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Case Report

Fecal Microbiota Transplantation (FMT) for the Treatment of Primary *Clostridium Difficile*-Associated Diarrhea: A Pioneer Case Study in ASEAN

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Abstract

Fecal microbiota transplantation (FMT) has been recently introduced in Association of Southeast Asian Nations (ASEAN) to treat many diseases affecting gut-bacterial dysbiosis. *Clostridium difficile* infection results from disruption of normal gastrointestinal tract flora. Hence, FMT has been approved to be an alternative treatment of recurrent *Clostridium difficile* (*C. difficile*) infection which reported from many studies with higher curative rate, lower recurrence rate, and lower cost of treatment than antimicrobial therapy. There was only one study reported higher efficacy of FMT for treating primary *C. difficile* infection and lower recurrence rate compared with metronidazole. This present report is a pioneer case in ASEAN who developed primary *C. difficile* infection treated with FMT. We report the case of a 51-year-old man was diagnosed with community-acquired pneumonia and admitted to Thammasat University Hospital, Thailand. He received ceftriaxone and oral azithromycin. On the next days after receiving antibiotics, he developed diarrhea with low-grade fever. Stool for *C. difficile* toxin B was positive. He was diagnosed with primary *C. difficile* infection. He received a single dose of 200ml FMT as the initial treatment. His symptoms were improved within one day after treatment. He had no adverse event and no recurrent infection. This case report showed effective response of FMT for primary *C. difficile* infection without any adverse event. FMT might be a treatment of choice for primary *C. difficile* infection. Further study should be performed to confirm this efficacy.

Keywords: *Clostridium Difficile*; Antimicrobial Therapy; Metronidazole; Gastrointestinal Tract Flora; Gut-Bacterial Dysbiosis; Hypotension; Diarrhea

Abbreviations: ASEAN: Association of Southeast Asian Nations; '*C. difficile*, *Clostridium difficile* (*C. difficile*); FMT: Fecal microbiota transplantation

Introduction

Fecal microbiota transplantation (FMT) is a method which infuses feces from healthy donor into the intestinal tract of a recipient to restore normal gut microbial composition owing to treat specific disease affecting gut-bacterial dysbiosis [1]. Hence, FMT has been proposed to be alternative effective treatment of recurrent *Clostridium difficile* (*C. difficile*) infection. It has higher success rate, lower recurrence rate, and lower cost of treatment than repeated antibiotic treatment [2]. So far, there has been increasing interest in the use of FMT to treat other gastrointestinal diseases and extra-intestinal diseases [3]. There is one study reported higher efficacy of FMT for treating primary *C. difficile* infection, as compared with metronidazole [4]. FMT may be an alternative treatment modality for primary *C. difficile* infection. However, FMT has been recently introduced in Thailand and in Association of Southeast Asian Nations (ASEAN). This present report is a pioneer case in ASEAN of 51-year-old man who developed primary *C. difficile* infection treated with FMT.

Case Report

A 51-year-old Thai man with well-controlled asthma, alcoholic cirrhosis child A, and no prior history of diarrhea, presented to

the Emergency Department with a 3-day of high-grade fever, productive cough, and progressive dyspnea. He was diagnosed with community acquired pneumonia and admitted to Thammasat University Hospital, Thailand. He received intravenous ceftriaxone 2 grams daily and oral azithromycin 500mg daily. On the next days after receiving antibiotics, his respiratory symptoms had improved, but he developed passing of watery stool with 3-4 bowel movements per day with low-grade fever. On physical examination, he was alert with no sign of respiratory distress. Initial vital signs were normal, without hypotension. His abdomen was mildly distension with normoactive bowel sound and no sign of peritonitis. Laboratory studies showed no leukocytosis and normal metabolic panels except for hypoalbuminemia with reversed albumin-to-globulin ratio from alcoholic cirrhosis. Stool exam showed brownish stool with no mucous, 1-2 cells/high power field (HPF) of red blood cells and 0-1 cell/HPF of white blood cells. The stool for *C. difficile* toxin revealed positive result of *C. difficile* toxin B. He was diagnosis with primary *C. difficile* infection. Initially, he was undergoing randomization in a trial evaluating the efficacy of FMT for treatment of primary *C. difficile*-associated diarrhea, but the trial was terminated due to the novel coronavirus disease (COVID-19) outbreak with only one patient who was allocated in the FMT group. The stool used in FMT was prepared from stool donor, a 25-year-old healthy man with no previous underlying disease. He denied any risk factor for sexually transmitted disease. The physical examination was normal. This fecal donor has successfully passed the stool donor's screenings including fecal transplant donor history questionnaire, stool and serum extensive tests [5,6]. After the donor is accepted, the donor has to commit to providing at least three samples a week for two months. The fecal material was stored each 50 grams of FMT in the sterile container at -80°C. The frozen feces would be warmed in water bath at 37°C within 2 hours until the feces melted before using of FMT. After that, it would be filtered with the double layer standard micropore for removing colonic content. Finally, it readied to use for FMT. The patient was received a single dose of 200ml FMT via rectal enema without any medical treatment for primary *C. difficile* infection. He had dramatic response to FMT. One day after FMT, the overall clinical symptoms were improved, and stool consistency and bowel movement returned to normal. He was then scheduled for a follow-up visit 10 days after FMT at the outpatient department. He reported having one bowel movement per day and rating 4 points on the Bristol stool scale. He denied any side effects according to FMT.

Discussion

This case report demonstrated a pioneer case in ASEAN of patient with primary *C. difficile* infection treated by FMT as an initial treatment. Tremendous result showed after the first day of treatment with 200ml FMT via rectal enema. Our patient had complete clinical response without recurrent infection or side effect during the follow-up period. *C. difficile* also known as *Clostridioides difficile* is a Gram-positive rod, spore-forming obligate anaerobe bacillus dividing into 2 strains, toxigenic and non-toxigenic strains. Both strains can colonize in human's large intestinal tract. However, only toxigenic strains are pathogen associating with disease [7]. The pathogenic bacterial growth along with toxin production damage entrecotes in large intestinal crypts as a result of application of antibiotic disrupting normal gut microbiota [8]. Toxin A (enterotoxin) and B (cytotoxin) are primary toxins produced by this bacterium. The major virulence factors are Toxin A and B which can induce mucosal inflammation leading to diarrhea [9]. *C. difficile*-associated diarrhea is a most common infectious cause of diarrhea in hospitalized patients and associates with increased mortality, length of stay, and health care cost [10]. High recurrence rate is one of the problems in treating *C. difficile* infection with antibiotics since new resistance and more virulent strains have been emerged.

The mainstay of *C. difficile* infection is antimicrobial agent. However, FMT has been approved as treatment of choice for second or subsequently recurrent *C. difficile* infection by American College of Gastroenterology as well as Infectious Diseases Society of America [11,12]. Treatment of recurrent *C. difficile* infection by FMT had high effectiveness showing disease resolution in 92% of case (ranged of 50 to 100% of case) along with lower recurrence rate, and lower cost of treatment compared with antimicrobial therapy [2,13]. There is a clinical trial which evaluate the use of FMT as treatment for primary *C. difficile* infection. The overall response to treatment was achieve in 7 (78%) patients in the FMT group, as compared with 5 (45%) patients in the metronidazole group [4]. There were no serious treatment-related adverse events in both groups. Our patient had clinical cure and had no recurrent *C. difficile* infection. The clinical outcome of our patient treated with FMT was corelated with the prior study. Adverse events of FMT are uncommon. There were some studies reported adverse events from FMT insertion via rectal enema such as abdominal discomfort, abdominal cramping, and abdominal tenderness [14]. Meanwhile, FMT has reported low rate of serious adverse events which were bacteremia [15,16]. However, there was no adverse event after FMT in primary *C. difficile* infection reported in the prior clinical trial as well as our patient. In the present case, patient was classified as mild disease of primary *C. difficile* infection confirmed by positive result of *C. difficile* toxin B. This case report shows the successful clinical response of primary mild *C. difficile* infection treating with FMT.

Conclusion

The FMT has been recently introduces as a treatment modality of many diseases in ASEAN. Interestingly, application of FMT as initial

treatment of primary *C. difficile* infection in our pioneer patient in ASEAN had high effective response without any side effect. Further research should be performed to evaluate the efficacy of FMT for primary *C. difficile* infection and also side effect of this treatment. FMT may be an alternative first-line treatment of mild to moderate primary *C. difficile* infection in the near future.

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