from CLL and aspiration pneumonia. In addition, he had reflux esophagitis and dysphagia, necessitating an indwelling gastric tube for a nasogastric diet (400 mL of a Total Protein-High Energy enteral nutrition emulsion administered 3 times daily), sequelae of a cerebral infarction resulting in left hemiplegia, mild hypoproteinemia and anemia, a history of prostate operation with ongoing catheterization, and left eye blindness due to trauma. The blood examinations showed a white blood cell count of $45.3 \times 10^9/L$, neutrophil percentage of 23.2 %, lymphocyte percentage of 71.3 %, absolute neutrophil count of $10.5 \times 10^9/L$, lymphocyte count of $32.3 \times 10^9/L$, red blood cell count of $3.66 \times 10^{12}/L$, hemoglobin level of 112 g/L, total protein level of 59.2 g/L, albumin level of 36.1 g/L, C-reactive protein level of 1.89 mg/L, and an erythrocyte sedimentation rate of 20 mm/h. The patient's age Charlson comorbidity index (aCCI) score was 10 [4,5]. A summary of the patient's medical conditions can be found in Table 1. A colonoscopy was performed to evaluate his intestinal health, which revealed a normal ileocecal valve and appendix opening. However, there was noticeable erythema on the mucosa from the ascending colon to the rectum (Fig. 2A–C). Following the colonoscopy, the patient underwent TET (Fig. 2D).

The new method of FMT was scheduled to treat the patient's rCDI. This new method of in-lab preparation based on an automatic purification system (GenFMTer, FMT medical, Nanjing, China) was named as washed microbiota transplantation in 2019 [6] and released by Chinese consensus [7]. The health status of the donors was rigorously assessed to ensure safety and efficacy. Colonic TET, a novel endoscopic technique, has garnered attention in China since 2015 [8,9]. A multicenter study has indicated that it is a promising, safe, and practical delivery method for microbial therapy [10]. Previous research has confirmed the safety of colonic TET in treating elderly patients with serious conditions [11]. WMT was delivered through colonic TET both on the day of the TET and the following day. One day after the second WMT, the patient reported the soft stool once a day, and was subsequently discharged. At a three-month follow-up, the patient continued to have normal stool without CDI recurrence. Additionally, the patient's body weight gained 2.5 kg since the first WMT.

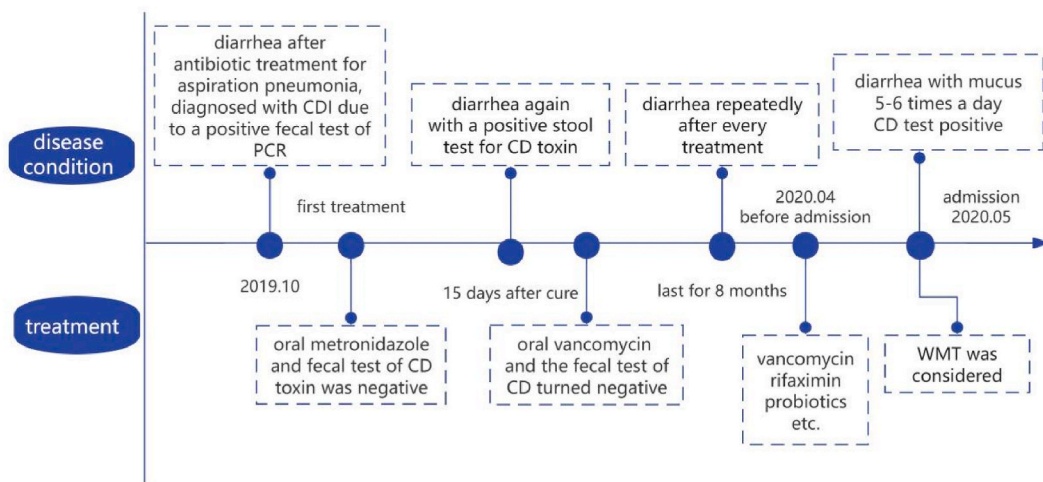


Fig. 1. Schematic diagram of disease timeline.

Table 1
Demographic, laboratory and clinical characteristics in patient.

Characteristic	
Age	94 years old
Gender	male
Course	8 months
WBC	$45.3 \times 10^9/L$
Neutrophils (%)	23.20 %
Lymphocytes (%)	71.30 %
Neutrophil count	$10.5 \times 10^9/L$
Lymphocyte count	$32.3 \times 10^9/L$
RBC	$3.66 \times 10^{12}/L$
Hemoglobin level(g/L)	112
Albumin level(g/L)	36.1
C-reactive protein(mg/L)	1.89
ESR (mm/h)	20
Stool test of CD	
CD antigen by PCR	+
CD toxin by PCR	+
Weight	10kg loss
Fever	-
Abdominal pain	-
Stool frequency	5-6 times/day
Comorbidities	CLL reflux esophagitis dysphagia with an indwelling gastric tube aspiration pneumonia sequelae of cerebral infarction with left hemiplegia prostate postoperation indwelling catheterization postoperation of gastroesophageal decompression left eye blindness due to trauma
aCCI score	10

WBC: White blood cell count, RBC: Red blood cell count, ESR: erythrocyte sedimentation rate, CD: *Clostridioides difficile*, L: liter, kg: kilogram, CLL: chronic lymphocytic leukemia, PCR: Polymerase chain reaction, aCCI: age Charlson comorbidity index.

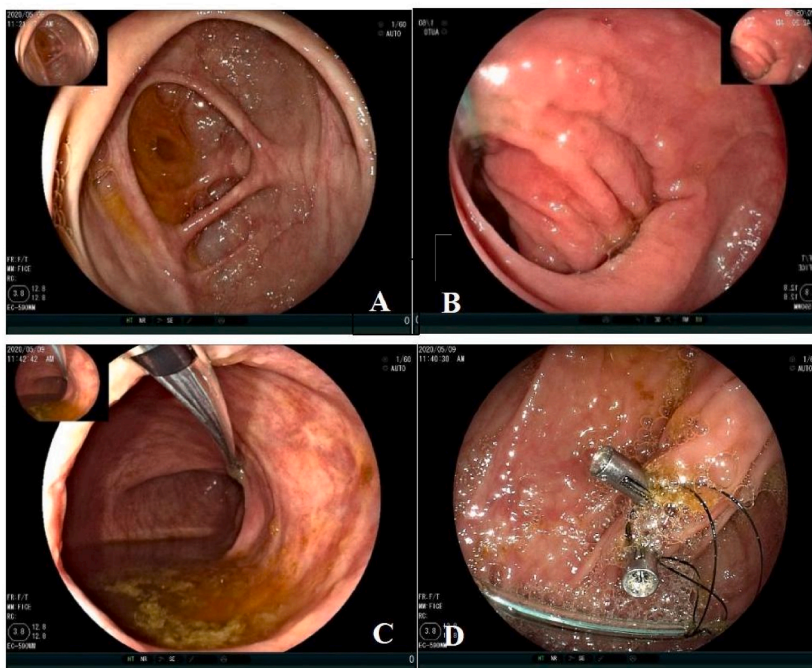


Fig. 2. (A) Normal ileocecal valve and cecum. (B, C) The erythematous mucosa. (D) The colonic TET for delivering WMT after the endoscopic procedure.

3. Discussion

We presented a rare case of an elderly patient with CLL complicated by rCDI. This case was characterized by several significant factors: (1) the patient was 94 years old; (2) the patient had immune dysfunction due to CLL; (3) the patient experienced rCDI after multiple rounds of conventional treatment. CDI is identified by symptoms of diarrhea with a positive stool test for *Clostridioides difficile* (CD) toxin, the presence of toxigenic CD, or the detection of pseudomembranous colitis via colonoscopy or histopathologic examination [12]. The spectrum of CDI symptoms varies from mild diarrhea to severe conditions or fulminant colitis, which may include bloody stools, mucosanguineous feces, refractory diarrhea, toxic megacolon, and pseudomembranous colitis. Approximately 30 % of patients may experience rCDI [13], defined as the recurrence of symptoms within eight weeks after completing a course of therapy with complete relief [13]. Previous studies have shown that 10–20 % of CDI cases recur within eight weeks post-treatment, and 40–65 % relapse after eight weeks [14].

The European Society of Clinical Microbiology and Infectious Diseases updated its guidelines in 2021, recommending FMT for treating rCDI [15]. Individuals affected by CDI are often elderly, frail, and critically ill [16]. However, patients with complex comorbidities are frequently excluded from randomized controlled clinical trials (RCTs) [17]. Consequently, existing studies on the efficacy and safety of FMT in the treatment of rCDI patients with complex conditions have limitations that hinder its broader clinical application. Importantly, the elderly population has a high risk of developing CDI [18]. The previous study showed no stricture on the use of FMT for older patients with the recurrent, severe, and/or complex CDI [19]. Therefore, there is a need for expanded strategies to prevent, optimize treatment, and reduce the risk of recurrence to improve outcomes in this population [20]. At present, case reports have highlighted the therapeutic potential of FMT in critically ill patients. For instance, five patients in intensive care unit (ICU) with unexplained diarrhea unresponsive to broad-spectrum antibiotics experienced rapid improvement after FMT [21]. The recent report on WMT use in China suggest its potential efficacy in serious or immunosuppressed CDI patients [16]. However, challenges such as patient heterogeneity and potential reporting bias still exist and need to be addressed [22].

In this case, the diagnosis of rCDI was confirmed, and the patient had undergone treatment with the available antibiotics. Despite the high risk of adverse reactions due to his complex conditions, WMT was considered a viable option to achieve the desired therapeutic effect. The successful outcome in this case provides evidence supporting the effectiveness of WMT in patients with complex conditions, and it furthers the exploration of its clinical indications.

The common adverse events (AEs) associated with FMT include diarrhea, abdominal discomfort, fever, and self-limiting [11,23]. However, serious AEs, such as infections and death have also been reported [23,24]. A systematic review noted that the incidence rate of FMT-related AEs, serious AEs, and deaths were 19 %, 1.39 %, and 0.12 %, respectively [11]. Additionally, some studies suggest that the safety and side effects of FMT might be underestimated [23]. The present had a risk of aggravating the patient's CLL, including potential disease progression and increased risk of infection during the WMT process. Despite these challenges, the patient was successfully treated with WMT without any adverse reactions. Our experience will encourage the broader application of WMT. Notably, the recent development of WMT has improved the safety of this treatment by washing the microbiota [6].

A fecal microbiota suspension can be administered via capsule, colonoscope, colonic TET, nasogastric tube, and enema [19]. A prior study revealed that 4 of the 5 patients treated with FMT through the upper gastrointestinal tract experienced FMT-related deaths. The incidence of AEs associated with colonic TET, colonoscopy, enema, capsule, mid-gut tube, and gastroscopy are 6 %, 15 %, 26 %, 29 %, 29 %, and 32 %, respectively [5]. Given the patient's need for nasal-jejunal tube feeding and existing dysphagia, transanal FMT was preferred [7]. We opted for WMT via colonic TET for several reasons. Firstly, the patient experienced frequent stooling, making it difficult to retain fecal bacteria through an anal enema. Secondly, colonic TET allows for repeated WMT administrations, direct assessment of mucosal lesions, and the collection of mucosal samples [25]. This case reported good tolerance to colonic TET and WMT via colonic TET.

FMT is recommended for CDI patients who have experienced two or more relapses [12]. For the initial onset of CDI, the recommended treatment typically includes vancomycin or metronidazole, as well as fidaxomicin, rifaximin, or tigecycline [8]. Many relevant guidelines, such as the Clinical Practice Guideline issued by the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America [25], strongly advocate these treatments. However, some of these recommendations regarding the diagnosis and treatment of CDI lack high-quality research evidence [26]. A real-world study, which did not impose restrictions on the age and comorbidities of the included patients, showed that FMT achieved comparable clinical cure rates in patients with both primary and recurrent CDI [16]. Previous studies have suggested the early use of FMT in treating primary CDI [27–29], indicating that FMT could potentially replace antibiotics. However, it remains unclear whether FMT can be applied in the early stages of CDI or before CDI relapse to maximize benefits for patients [16,30]. For elderly patients, FMT has been recommended early in the course of the disease, such as after the second recurrence or after the first severe CDI [31]. In this case, the patient was successfully treated with WMT after long-term treatment of using medications. The prospective RCTs are required to evaluate the efficacy of early WMT.

In this case, we utilized frozen WMT and achieved satisfactory efficacy. A recent study has demonstrated that the frozen WMT is as effective as the fresh FMT in the clinical resolution of diarrhea in rCDI patients [32]. The use of frozen feces would decrease the need for frequent donor recruitment and screening, reduce costs, enhance acceptance among patients and doctors, minimize the patient's discomfort during the operation, presenting a promising option for clinical application [33]. Given these benefits, the methods in treating this case are practical and have the potential for widespread adoption in clinical settings.

4. Conclusion

This article provided the evidence of supporting the safety and efficacy of WMT for elderly rCDI patients with complex

comorbidities. It especially offers experience regarding the challenging administration of WMT via colonic TET.

Ethics approval and consent to participate

This study was reviewed and approved by the Ethnic Committee of Beijing Rectum Hospital, with the approval number: 2021ELLHA-023-01. The patient and his legal guardians provided informed consent to participate in the study and to the submission and publication of this case report, including all images, data and associated text.

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Data availability statement

All data generated or analyzed during this study are included in this published article. All data and materials are available with the corresponding author on reasonable request.

CRedit authorship contribution statement

Xinyu Zhang: Writing – original draft, Conceptualization. **Yuan Li:** Writing – review & editing. **Bo Li:** Writing – review & editing, Methodology. **Jingwei Wu:** Project administration, Data curation. **Junmei Zhang:** Writing – review & editing, Supervision, Funding acquisition. **Xia Ding:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Junmei Zhang reports financial support was provided by Beijing Xicheng District Health Bureau. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

FMT	Fecal microbiota transplantation
CD	Clostridioides difficile
CDI	Clostridioides difficile infection
rCDI	recurrent Clostridioides difficile infection
CLL	Chronic lymphocytic leukemia
TET	Transendoscopic enteral tubing
AEs	Adverse Events
SAEs	Serious AEs
GI	Gastrointestinal
PCR	Polymerase chain reaction
CCI	Charlson comorbidity index
aCCI	age Charlson comorbidity index
ICU	Intensive care unit

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