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Clostridioides difficile Infection in a Japanese Tertiary Children's Hospital

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ABSTRACT

Purpose: Toxins produced by *Clostridioides difficile* infection (CDI) can cause enteritis and diarrhea. Although the number of pediatric CDI cases is increasing, the clinical management of pediatric CDI, including patient characteristics and prognosis, remains unclear. This study aimed to elucidate the background and clinical course of patients with CDI and evaluate the reliability of diagnostic tests in a tertiary pediatric hospital in Japan.
Methods: We retrospectively analyzed the clinical data of children diagnosed with CDI between 2011 and 2021 at the Saitama Children's Medical Center in Saitama, Japan.
Results: During the study period, 1,252 *C. difficile* antigen/toxin tests were performed, and 37 patients were diagnosed with CDI. The main underlying diseases among the patients were hematological and malignant disorders and gastrointestinal diseases, including inflammatory bowel disease (IBD) (59.4%). Two patients (5.4%) had an unremarkable medical history. Among the 37 patients, 27 (73.0%) were immunocompromised, 25 (67.6%) had a history of antibiotic use within the past two months, and 6 (16.2%) were negative on the initial test but were positive on the second test. Finally, 28 patients (75.7%) required primary antibiotic therapy only, and two patients with IBD required additional antibiotic therapy as secondary treatment.
Conclusion: The number of pediatric patients with CDI is increasing. Both a comprehensive interview, including underlying diseases and history of antibiotic use, and an understanding of the features of clinical examinations should be emphasized to appropriately diagnose and treat CDI.

Keywords: *Clostridioides difficile*; Enterocolitis, pseudomembranous; CD toxin; Antigens, CD; Colonoscopy

INTRODUCTION

Clostridioides difficile is an anaerobic, gram-positive, spore-forming pathogen. *C. difficile* infection (CDI), typically caused by strains that produce toxins A and B, results in severe diarrhea and enteritis and accounts for 15–25% of antibiotic-associated diarrhea [1]. Patients with CDI may develop pseudomembranous colitis (PMC), a severe disease where yellowish white plaques adhere to the mucosa and form pseudomembranes [2]. CDI is diagnosed based on clinical symptoms and stool examination. CDI is suspected in children with risk factors

Conflict of Interest
The authors have no financial conflicts of interest.

such as a history of antibiotic use, hospitalization, underlying diseases that reduce immunity, diarrhea more than three times daily, or a score >5 on the Bristol Stool Scale (BSS) [3,4].

Although the number of CDI cases is gradually increasing worldwide [5], the background characteristics and clinical management of pediatric patients with CDI have not been fully clarified. In addition, despite some researchers reporting the accuracy (sensitivity and specificity) of *C. difficile* antigen/toxin tests, their reliability in diagnosing CDI in pediatric patients remains unknown [6-9]. Therefore, this study investigated the background and clinical course of pediatric patients with CDI in a tertiary children's hospital in Japan and analyzed the reliability of each diagnostic test.

MATERIALS AND METHODS

Study design and patients

We sought to clarify the background and clinical course of patients with CDI and to analyze the reliability of various tests for its diagnosis. First, we selected pediatric patients aged 18 years or younger who underwent *C. difficile* antigen/toxin tests at Saitama Children's Medical Center (Saitama, Japan) between January 2011 and May 2021. This medical center is the only tertiary children's hospital in Saitama Prefecture with pediatric gastroenterologists who can perform endoscopy in children. We then identified patients who tested positive for the *C. difficile* antigen/toxin. In this study, CDI was diagnosed when there was diarrhea more than three times daily or defecation more frequently than usual with a BSS score >5 and proven *C. difficile* toxin-positive results, isolated toxin-producing *C. difficile*, PMC observed during colonoscopy, or pathological findings were present based on clinical practice guidelines [10]. Hence, consistent with our definition of patients who tested positive for the *C. difficile* antigen/toxin, we excluded patients without gastrointestinal symptoms. Data from the medical records of patients diagnosed with CDI were retrieved and analyzed in detail. The parameters evaluated included age, sex, symptoms at diagnosis, laboratory test findings (white blood cell count [WBC], hemoglobin [Hgb], albumin [Alb], and C-reactive protein [CRP] levels), number of *C. difficile* antigen/toxin tests before diagnosis, colonoscopy findings (if performed), antibiotic use within the past 1–2 months before CDI onset, immunity status, hospitalization, underlying diseases, and treatment for CDI. To assess trends among CDI patients in our hospital, we divided the 11-year study period into three (2011–2014, 2015–2018, and 2019–2021) slots and estimated the percentage of patients diagnosed with CDI among all patients who underwent *C. difficile* antigen/toxin testing. Two pediatricians and one microbiology technician retrieved relevant data from the medical records of the patients.

The Ethical Review Board of Saitama Children's Medical Center approved the study protocol (2021-03-018). Patient data were assessed after anonymization at the center. Patients and their guardians had the opportunity to withdraw from participation.

Antigen/toxin test methods

The C. DIFF QUIK CHEK COMPLETE (Abbott Diagnostics Medical, Blacksburg, VA, USA) was used to detect *C. difficile* antigen and toxin simultaneously. The stool specimens were mixed with a diluent/enzyme-labeled antibody solution after submission. CDI was diagnosed if both antigen and toxin were positive. In case of a discrepancy between the two results, such as antigen (+)/toxin (−) or antigen (−)/toxin (+), the toxigenic culture method was considered more reliable for capturing toxin-producing *C. difficile*. As previously reported, stool

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specimens were incubated on cycloserine–cefoxitin fructose agar for 72 hours at 37°C under anaerobic conditions [11]. Next, the *C. difficile* antigen/toxin test was performed in a 1–3-mm diameter dish, with white-to-gray colored colonies obtained by isolated culture using the kit described above. Thus, the final diagnosis of CDI was based on the results of the toxigenic culture methods, as needed.

RESULTS

Characteristics of patients with CDI

During the study period, 1,252 antigen/toxin tests for *C. difficile* were performed. Of these, 65 were positive for both the *C. difficile* antigen and toxin in 44 patients, and two tests with antigen (+)/toxin (−) were finally judged positive via toxigenic culture. Nine asymptomatic patients were excluded. Finally, 37 patients who had diarrhea met the definition of CDI (**Fig. 1**). As an indicator of the increase in the number of patients with CDI at our hospital, the percentage of patients diagnosed with CDI among all patients who underwent *C. difficile* antigen/toxin testing had increased over time (2011–2014: 2.57%; 2015–2018: 4.95%; and 2019–2021: 6.70%).

Patient characteristics are shown in **Table 1** and **Supplementary Table 1**. Patients with CDI included 20 males and 17 females; the median age was 5.43 years (range, 0.1–15.6). The number of positive results in children younger than 3 years was higher (40%) than that in other age groups and decreased with age (**Fig. 2**). All 37 patients with CDI had diarrhea, while fever, vomiting, and bloody stools were observed in 11 (29.7%), 7 (18.9%), and 6 (16.2%) patients, respectively. Hematological findings were abnormal in approximately 30% of the patients in each parameter tested: WBC >10,000 /μL in 10 patients (27.0%); Hgb level <11.0 g/dL in 12 patients (32.4%); Alb level <3.7 g/dL in 11 patients (29.7%); and CRP level >1.0 mg/dL in 12 patients (32.4%).

Underlying conditions were categorized into hematological and malignant disorders (n=12, 32.4%), gastrointestinal disorders (n=10, 27.0%), neurological disorders (n=5, 13.5%), perioperative periods (n=5, 13.5%), sepsis (n=2, 5.4%), obstructive jaundice (n=1, 2.7%), and no medical history (n=2, 5.4%) (**Table 2**). Among the patients with hematological and malignant disorders, five underwent hematopoietic stem cell transplantation and one

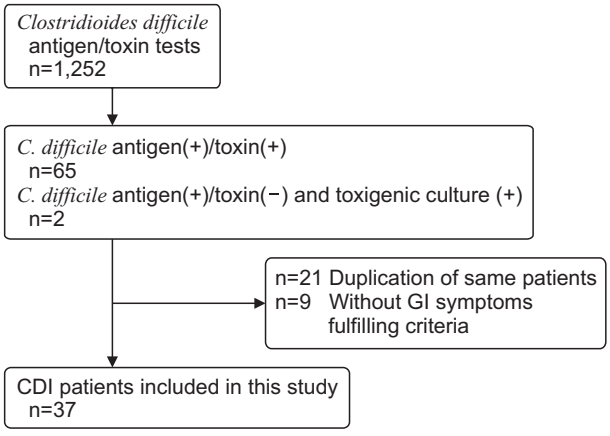

Fig. 1. Flow chart of the eligible cases in this study. Overall, 37 of the 1,252 examinations were included.
GI: gastrointestinal, CDI: *C. difficile* infection.

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Table 1. Characteristics of patients with *Clostridioides difficile* infections

Characteristic	Value (n=37)
Sex, M:F	20:17
Age (yr)	5.43±4.86
Symptoms	
Diarrhea	37 (100)
Fever	11 (29.7)
Vomit	7 (18.9)
Bloody stool	6 (16.2)
Blood tests	
WBC (/μL)	7,649±4,980
>10,000/μL	10 (27.0)
Hgb (g/dL)	11.0±2.2
<10.0 g/dL	12 (32.4)
Alb (g/dL)	3.6±0.7
<3.7 g/dL	11 (29.7)
CRP (mg/dL)	2.8±5.8
>1.0 mg/dL	12 (32.4)
History of antibiotic use	27 (73.0)
Immunosuppressive status	25 (67.6)
Long term hospitalization (>3 mo)	12 (32.4)
Treatment*	
Metronidazole	26 (70.3)
Vancomycin	4 (10.8)
None	9 (24.3)

Values are presented as number only, median±standard deviation, or number (%).
M: male, F: female, WBC: white blood cell, Hgb: hemoglobin, Alb: albumin, CRP: C-reactive protein.
*Two patients used both antibiotics.

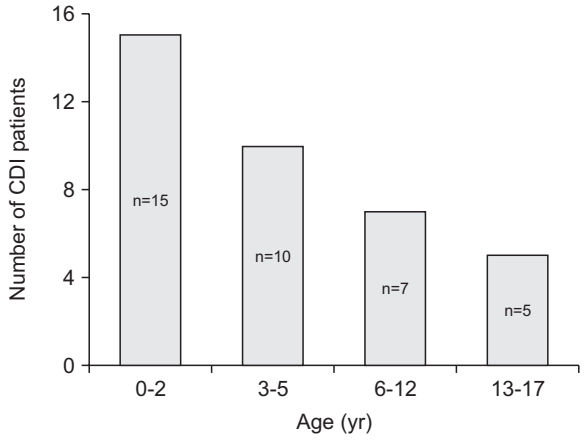

Fig. 2. Number of pediatric patients with *Clostridioides difficile* infection (CDI) in each age group.
The number of infections was higher in patients younger than 3 years than in other age groups and decreased with age.

underwent liver transplantation. Among patients with gastrointestinal disorders, six patients with inflammatory bowel disease (IBD) had monogenic IBD due to *XIAP* deficiency and *STAT3* gain-of-function. In total, 73.0% (n=27) of the patients were immunocompromised, and 32.4% (n=12) had been hospitalized for more than 3 months. A history of antibiotic use within the past 2 months was noted in 25 patients (67.6%), including two patients with no medical history.

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Table 2. Underlying disorders in patients with *Clostridioides difficile* infection

Underlying disorder	Value
Hematological and malignant disorder	12 (32.4)
Leukemia	4
Neuroblastoma	3
Retinoblastoma	1
Hepatoblastoma	1
Medulloblastoma	1
Aplastic anemia	1
Hemophagocytic lymphohistiocytosis	1
Gastrointestinal disorder	10 (27.0)
Ulcerative colitis	3
Monogenic IBD	2
Crohn's disease	1
IgA vasculitis	1
Hirschsprung's disease	1
Refractory constipation	1
Infectious gastroenteritis	1
Neurologic disorder	5 (13.5)
Cerebral palsy	1
Dravet syndrome	1
Acute encephalopathy by Norovirus	1
Kearns–Sayre syndrome	1
L1CAM deficiency	1
Perioperative	5 (13.5)
Sepsis (bacterial infection)	2 (5.4)
Obstructive jaundice	1 (2.7)
No past medical history	2 (5.4)

Values are presented as number (%) or number only.
IBD: inflammatory bowel disease, IgA: immunogloblin A, L1CAM: L1 cell adhesion molecule.

Reliability of *C. difficile* antigen/toxin tests

Among the 37 patients diagnosed with CDI, 31 (83.8%) were confirmed on the first antigen/toxin test. In contrast, six patients (16.2%) initially had negative antigen/toxin results and were diagnosed with CDI on the second test (76 patients with an initial negative test underwent a second test within a short period). The median time between the first and second tests was five days (interquartile range, 3.25–8.25 days). None of the patients required more than three tests to confirm diagnosis.

Colonoscopy for CDI

Among the 37 patients diagnosed with CDI, six underwent colonoscopy, and PMC was observed in one patient. In addition, two patients had nonspecific inflammatory findings, two patients had normal findings, and one patient had ulcerative colitis (UC) combined with CDI based on typical macroscopic findings of UC. The patient with PMC was a 13-year-old boy, with no underlying disease, who was diagnosed with CDI by colonoscopy, although his initial *C. difficile* antigen/toxin test was negative.

Medication and prognosis

Overall, 28 patients with CDI were treated with metronidazole (MNZ) or vancomycin (VCM). Among the 28 patients, resolution was achieved in 26 after completion of primary antibiotic therapy; VCM was required in the other two patients, both with IBD, as a secondary therapy because MNZ did not result in improvement. Eventually, CDI improved in all 37 patients, but three (8.1%) (two with UC and one with medulloblastoma) experienced a recurrence within three months after antibiotic treatment.

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DISCUSSION

We conducted a retrospective analysis at a single tertiary children's hospital to elucidate the characteristics, clinical course, and prognosis of CDI in children. Hematological, malignant, and gastrointestinal disorders accounted for 60% of the cases. However, 5.4% of patients had no underlying disease. In addition, 16.2% of the patients with CDI had an initial negative *C. difficile* antigen/toxin test and a positive second test, one of whom had an initial negative *C. difficile* antigen/toxin test but was diagnosed with PMC on endoscopy. Almost all cases achieved resolution with initial antibiotics or without secondary therapy; however, two patients (5.4%) with IBD required secondary therapy due to resistance to initial therapy.

C. difficile is a representative microorganism that causes nosocomial infections [12]. Most CDI occur in patients with risk factors such as multiple complications and immunodeficiency [13]. Consistent with our findings, a previous study showed an increase in CDI incidence especially in patients with particular comorbidities such as hematological malignancies and IBD [14]. Salamonowicz et al. [15] reported that pediatric patients treated for malignancy with hematopoietic stem cell therapy had a high incidence of CDI (14% and 8%, respectively). Martinelli et al. [16] reported that 8% of pediatric patients with IBD developed CDI, and that long-term hospitalization was a risk factor for CDI in patients with IBD. CDI is associated with immunosuppressive conditions caused by the patient's underlying disease or treatment, such as hematological and malignant disorders, gastrointestinal disorders, and a history of long-term hospitalization. A history of antibiotic use is also a risk factor even if patients do not have any underlying diseases. As supported by the results of this study, the number of CDI cases in pediatric patients has been increasing worldwide, and CDI may occur even in those without a remarkable medical history [2]. The onset of CDI is generally 4–9 days after antibiotic use; however, reports have documented a delayed onset of 1–2 months after discontinuation of antibiotics [17,18]. Therefore, it is very important to consider CDI based on a detailed patient interview, history of antibiotic use, primary complaint, and any underlying disease.

Approximately 20% of patients with CDI tested negative in the initial antigen/toxin test for *C. difficile* but were positive in the second test. This suggests that CDI may be diagnosed by retesting even in cases wherein the initial *C. difficile* antigen/toxin test was negative. The *C. difficile* antigen test detects glutamate dehydrogenase, whereas the *C. difficile* toxin test detects toxins A and B. In addition, the *C. difficile* antigen test has better sensitivity, whereas the *C. difficile* toxin test has better specificity. However, Senoh et al. [9] reported that the sensitivity and specificity of the *C. difficile* antigen test were 73% and 87%, respectively, which are lower in Japan than in Western countries. In addition, Deshpande et al. [19] reported that among patients diagnosed with CDI who were positive for the *C. difficile* toxin, results were positive in the second (2.7%) and third tests (2.3%) despite a negative first test. Notably, the *C. difficile* toxin is very unstable and degrades at room temperature in as little as 2 hours [20]. In our study, specimen mishandling may have resulted in false negatives in addition to compromising test accuracy. In addition, our study may have included cases that developed CDI within a short period. In any case, retesting may correctly diagnose CDI, and CDI should not be excluded from the differential diagnosis based only on a single negative result obtained in clinical practice.

Although a definitive diagnosis of PMC, which is rare in children, has been made in only one case in the past 10 years at our hospital, colonoscopy may be key to diagnosing CDI in children without an underlying disease or when both the *C. difficile* antigen/toxin tests are negative.

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Colonoscopy is less sensitive than fecal examination; however, it is rapid, provides visual confirmation, and is useful for excluding other diseases such as IBD and eosinophilic enteritis [1]. Because the number of PMC cases in pediatric patients with CDI is expected to increase in the future, colonoscopy may be helpful in cases wherein arriving at a diagnosis is difficult even after a comprehensive evaluation of the patient's background and clinical findings.

Almost all patients recovered from CDI after primary antibiotic therapy or without antibiotics, and no deaths occurred due to CDI. These findings indicate that the prognosis of pediatric patients with CDI is good. At present, CDI in other countries, especially the United States, is associated with significant morbidity and mortality and a poorer prognosis than that in Japan [5]. According to a report from a children's hospital in the United States, improvement rates of 72–86% with primary antibiotic therapy and recurrence rates of 16–22% within three months were observed [21]. An explanation for these differences is that the lipotype (RT) 027 strain, which is commonly isolated in North America, is highly virulent and can cause serious illness; however, this strain is relatively uncommon in Japan [14,22].

In this study, CDI in patients with IBD tended to be treatment-resistant, compared to other underlying conditions. In addition, two of the three patients who relapsed within three months had UC. A previous study reported that the incidence of CDI was higher in children with IBD than in those with other underlying conditions, and that 20% of patients initially treated with MNZ received secondary treatment with VCM due to inadequate remission of CDI [23]. Furthermore, a previous study reported that 25% of the children had CDI recurrence, which is similar to the findings of the present study. Therefore, appropriate observation and intervention for CDI in patients with IBD should be implemented, although the prognosis of patients with CDI in Japan is good.

This study has four main limitations. First, this was a single-center retrospective study. Second, a comparison between patients with and without CDI was not feasible as it was not possible to remove bias in testing indications. Prospective studies with matching test indications are required for more accurate comparisons. Third, although our center is the only children's hospital that can perform pediatric endoscopy in Saitama Prefecture, cases of CDI and PMC without underlying disease may be treated more often in general pediatric hospitals and clinics. If so, pediatric CDI in patients without a previous medical history may be more common than that reported in our study. Fourth, some patients diagnosed with CDI who did not undergo colonoscopy may have presented with PMC. Therefore, the number of CDI cases presenting with PMC may be higher than that reported.

We retrospectively analyzed data from patients with CDI who were treated at our center and showed that CDI was more frequent among those with underlying immunosuppression, hematological and malignant disorders, or gastrointestinal diseases. Nevertheless, 5% of the patients had CDI with no underlying disease. Although the prognosis of CDI in this study was good, a correct diagnosis is necessary, which requires information from a detailed interview and examination that includes a history of antibiotic use.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1

Characteristics of patients with *Clostridioides difficile* infection in this study

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