Systematic Review: Efficacy and Safety of Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection in Children

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Abstract

Background: *Recurrent Clostridium difficile infection (RCDI) continues to increase in incidence and severity around the world. Fecal microbiota transplantation (FMT) is commonly used to treat RCDI in adults, but its efficacy and safety in the pediatric population are infrequently studied. Here, we performed a systematic review to evaluate the efficacy and safety of FMT for RCDI in children.*
Methods: *Systematic literature search was performed using PubMed, Science Direct, Nature, Cochrane Library, and Springer to identify original studies in English language published from 2010-2020. The clinical resolution, bacterial resolution, and failure of therapy were calculated as indicators of efficacy of FMT. Adverse events were also calculated as indicators of FMT safety.*
Results: *A total of 21 studies, with 498 pediatric patients were included in this review. There were 418/498 (84%) patients reported clinical and bacterial resolution. There were 67/498 (13%) patients who experienced FMT-related adverse events, with 97% of them had mild adverse event. There was one patient who reported FMT-related serious adverse events which were aspiration pneumonia and dehydration.*
Conclusion: *We found evidence that supports the efficacy and safety of the use of FMT for treatment of recurrent C. difficile infection in children.*

Keywords: *Children, Fecal Microbiota Transplantation, Recurrent Clostridium difficile Infection*

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Tinjauan Sistematik: Efektivitas dan Keamanan Fecal Microbiota Transplantation pada Infeksi Clostridium difficile Berulang pada Anak

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Abstrak

Pendahuluan: *Insidensi, mortalitas, serta morbiditas dari infeksi Clostridium difficile berulang terus meningkat setiap tahunnya. Transplantasi mikrobiota feses merupakan metode terapi yang sudah banyak digunakan sebagai terapi infeksi Clostridium difficile berulang pada pasien dewasa, namun penelitian terkait tingkat efektivitas dan keamanannya pada pasien anak masih sangat terbatas. Studi ini bertujuan untuk mengetahui tingkat efektivitas dan keamanan FMT sebagai terapi infeksi Clostridium difficile berulang pada anak.*
Metode: *Proses pencarian literatur pada tinjauan pustaka sistematis ini dilakukan pada basis data PubMed, Science Direct, Nature, Cochrane Library, dan Springer untuk mendapatkan studi berbahasa Inggris yang dipublikasi pada tahun 2010-2020. Data resolusi klinis, resolusi bakteriologis, dan kegagalan terapi digunakan sebagai indicator penilaian efektivitas. Data kejadian tidak diharapkan digunakan sebagai indikator keamanan transplantasi mikrobiota feses.*
Hasil: *Sebanyak 21 studi dengan 498 pasien diikutsertakan pada penelitian ini. Terdapat 418/498 (84%) pasien yang dilaporkan mengalami resolusi klinis dan bakteriologis. Sebanyak 67/498 (13%) pasien dilaporkan mengalami kejadian tidak diharapkan yang berhubungan dengan transplantasi mikrobiota feses, dengan 97% diantaranya adalah kejadian tidak diharapkan derajat ringan. Terdapat satu pasien yang mengalami kejadian tidak diharapkan derajat berat berupa pneumonia aspirasi dan dehidrasi.*
Kesimpulan: *Penggunaan transplantasi mikrobiota feses sebagai terapi infeksi Clostridium difficile berulang pada anak terbukti efektif dan aman.*

Kata kunci: *Anak, infeksi Clostridium difficile berulang, transplantasi mikrobiota feses*

Introduction

Clostridium difficile infection (CDI) is an infection in gastrointestinal tract that becomes the leading cause of nosocomial diarrhea in the USA, and continues to increase in incidence and severity around the world.[1,2] The high prevalence of CDI is not only found in the adult but the pediatric population as well. Even in the USA, the prevalence of CDI in the pediatric population has raised by 100.000 cases in the last two decades, and causes 29.000 deaths/year.[3]

The use of antibiotics like vancomycin, metronidazole, and fidaxomicin are not completely effective to counter CDI, because 15-35% of CDI patients were likely to experience recurrent RCDI.[4] In the pediatric population, the rate of recurrence is up to 12-24%.[5]

Fecal microbiota transplantation (FMT) is a therapeutic method that uses the fecal bacteria from a healthy donor to normalize and maintain the patient's normal composition of intestinal microbiota by administering it to the colon of the patient.[6] Recently, FMT is known as the potential therapeutic method for RCDI. In Indonesia, this method is never been used, but this method has so much potential to be used because of the high RCDI incidence in Indonesia (10,9%), and there are plenty hospital that has facility to do this method.[7] There are plenty of studies that studied the efficacy and safety of FMT, but the pediatric population was often excluded from FMT trials. Therefore, the efficacy and safety of FMT for the therapeutic of RCDI in children are unknown. Our study aims to conduct a systematic review of the existing literature to collate the evidence for the efficacy and safety of FMT for RCDI in children.

Methods

The systematic literature search was performed using PubMed, Nature, Springer, Science Direct, and Cochrane Library for English-written literature that studied the efficacy or safety of FMT for RCDI in children and were published from inception until December 2020. A literature search was conducted from November 2020 until December 2020.

We searched the literature in the databases using terms under two broad search themes of 'fecal microbiota transplantation', and 'Clostridium difficile infection'. For the term 'fecal microbiota transplantation', we used a combination of MeSH entry term words fecal microbiota transplantation, fecal transplantation, intestinal microbiota transfer, donor feces infusion, and stool transplant. For the term words 'Clostridium difficile infection' we used a combination of the entry term Clostridium difficile infection, Clostridium difficile, and C. difficile. These keywords were combined using a Boolean operator AND and OR. We decided to not include the term children or pediatric because there are not many studies that specifically research FMT only in the children population. So, we decided to review all the selected literature we had and search any children patients included. After full text review, we exclude literatures that don't differentiate or mention the specific age of the samples (n=81), we exclude literatures that the age of the samples is more than 18 years old (n=93), we exclude literatures that don't mention the episodes of C.difficile infection before getting FMT, because we only search for RCDI patient who had undergone ≥2 episodes of RCDI (n=19). So in total after fulltext review we exclude 193 literatures. Flow diagram describing the study selection process is shown in Figure 1.

We defined children or pediatric patients as someone who is ≤18 years old and has undergone ≥2 episodes of RCDI and been treated with FMT. Our outcomes of interest were clinical resolution, bacteriologic resolution, and failure of therapy as an indicator of the efficacy. We also collect the data of adverse events (AE) and serious adverse events (SAE) as an indicator of the safety of FMT. We define clinical resolution as the absence of diarrhea and hematochezia within three months post-FMT. The bacteriologic resolution is defined as the absence of toxigenic or non-toxigenic C. difficile in patients' feces within three months post-FMT from laboratory testing. The failure of therapy is defined as the absence of the response or there is diarrhea recurrency with or without positive toxin C. difficile. We define AE as any undesirable medical event occurrence in a patient that has a causal relationship with FMT. A serious adverse event is defined as any untoward life-threatening medical event occurrence in a patient that has a causal relationship with FMT.

We reviewed all study types with original data published in the English language. Our literature eligibility criteria are using PICOS (population, intervention, comparison, outcome, studies). We performed the quality assessment of all the included studies to assess the risk of bias in the study. The methodological quality of cohort study is by using JBI Critical Appraisal tools for cohort study. The methodological quality of case series is by using JBI Critical Appraisal tools for case series. The methodological quality of case report study is by using JBI Critical Appraisal tools for case report. Only studies that surpass the cut-off ≥50% of the assessment that included in this review.

One reviewer (F.R) independently screened literature titles and abstracts and excluded irrelevant studies. Data from eligible studies were extracted by one reviewer (F.R) and then crosschecked to review the accuracy by the second and the third author (E.S and I.F.K). We extracted the patient's characteristic data, including age, gender, number of RCDI episodes before FMT, intervention prior to FMT, and comorbid. We collected literature characteristic data, including study design, location, clinical setting, and follow-up duration. We also extracted therapy characteristic data, including delivery method, number of FMT, feces type, dose, and the relation between donors and patients. The efficacy data that we collected including clinical resolution, bacterial resolution, and the failure of therapy. We also collected the safety data, including AE and SAE.

Results

We identified 21 studies that met our inclusion criteria describing 498 patients. Eight of them were cohort studies, five were case series, and eight were case reports. The most common location of the studies was in the USA that comprises seventeen literature, three literature from China, and one from Japan. Twenty of them were single-center studies and only one multicenter study. The characteristic of the studies included is shown in Table 1.

Table 1. Characteristics of The Studies

Author	Year	Study Design	Location	Clinical Setting	Duration (month)
Bluestone, et al	2018	Case Series	USA	Hospital	8,5
Brumbaugh, et al	2018	Cohort Study	USA	Hospital	3,0
Cho, et al	2019	Cohort Study	USA	Hospital	2,0-6,0
Dow, et al	2018	Case Report	USA	Hospital	60,0
Fareed, et al	2018	Cohort study	USA	Hospital	3,0
Flannigan, et al	2017	Case Report	Japan	Hospital	2,7-30,0
Garg, et al	2012	Case Report	USA	Hospital	3,0
Hourigan, et al	2015	Cohort study	USA	Hospital	6,0
Hourigan, et al	2019	Case Series	USA	Hospital	6,0
Kronman, et al	2015	Case Series	USA	Hospital	0,4-23,0
Li, et al	2018	Cohort study	China	Hospital	9,0-36,0
Nicholson, et al	2020	Cohort study	USA	Hospital	2,0
Pierog, et al	2014	Case Series	USA	Hospital	3,0
Rubin, et al	2013	Case Series	USA	Hospital	2,0
Russell, et al	2014	Case Series	USA	Hospital	2,0-48,0
Russell, et al	2010	Case Report	USA	Hospital	6,0
Singh, et al	2012	Case Report	USA	Hospital	3,0
Suskind, et al	2015	Cohort Study	USA	Hospital	3,0
Walia, et al	2014	Case Report	USA	Hospital	8,0-27,0
Wang, et al	2015	Case Report	China	Hospital	4,0
Zhang, et al	2018	Cohort Study	China	Hospital	23,0

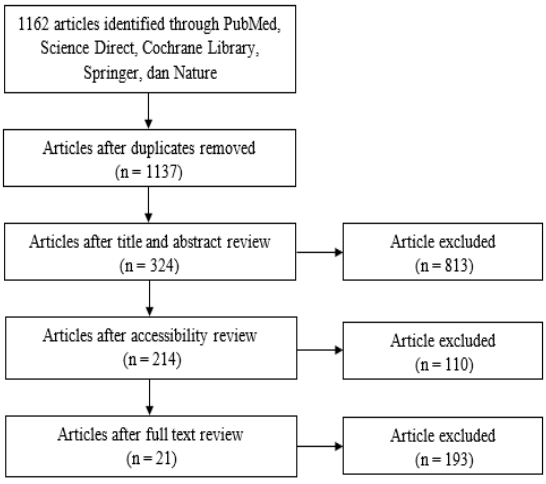

Figure 1. Flowchart for Study Selection

Relating to the journal that reports gender, there were similar proportions, about 48,5%, among females and male. The range of the patient's age was from thirteen-month until eighteen years old. The most common comorbid disease among the patients was inflammatory bowel disease (34%) and immunocompromised (33%). Before the first FMT, patients experienced 3-14 episodes of RCDI. Most patients (91%) had received vancomycin as the treatment for the CDI before FMT. Other's treatments that patients had received prior to the FMT were metronidazole (71%), and vancomycin taper (57%). Other treatments that patient had received before the FMT included intravenous immunoglobulin, probiotic, surgery, and immunosuppressant.

There were many routes of FMT that

Table 2. Summary of Included Articles

Author, Year	(n) Patients Included	FMT Delivery	Comorbid disease	Feces Type	Clinical Resolution (n)	Bacteriological Resolution	Failure of Therapy	AE	SAE
Bluestone et al, 2018[8]	3	CC; GT	Leukemia, hirschsprung disease	Fr; Fz	Yes (1); no (2)	AC and TC positive; AC negative	Yes	Vomit	NR
Brumbaugh et al, 2018[9]	42	NGT; GT; oral	IBD, Malignancy	Fr	Yes (32); no (10)	NR	No	Vomit	No
Cho et al, 2019[10]	8	CC	IBD, UC, CD	Fz	Yes (6); no (2)	NR	No	Fever; AP	No
Dow et al, 2018[11]	1	GT	Pompe disease, B cell immunodeficiency	Fr	Yes (1)	TC negative	No	No	No
Fareed et al, 2018[12]	15	CC; NIT	IBD	Fz	Yes (15)	AC negative	No	No	No
Flannigan et al, 2017[13]	1	Enm; oral	Heart transplant, atopy	Fr	Yes (1)	TC negative	No	No	No
Garg et al, 2012[14]	1	CC	GERD, premature, chronic lung disease	Fr	Yes (1)	NR	No	No	No
Hourigan et al, 2015[15]	8	CC	IBD, POTS	Fr	Yes (8)	TC Negative	No	No	No
Hourigan et al, 2019[16]	8	CC	GERD, cystic fibrosis, POTS	Fr; Fz	Yes (8)	TC Negative	No	No	No
Kronman et al, 2015[17]	10	NG; NIT	IBD, cerebral palsy, wilms tumor	Fr	Yes (9); no (1)	NR	Yes	Vomit	No
Nicholson et al, 2020[19]	335	CC; NGT; NIT	IBD, colitis immocompromised	Fr; Fz	Yes (271)	NR	Yes	AP; diarhea AD	PA; dehidration
Pierog et al, 2014[20]	4	CC	Hirschsprung disease, ES	Fr	Yes (4)	TC negative	No	No	No
Rubin et al, 2013[21]	2	NR	NR	NR	Yes (1) no (1)	TC negative	Yes	No	No
Russell et al, 2014[22]	10	NGT; CC	IBS, IBD, CD, UC	Fr	Yes (10)	EIA negative	No	Diarhea; HMC	No
Russell et al, 2010[23]	1	NGT	Acute otitis media	Fr	Yes (1)	EIA negative	No	No	No
Singh et al, 2012[24]	1	NGT	UC	Fr	Yes (1)	AC dan TC negative	No	No	No
Suskind et al, 2015[25]	1	NGT	UC	Fr	No (1)	C. difficile positive	Yes	NR	No
Walia et al, 2014[26]	2	CC	GERD, premature, chronic lung disease	Fr	Yes (2)	TC negative	No	No	No
Wang et al, 2015[27]	1	NIT	Pseudomembranous colitis, malnutrition	Fr	Yes (1)	NR	No	No	No
Zhang et al, 2018[28]	33	NIT,NGT, Enm	NR	Fz	Yes (33)	NR	No	AP; diarrhea; Fever; vomit	No

AC= antigen Clostridium difficile; AD= abdominal distension; AP= abdominal pain; CC= colonoscopy; CD= crohn disease; Enm= enema; Fr= fresh stool; Fz= frozen stool; GERD= gastroesophageal reflux disease; GT= gastric tube; G-tube= gastrostomy tube; HMC= hematochezia; IBD= irritable bowel syndrome; MD= mitochondrial disease; NGT= nasogastric tube; NIT= nasointestinal; NR= not reported; AP= aspiration pneumonia; POTS= postural orthostatic tachycardia syndrome; TC= toxin Clostridium difficile; Sig= sigmoid; UC= ulcerative colitis

were used, including colonoscopy, gastrostomy tube, nasointestinal tube, gastrointestinal tube, enema, and per oral. Colonoscopy was the most common route of delivery of FMT in 65% of patients, while the other 25% had FMT through the upper gastrointestinal route such as via nasogastric tube and gastrostomy tube. 260 FMT procedures (47%) used frozen stool and 260 procedures (46%) used a fresh stool. Among those reporting sources of stool, the unrelated donor becomes the most common source that was employed in 55,6% of patients.

A total of 498 patients had data on outcome and were included in the analysis of FMT efficacy. Of these, 418 patients (84%) had clinical resolution of RCDI that consists of 379 patients (76%) after the first treatment of FMT, and 39 patients (85) after multiple FMT. Meanwhile 80 patients (16%) experienced failure of therapy, including 61 patients (12%) failure at the first FMT, and 19 patients (4%) after multiple FMT. In the analysis of bacteriological resolution, there were just 78 patients who had the data. Based on the data, 65 patients had bacteriological resolution (83%). Compared to the route of the delivery of FMT, colonoscopy has the highest success rate (86%). In terms of comorbid disease, patients with IBD had a77% success rate, and patients with immunocompromised had a success rate of 73%.The summary of all studied articles is shown in Table 2.

All 497 patients were included in the analysis of the FMT safety. AE was found in 83 patients, but only 67 patients (13%) who had FMT-related AE. Among those AE, 97% of it was mild AE, including abdominal pain (44%), diarrhea (41%), abdominal distension (31%), vomit (28%), and fever (3%). There were 2 patients (3%) who had a moderate AE that was hematochezia.

Discussion

Our review on 21 literatures found that the use of FMT for RCDI in children is effective, with an 84% success rate, because 418 patients from 498 patients had clinical resolution after getting FMT therapy. This result is parallel with the success rate of FMT for the adult patient which is 80-90%.[28,29] In comparison, a cohort study that studied the efficacy of FMT found that the efficacy of this method in children is 86,6%.[19]

In terms of the route of FMT, we found that the use of colonoscopy had the highest success rate at 86%, with 279 patients from 322 patients had resolution. Another study by Postigo et. al also found that colonoscopy is the most effective route of FMT delivery.[30] Nicholson et al.[19] in his cohort study identified that the use of colonoscopy had a significant correlation with the success of FMT in children (p= 0,008). Brumbaugh et. al on his study stated that the reason of the use of colonoscopy as the route of FMT had the highest efficacy because it is does not pass the stomach and small bowel that may reduce the viable bacterial load reaching the colon because of its high acidity environment, so there are greater bacteria counts in the feces that achieve the colon via colonoscopy rather than other routes.[9]

In our review, the presence of the comorbid disease had an impact on the FMT success rate. Patients with the comorbid disease are more likely to have a lower FMT efficacy. Among patients with IBD, we found that the success rate is 77% (129 patients from 168 patients), and in the immunocompromised patient is 73% (119 patients from 163 patients), when the success rate of patients without any comorbid disease is 100% (203 patients). Another study also found the same, that the patients with IBD have a lower success rate 54% rather than patients without comorbid 94%.[8] In the other systematic review by Shogbesan et.al the efficacy of FMT in immunocompromised patients is 87%, they stated that this lower efficacy can occur because the most immunocompromised patient had been exposed to antibiotics, chemotherapy, and formula-based diet for a long time.[5] In line with the RCDI patients with IBD, the long exposure to the antibiotic, immunosuppressant, chemotherapy, and formula-based diet are likely to reduce the normal microbiota diversity in intestinal, and triggering the regrowth of C. difficile colony after FMT.[8]

In the analysis of FMT safety for children, we found that only 13% (67 patients from 498 patients) of patients who had experienced AE, with 97% (64 patients) of them were mild AE that doesn't require any medical intervention. The retrospective study by Zhang et al.[6] also found that the incidence of AE in children after FMT were 26,3% that consists of mild AE. Our study on SAE found that there are 1,8% of patients that had RCDI along with immunocompromised disease or in immunosuppressant therapy. In terms of the comorbid disease presence, we found that 90% of patients who experienced AE were the ones who had the comorbid disease, including eleven patients with IBD, thirty-two patients with the immunocompromised disease, and

four patients with pseudomembranous colitis. The same result was also found in another study which show that all of the patients with AE were the ones with comorbid such as leukemia, IBD, GERD, congenital heart disease, and short bowel syndrome.[19]

Our study has the following strengths. This study addresses a very specific population, children with RCDI that has a high incidence and recurrence rate. We also only include the literature that suits our criteria, had a minimal risk of bias and high quality. We also included the only patient who met our standard, predetermined as a child who had age ≤18 years old with minimal 2 episodes of RCDI. However, our review also has some limitations. We only reviewed cohort study, case series study, and case report without any RCTs, because until this time there are no RCTs that studied FMT for RCDI in children. We also had some missing data in the data of demography, route of delivery of FMT, comorbid disease, the dose of feces suspension, the presence of AE and SAE, and the data of bacteriological resolution. We had tried to search the supplementary data of the literature, but not all of them provide it. However, the number of patients who were included in this study that reach up to 498 patients from the various country was able to describe and represented the aim of this study.

Conclusion

Fecal Microbiota Transplantation (FMT) is a promising therapy for RCDI in children because of its high success rate and low incidence of AE and SAE. The use of FMT in RCDI patients with comorbid disease is still effective but requires special attention before and after the FMT procedure. Colonoscopy becomes the most appropriate route of FMT delivery for pediatric patients. We also conclude that the presence of comorbid disease had an impact on the presence of AE and SAE after FMT.

Conflicts of Interest

The authors declare that they have no conflicts of interest

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