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Characteristics and management of children with Clostridioides difficile infection at a tertiary pediatric hospital in China

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ABSTRACT

Background: Clostridiodes difficile infection (CDI) is one of the most common causes of antibiotic-associated diarrhea in children. Conventional antibiotics and emerging fecal microbiota transplantation (FMT) are used to treat CDI.

Methods: Children with CDI admitted to the Shanghai Children's Hospital, from September 2014 to September 2020, were retrospectively included to this observational study. Pediatric patients were assigned as initial CDI and recurrent CDI (RCDI), and symptoms, comorbidities, imaging findings, laboratory tests, and treatments were systematically recorded and analyzed.

Results: Of 109 pediatric patients with CDI, 58 were boys (53.2%), and the median age was 5 years (range, 2-9 years). The main clinical symptoms of CDI children were diarrhea (109/109, 100%), hematochezia (55/109, 50.46%), abdominal pain (40/109, 36.70%); fever, pseudomembrane, vomit, and bloating were observed in 39 (35.78%), 33 (30.28%), and 24 (22.02%) patients, respectively. For the primary therapy with conventional antibiotics, 68 patients received metronidazole, and 41 patients received vancomycin. RCDI occurred in 48.53% (33/68) of those initially treated with metronidazole compared with 46.33% (19/41) of those initially treated with vancomycin (p=0.825). The total resolution rate of FMT for RCDI children was significantly higher than with vancomycin treatment (28/29, 96.55% vs 11/23, 47.83%, $p < 0.001$). There were no serious adverse events (SAEs) reported after two months of FMT.

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CDI, Clostridium difficile infection; RCDI, recurrent Clostridium difficile infection; FMT, fecal microbiota transplantation; CRP, C-reactive protein; CT, computerized tomography; IQR, interquartile; PCT, plateletcrit; PPI, proton pump inhibitor; WBC, white blood cells

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Conclusions: The major manifestations of children with CDI were diarrhea, hematochezia, and abdominal pain. The cure rate of FMT for pediatric RCDI is superior to vancomycin treatment.

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Introduction

Clostridiodes (formerly Clostridium) difficile (C. difficile) infection (CDI) is a major cause of healthcare-associated diarrhea especially antibiotic-associated diarrhea that poses a serious public health challenge.[1,2] In the past decades, the prevalence and severity of CDI in children increased because of the emergence of more virulent C. difficile strains.[3-5] CDI is generally treated by conventional antibiotics, including metronidazole and vancomycin, but with a high risk of recurrence.[3] Recurrence rate of CDI has been reported to vary from 5% to 50%, with an average of 20%, and it can be as high as 45-75% after the first recurrence.[4,6] The causes of recurrence are multifactorial, such as dysbiosis of gut microbiota, continued C. difficile exposure, and incomplete host immune response.[7,8] A high burden to patients and a growing economic burden to the healthcare system are consequences of the high morbidity and mortality of CDI.[9–12] Thus, it is important to understand the epidemiology and risk factors of CDI to help guiding priorities for disease prevention and treatment. Fecal microbiota transplantation (FMT) has received increasing attention as an emerging therapeutic option for recurrent CDI (RCDI) with cure rates of 90-100% in adults.[13-15] According to the newest guideline, the first-line treatment for pediatric CDI is vancomycin.[3] Although FMT is recommended as a therapy for RCDI that failed to respond to antibiotics and other treatments in adults, FMT is indicated in only about 25% of hospitals.[16] The lack of randomized controlled trial (RCT) data, the paucity of standard treatment protocols, and uncertainty about long-term safety of FMT may explain the poor uptake. Researches about FMT or other treatments in children with CDI are still not sufficient, especially in Asia.

In this study, we aimed to analyze the characteristics and management of children with CDI at a tertiary pediatric hospital in China. The outcomes of metronidazole and vancomycin as initial therapies for CDI, as well as FMT and vancomycin for RCDI in children were compared to evaluate the clinical efficacy of different options.

Materials and methods

Study cohorts

A total of 109 children diagnosed as CDI at the Shanghai Children's Hospital were retrospectively recruited to the study cohort between September 2014 to September 2020. Inclusion criteria were children with CDI presenting clinical symptoms that required hospital admission. Enrolled patients were classified as either initial CDI or RCDI. Initial CDI was defined as patients with three or more liquid stools (Bristol 6-7) per day, and either a positive stool test for CD toxins or a PCR detection of toxigenic CD, or colonoscopic findings revealing pseudomembranous colitis without CDI diagnosis in the past eight weeks.[3] RCDI was defined as initial CDI followed by either absence of symptom remission or recurrence of symptoms within eight weeks following the previous treatment. Children with allergy to the study drug, fulminant colitis that contraindicated medical treatment were excluded. Symptoms, presence of comorbidities (e.g., inflammatory bowel disease, IBD), imaging findings, including abdominal computerized tomography (CT) scan and endoscopy, laboratory tests, recent antibiotic and proton pump inhibitor (PPI) use (any antibiotics or PPI received in the 30 days before CDI diagnosis) and treatments were extracted from the inpatient electronic medical records (EMRs) and systematically analyzed. Written informed consent was obtained from all participants or from parents or legal guardians for those under 16 years old. This study was approved by the Medical Ethics Committee of Shanghai Children's Hospital. The data used in this study was anonymized before use.

Treatment

Following the guidelines,[3,17] 10-14 days of oral metronidazole (7.5 mg/kg, 3 or 4 times daily) or vancomycin (10 mg/kg, 4 times daily) was administered for children with an initial episode of CDI. For RCDI, 10-14 days of oral vancomycin (10 mg/kg, 4 times daily) or FMT was used. FMT was recommended for children at the second or subsequent RCDI who had failed standard antibiotic treatments at our institution.[3] Before FMT patients or their guardians had to complete an informed consent for this procedure. Healthy stool donors were screened based on medical history and laboratory testing. The collected fresh stools from donors were mixed using 200–250 ml sterilized saline per 150 g stools and centrifuged at 700 g for 2–3 min. Then, to remove large particles, the stool suspension was filtered by two layers of medical gauze. Stool supernatant was collected into 50 ml syringes for immediate FMT, fecal capsules preparation, or stored in 50 mL tubes frozen in -80°C for further FMT. The donated fecal solution was infused to the recipient's gut via nasointestinal tube, retention enema, or capsule. Children with CDI stopped antibiotic treatment 48 hours before the FMT procedure. The detailed FMT protocol was described elsewhere.[18] The administration method was chosen according to the patient's condition. The definition of cure was no clinical symptoms of CDI, and either a negative stool test for CD toxins or a negative PCR detection of toxigenic CD after eight weeks of treatment.[3] Treatment failure was deemed in case of symptoms return and need of further CDI therapy within eight weeks after finishing the

management course (a recurrence). The clinical efficacy and adverse events (AE) were assessed at 1, 2 weeks, and three months after FMT.

Statistical analyses

Statistical analysis was performed with SPSS 25.0 software. Demographic and clinical characteristics are expressed as frequencies and proportions for categorical variables, mean SD or median and interquartile (IQR) for continuous variables. One-way ANOVA was used for categorical variables and the Mann-Whitney U test for continuous variables. A p-value of <0.05 was considered as statistically significant.

Results

Patients' characteristics

Of all 109 enrolled patients, 58 were boys (53.2%), median age of 4.9 years (range, 2-9 years). Sixteen (14.68%) CDI cases had known or later found with inflammatory bowel disease (IBD), 5 (4.59%) patients were later confirmed as immunodeficient, and 4 (3.67%) children were diagnosed with neoplastic hematologic disorder. Exposure to antibiotics and proton pump inhibitor (PPI) occurred in 86 (78.89%) and 24 (22.02%) cases, respectively. The main clinical symptoms of CDI children were diarrhea (109/109, 100%), hematochezia (55/109, 50.46%), abdominal pain (40/109, 36.70%); fever, pseudomembrane, vomit, and bloating were observed in 39 (35.78%), 33 (30.28%), 24 (22.02%) patients, respectively. Laboratory testing revealed increased white blood cells (WBC) in most patients. After the primary treatment, the recurrence rate was about 47.7% (Table 1).

Table 1 – Characteristics of the pediatric patients with Clostridiodes difficile infection.

Variables	N = 109
Sex, male, n (%)	58 (53.21)
Age (year, median, range)	5.00 (2.00-9.00)
Exposure history, n (%)	
Antibiotics	86 (78.89)
PPI	24 (22.02)
Symptoms, n (%)	
Fever	29 (26.61)
Vomit	28 (25.69)
Diarrhea	109 (100.00)
Bloating	12 (11.01)
Abdominal pain	40 (36.70)
Hematochezia	55 (50.46)
Pseudomembrane	33 (30.28)
Laboratory finding, median (IQR)	
WBC (*10^9/L)	8.89 (6.95-12.40)
Neutrophil (%)	52.40 (34.90-69.00)
Hemoglobin (g/L)	127.00 (117.00-135.00)
CRP (mg/L)	5.00 (4.00-36.00)
PCT (ng/ml)	0.10 (0.05-0.15)
Albumin (g/L)	42.48 (38.36-44.52)
Creatinine (μmol/L)	35.00 (25.00-40.00)
ALT (U/L)	12.00 (9.00-18.00)
AST (U/L)	31.00 (24.00-36.00)
Endoscopy, n (%)	
Pseudomembranous colitis	12 (11.01)
Inflammation	51 (46.79)
Abdominal CT scan, n (%)	
Effusion	19 (17.43)
Pneumatosis	24 (22.02)
Recurrence rate, n (%)	52 (47.7)

ALT, alanine transaminase; AST, aspartate aminotransferase; CDI, Clostridiodes difficile infection; CRP, C-reactive protein; CT, computerized tomography; IQR, interquartile; PCT, plateletcrit; PPI, proton pump inhibitor; WBC, white blood cells.

Outcome of pediatric CDI treated with antibiotics

For the initial therapy with antibiotics, 68 patients received metronidazole, and 41 received vancomycin. As shown in Table 2, there were no significant differences in characteristics and clinical symptoms between patients treated with metronidazole or vancomycin, including age, sex, laboratory tests, endoscopy, and abnormal CT scan findings. Thirty-five patients were cured by metronidazole (35/68, 51.47%), and 22 patients were successful treated with vancomycin (22/41, 53.67%). There were no significant difference in cure rates of CDI between metronidazole and vancomycin treatment groups ($p = 0.825$).

FMT is superior to vancomycin for pediatric RCDI

After first round of conventional antibiotics treatments, 52 patients (52/109, 47.7%) who presented with RCDI were further treated either by second round of antibiotic or FMT. As showed in Table 3, 23 RCDI patients received vancomycin and 29 patients received FMT. There were no significant differences in age, sex, clinical symptoms, endoscopy, and abdominal CT findings between the two groups. The laboratory findings showed that the CRP was higher ($p = 0.048$) and albumin was lower ($p = 0.048$) in patients treated with vancomycin compared to those treated with FMT different ($p = 0.048$). A cure rate of 47.8% (11/23) was observed in RCDI patients treated with vancomycin.

In the FMT treated group, a total of 56 FMT procedures were performed, 64.3% (36/56) using an upper route with a nasointestinal tube, 28.6% (16/56) with lower route by retention enema, and 7.1% (4/56) by capsule. Twenty-two donors (22/29, 68.2%) were unrelated donors, and 7 (7/29, 31.8%) were parents of children. Nineteen (19/29, 65.5%) children were cured after a single FMT, and 9 (9/29, 31.1%) children were cured after 2 to 3 FMT (Table 4). Three months after FMT, there was no recurrence of symptoms and CD toxin tests were all negative. The cure rate of RCDI by FMT was significantly higher than that of vancomycin (96.6% vs 47.8%, $p < 0.001$).

Adverse events (AEs)

There were no severe AEs reported after FMT within 24 hours and after three months. Four children (4/56, 5.4%) were reported with mild and self-limited AEs. Transient diarrhea was found in one patient on the day of FMT, and spontaneously disappeared after two days. Transient mild abdominal pain was reported in a child immediately after the FMT procedure. No other immediate or delayed side effects of FMT were

Table 2 – Characteristics of pediatric patients with Clostridiodes difficile infection treated with antibiotics.

Variables	Metronidazole (n = 68)	Vancomycin (n = 41)	p-value*
Gender, male, n (%)	38 (55.88)	20 (48.78)	0.474
Age (year, median, range)	5.00 (2.00-9.75)	4.55 (1.88-7.85)	0.817
Exposure history, n (%)			
Antibiotics	51 (75.00)	35 (85.37)	0.201
PPI	16 (23.53)	9 (21.95)	0.850
Symptoms, n (%)			
Fever	18 (26.47)	11 (26.83)	0.967
Vomit	17 (25.00)	7 (17.07)	0.336
Diarrhea	68 (100)	41 (100)	0.214
Bloating	9 (13.24)	3 (7.32)	0.341
Abdominal pain	28 (41.18)	12 (29.27)	0.214
Hematochezia	32 (47.06)	23 (56.10)	0.363
Pseudomembrane	17 (25.00)	16 (39.02)	0.124
Laboratory finding, median (IQR)			
WBC (*10^9/L)	10.03 (7.01-14.11)	9.09 (6.54-12.89)	0.283
Neutrophil (%)	53.20 (35.65-75.25)	53.20 (33.70-64.23)	0.145
Hemoglobin (g/L)	127.00 (110.00-133.00)	124 (115.75-133.75)	0.541
CRP (mg/L)	5.00 (4.00-36.00)	5.00 (5.00-6.25)	0.130
PCT (ng/ml)	0.10 (0.05-0.18)	0.10 (0.06-0.16)	0.912
Albumin (g/L)	42.74 (37.43-44.71)	42.18 (34.86-46.31)	0.225
Creatinine (μmol/L)	32.00 (23.50-37.50)	29.00 (21.00-37.00)	0.063
ALT (U/L)	12.00 (9.50-18.00)	14.50 (9.75-21.25)	0.756
AST (U/L)	31.00 (22.00-33.00)	32.00 (20.75-40.00)	0.456
Endoscopy, n (%)			
Pseudomembranous colitis	6 (8.82)	6 (14.63)	0.350
Inflammation	27 (39.71)	24 (58.54)	0.057
Abdominal CT scan, n (%)			
Effusion	11 (16.18)	8 (19.51)	0.658
Pneumatosis	14 (20.59)	10 (24.39)	0.644
Cure rate, n (%)	35 (51.47)	22 (55.67)	0.825

* The data were compared by the nonparametric Mann–Whitney test.
ALT, alanine transaminase; AST, aspartate aminotransferase; CDI, Clostridiodes difficile infection; CRP, C-reactive protein; CT, computerized tomography; IQR, interquartile; PCT, plateletcrit; PPI, proton pump inhibitor; WBC, white blood cells.

reported during follow-up. One patient had transient fever and returned to normal by the time of second FMT. In addition, another child had vomited during FMT procedure and improved at the second day. During the follow-up period, no deaths occurred and no adverse events could be associated to a specific antibiotic treatment (Table 4).

Discussion

This was the first study of children with CDI in China. We analyzed the characteristics and compared the efficacy of different treatments for CDI patients in a tertiary pediatric hospital. A higher recurrence rate (47.7%) was showed in this research compared with previous pediatric literature (20%–29%).[19-21] The increasing antibiotic use and the presence of a hypervirulent strain have been described to be associated with the rising incidence of CDI in adults.[22,23] Most of our patients (78.89%) had antibiotic exposure, which has been reported in 22%–76% of children with CDI in other studies.[24-26]

For primary therapy, according to the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), oral vancomycin is recommended as the first-line option for children with an initial episode of severe CDI or a second or greater episode of RCDI.[3] Our data showed that the resolution rates for metronidazole and vancomycin were similar, which indicated that metronidazole could be used as primary treatment for pediatric CDI. But the number of patients in this study was not sufficient to demonstrate a difference between the two antibiotics, and larger, randomized, blinded studies are needed. Furthermore, fidaxomicin is recommended as the preferred alternative for non-severe CDI cases in adults since 2011, but it is not applicable for children with CDI.[3]

RCDI in children is the main cause of increased morbidity and represents a substantial economic burden in recent years. FMT was recommended as a cost-effective strategy for treating second or subsequent recurrences in the 2018 IDSA guidelines.[27] FMT proved to be superior to conventional antibiotics for RCDI treatment.[12] A systematic review found that the cure rate of adult RCDI without recurrence after FMT was 85%.[15] Although FMT for adults with RCDI has been well studied in recent years, the data in children were limited and controlled trials were rarely reported. A large multicenter cohort study demonstrated the efficacy of FMT for the treatment of pediatric CDI was 81%.[28] Our previous research also showed that the cure rate of single FMT in RCDI was 63.6%.[18] In this study, the overall clinical efficacy of FMT for RCDI was 96.6%, which is consistent with the findings in previous clinical studies.[12,15,20]

Table 3 – Characteristics of pediatric patients with recurrent Clostridiodes difficile infection treated with vancomycin or FMT.

Variables	Vancomycin (n=23)	FMT (n=29)	P-value*
Sex, male, n (%)	11 (47.8)	12 (41.4)	0.645
Age (year, median, range)	6.5 (2.5-9.75)	4.0 (1.635-8.5)	0.196
Exposure history, n (%)			
Antibiotics	22 (95.7)	23 (79.3)	0.089
PPI	8 (34)	9 (31.0)	0.777
Symptoms, n (%)			
Fever	7 (30.4)	6 (20.7)	0.425
Vomit	5 (21.7)	3 (10.3)	0.442
Diarrhea	19 (82.6)	26 (89.7)	0.464
Bloating	5 (21.7)	3 (10.3)	0.263
Abdominal pain	13 (56.5)	9 (31.0)	0.067
Hematochezia	14 (60.9)	20 (69.0)	0.546
Pseudomembrane	12 (52.2)	14 (48.3)	0.782
Laboratory finding, median (IQR)			
WBC (*10^9/L)	9.46 (7.08-16.36)	10.04 (7.91-15.8)	0.381
Neutrophil (%)	62.3 (39.6-72.3)	52.5 (35-64.98)	0.061
Hemoglobin (g/L)	126 (101.5-131.75)	124.5 (108.5-132)	0.561
CRP (mg/L)	5 (3.5-26)	5 (1.25-11.75)	0.048
PCT (ng/ml)	0.1 (0.07-0.20)	0.1 (0.05-0.23)	0.484
Albumin (g/L)	38.9 (35.35-45.84)	42.35 (35.35-44.54)	0.048
Creatinine (μmol/L)	29 (21-35)	26.5 (20-35.75)	0.523
ALT (U/L)	14 (11-28)	15 (10.5-26)	0.684
AST (U/L)	32 (22.5-35.5)	31.5 (20.25-36)	0.726
Endoscopy, n (%)			
Pseudomembranous colitis	5 (21.7)	4 (13.8)	0.456
Inflammation	10 (43.5)	18 (62.1)	0.186
Abdominal CT scan, n (%)			
Effusion	6 (26.1)	6 (20.7)	0.650
Pneumatosis	7 (30.4)	6 (20.7)	0.425
Cure rate, n (%)	11 (47.8)	28(96.6)	<0.001

* The data were compared by the nonparametric Mann–Whitney test.
ALT, alanine transaminase; AST, aspartate aminotransferase; CDI, Clostridiodes difficile infection; RCDI, recurrent Clostridiodes difficile infection; FMT, fecal microbiota transplantation; CRP, C-reactive protein; CT, computerized tomography; IQR, interquartile; PCT, plateletcrit; PPI, proton pump inhibitor; WBC, white blood cells.

In the present study, the single resolution rate of FMT was 65.5%, and the multiple resolution rate of FMT was 31.1%. The lower cure rate of single FMT may have been due to the low dose of feces infused into the gut, frozen donor stools, or short retention time. Fresh versus frozen donor stools for CDI were compared in previous adult studies. In a randomized, double-blind, noninferiority trial of adults undergoing FMT for CDI, there were no significant differences in clinical effect between the use of frozen/thawed versus fresh FMT.[29] Most (64.3%) of FMT procedures were performed using an upper route with a nasointestinal tube, 28.6% (16/56) with lower route by retention enema, and 7.1% (4/56) by capsule. In adult studies, trends have suggested that FMT via colonoscopy is slightly more effective. A systematic review demonstrated that there was a significant difference between lower gastrointestinal and upper gastrointestinal routes of delivery, with clinical resolution in 95% versus 88%, respectively.[30]

Risk versus benefit needs to be carefully considered in pediatric patients undergoing FMT, especially children with IBD and immune deficiency.[31-33] One of the major concerns about FMT in children is the unknown impact of FMT on the developing gut microbiota. Luckily, by using FMT, we are often able to shorten the course of antibiotic treatment of CDI. Suchitra et al. found that FMT for CDI in children decreased antimicrobial resistance (AMR) genes, potential

Table 4 – Characteristics of children treated with fecal microbiota transplantation (FMT) for recurrent Clostridiodes difficile infection (RCDI).

Variables	RCDI (n = 29)
Donors' relationship to patient	
Parent, n (%)	7 (31.8)
Unrelated volunteer, n (%)	22 (68.2)
Donors' sex, male, n (%)	22 (68.2)
Median age of donors (years, range)	32 (27,36)
Time of RCDI	1 (0-2)
Route of FMT (n=56), n (%)	
Nasal jejunal tube	36 (64.3)
Retention enema	16 (28.6)
Capsule	4 (7.1)
Time from FMT to resolution of diarrhea (days)	1 (0-1)
Adverse events, n (%)	
Fever	1 (1.8)
Transient diarrhea	1 (1.8)
Transient mild abdominal pain	1 (1.8)
Vomit	1 (1.8)

pathogens and changes of microbiota composition and function.[19] In some pediatric cases, adverse events of FMT, for example, mild transient symptoms including diarrhea, abdominal pain, and vomiting, were reported.[34] In the present study, only a few children were reported with mild and self-limited adverse events, including transient diarrhea, transient mild abdominal pain, transient fever, and vomiting during FMT procedure.

Our study was limited by its retrospective nature and the collection of available data from the clinical records, and a follow up not long enough. Another limitation was the relatively small sample size of the study cohort from a single center. Studies with larger cohorts from multiple centers are needed to further evaluate the clinical features and therapies of CDI in children. Finally, the assessment of treatment outcomes may be affected by physicians' experiences and short-term follow-up after discharge.

Conclusions

Our data show cure rates of various therapy options for CDI in children. We found that FMT is superior to vancomycin in pediatric RCDI. Metronidazole may be used as primary treatment for nonrecurrent CDI in children which can reduce expenses. With FMT treatment, we had overall great success for children with RCDI, which demonstrated that FMT can be a cost-effective and safe alternative option for children with RCDI. But the efficacy, optimal timing, dose, delivery route, safety, and preparation of FMT in children with CDI need to be better evaluated in future prospective controlled studies.

Ethics approval and consent to participate

Written informed consent was obtained from all participants. Patients under 18 years old were obtained from parents or legal guardians of all pediatric subjects. This study was approved by the the Regional Ethical Review Board of Shanghai Children's Hospital (2021R067-E01). The data used in this study was anonymised before its use.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due individual privacy of patients could be compromised, but are available from the corresponding author on reasonable request.

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Authors' contributions

TZ and YZ designed the study. XL, XF and YL interpreted the data, created figures, and wrote the manuscript. XL, HH, TG, CY, YX, QX, DL and GY analyzed and interpreted the patient data regarding the RCDI. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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