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Original Article

Clostridium difficile Infection at a Medical Center in Southern Taiwan: Incidence, Clinical Features and Prognosis

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BACKGROUND/PURPOSE: An increase in incidence of *Clostridium difficile* infection (CDI) among Western countries has been noted in recent years. Epidemiological data of CDI are scarce in Taiwan. This study is intended to depict the clinical features of CDI at a medical center in Southern Taiwan.

METHODS: From January 1, 2007 to March 31, 2008, hospitalized patients with CDI (defined as the presence of gastrointestinal symptoms and fecal *C. difficile* toxin) were identified. Their medical records were reviewed for further evaluation.

RESULTS: A total of 86 cases of CDI were identified in the study period. The incidence was 42.6 cases per 100,000 patient-days, or 3.4 cases per 1,000 discharges, and was highest in intensive care units (110.6 cases per 100,000 patient-days). Variable incidence rates were noted in different wards, and prevalence was higher in the infectious ward. Diarrhea, fever, and abdominal distension were common in 82 (95.3%), 47 (54.7%), and 29 (33.7%) patients, respectively. Metronidazole was the initial therapeutic regimen for 83 (96.5%) patients. Prolonged diarrhea was noted in 31 (36.4%) patients, especially in those on hemodialysis therapy. Recurrence was noted in 7 (8.1%) patients. Fecal carriage of vancomycin-resistant *Enterococcus* colonization was found in three patients after therapy for CDI. All-cause mortality rate of patients with CDI at 30 days was 23.3%.

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CONCLUSION: CDI is increasingly being recognized within the medical departments, and should be considered in hospitalized adults with diarrhea, fever, or abdominal distension alone, or in combination.

KEYWORDS: *Clostridium difficile* infection, prevalence, prolonged diarrhea, Taiwan

Introduction

Clostridium difficile is a Gram-positive, anaerobic, spore-forming bacillus that was first described in 1935 by Hall and O'Toole as part of the normal flora of neonates.[1] By 1978, *C. difficile* was proven to be the etiologic pathogen of antibiotic-associated colitis.[2] Clinical manifestations of *C. difficile* infections (CDI) range from asymptomatic colonization, mild to severe diarrhea, pseudomembranous colitis, toxic megacolon, and even death.[3] *C. difficile* has been responsible for 10–25% of antibiotic-associated diarrhea cases, and 90–100% of those with antibiotic-associated pseudomembranous colitis.[3,4]

Over the last decade, the incidence of CDI has progressively increased in both the United States and the United Kingdom.[5,6] A hypervirulent strain, North American pulsefield type 1, or PCR ribotype 027 NAP1/027, has resulted in increasing mortality rates.[7] Despite the fact that the English literature concerning *C. difficile* infection is voluminous, epidemiological data regarding CDI is scarce in Taiwan. Therefore, we conducted a retrospective study of the prevalence, clinical features, prognosis, and risk factors of prolonged diarrhea in symptomatic patients with fecal carriage of *C. difficile* toxin at a tertiary hospital in Southern Taiwan.

Methods

Patients

The National Cheng Kung University Hospital is a medical center in Southern Taiwan with approximately 1,100 beds. The Department of Internal Medicine includes eight medical wards (369 beds) and four intensive care units (ICU, 50 beds). This retrospective study was based on the laboratory data from inpatients in the medical department in whom *C. difficile* toxin was detected in fecal samples between January 1, 2007 and March 31, 2008. Adults, aged ≥ 18 years, with CDI were included. CDI was defined as the presence of fecal *C. difficile* toxin and concurrent gastrointestinal symptoms, such as diarrhea, abdominal discomfort or distension, or ileus.[8] *C. difficile* toxin was detected by qualitative enzyme immunoassay (Premier^{TM} toxin A&B; Meridian Bioscience Inc., Cincinnati, OH, USA).

Data collection

Clinical data, such as demographic information, comorbidities, clinical presentations, recent medications within 30 days of diagnosis of CDI, laboratory parameters obtained 2 days before or 1 day after the diagnosis of CDI, radiological findings, and treatment regimens and outcomes, were obtained from medical records. In addition, recurrence rates of CDI, fecal carriage of vancomycin-resistant *Enterococcus* (VRE) colonization after antimicrobial therapy for CDI, and crude mortality rate at 30 days were recorded.

Definitions

Diarrhea was defined as at least three loose or watery stool passages within 24 hours for at least 2 consecutive days[9], and a bowel frequency of less than three loose or watery stools per day for at least 48 hours was regarded as recovery from diarrhea. Fever was defined as a body temperature ≥ 38°C. After the prescription of metronidazole treatment, diarrhea persisting for more than 7 days was regarded as prolonged diarrhea in the study.

CDI was categorized according to the modified classification proposed by McDonald et al.[10] In brief, healthcare facility-onset, healthcare facility-associated CDI is defined the onset of CDI more than 48 hours after the admission of a patient to a healthcare facility. Community-onset, healthcare facility-associated, CDI is defined as the onset of gastrointestinal symptoms of CDI in the community, or 48 hours or less, after the admission of a patient to a healthcare facility, provided that symptom onset was less than 30 days after the last discharge from a healthcare facility.[10]

Immunosuppression status was regarded as present if immunosuppressive agents, or prednisolone ≥ 15 mg/day, was given for more than 1 month. CDI was regarded as recurring when there was reappearance of fecal *C. difficile* toxin, with relevant symptoms, within 8 weeks of the previous episode, and at least 10 days after the cessation of antibiotic therapy. Chronic kidney disease was defined as elevated serum creatinine levels (≥ 1.5 mg/dL) for more than 3 months.

A score developed by Charlson et al was used for evaluating the prognosis based on age and comorbidities.[11] The weighted index of comorbidity ranged from 0 to 37, and with an increasing comorbidity index, the cumulative mortality attributable to the comorbidities increased in a step-wise fashion.

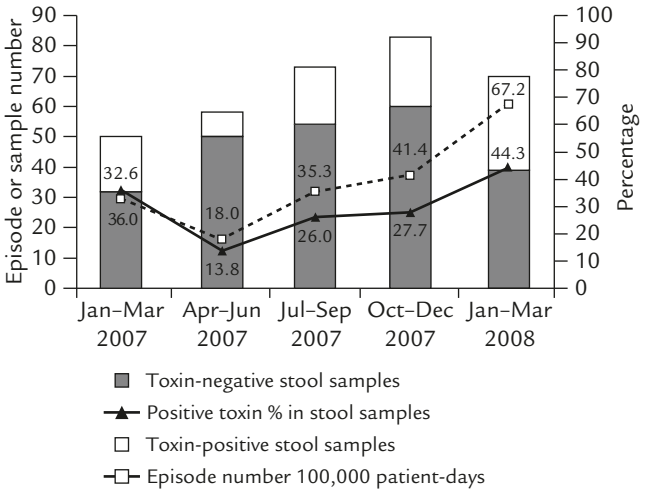

Figure. Yield rates of *Clostridium difficile* fecal toxin assay and incidence rates of *C. difficile* infections among hospitalized patients in the Department of Internal Medicine.

Statistic analysis

Statistical analysis was performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are described as mean ± standard deviation. Categorical variables are described as numbers (percentages). Risk factors and mortality rates of CDI with and without prolonged diarrhea were compared using the χ^2 test. A p value of < 0.05 was regarded as statistical significant.

Results

A total of 329 stool samples were tested for *C. difficile* toxin during the study period. Ninety-nine samples from 86 patients, including 26 patients from the ICU and 60 patients from the medical wards, had *C. difficile* toxin, and these 86 patients were included for further analysis. Among those patients with CDI, six patients received colonoscopy examinations, and only one had pseudomembranous colitis. The overall incidence of CDI was 42.6 cases per 100,000 patient-days, or 3.4 cases per 1,000 discharges, with an increase in the quarterly incidence during the study period (Figure). The incidence was highest in the ICU, 110.6 cases per 100,000 patient-days. Regarding the incidence in the medical wards; incidence in the infection ward (105 per 100,000 patient-days) was higher than in the other medical wards.

The clinical characteristics, comorbidities, place of acquisition, and risk factors for CDI are shown in Table 1. All patients were regarded as having healthcare facility-associated infections and most patients (91.9%) were hospital-onset. The mean age was 61.1 years (range, 18–90 years). The mean Charlson comorbidity score was 6.6 (range, 0–15). Eighty (93.0%) patients had been treated with antibiotics in the preceding 30 days before diagnosis, and 36 (41.9%) had received more than three antibiotics. The most common class of antibiotic administered was a third-generation cephalosporin (32 patients, 40.0%). Forty-four patients (55.0%) had received proton-pump inhibitors (PPIs) or histamine H2-blockers in the preceding 30 days before diagnosis.

Clinical presentations, laboratory parameters, and clinical outcomes are listed in Table 2. Diarrhea was noted in 82 (95.3%) patients, and 44 (53.7%) patients had watery diarrhea. Abdominal distension was the most frequent presentation of abdominal symptoms, noted in 29 (33.7%) patients. Fever was detected in 47 (54.7%) patients. The mean duration of hospitalization before the diagnosis of CDI was 20.6 days (range, 1–259 days). Pus cells were present in 15/67 (22.4%) available stool specimens. Eighteen patients had been evaluated by abdominal computed tomography (CT), and bowel wall thickening (defined as a bowel wall thickness of > 3 mm) was detected in eight (44.4%) patients.

Metronidazole was the initial therapeutic regimen for 83 (96.5%) patients, and three patients were not treated due to self-limiting courses. Oral vancomycin was substituted thereafter in nine (10.8%) patients because of unsatisfactory

Table 1. Clinical characteristics and risk factors of 86 hospitalized patients with *Clostridium difficile* infections

Clinical characteristics	Case[a]
Age, ≥65 yr	47 (54.7)
Sex, male	44 (51.2)
Hospitalization in prior 30 days before diagnosis	38 (44.2)
Nursing home residency	5 (5.8)
Location[b]	
Medical ICU	23/110.6 (26.7)
Oncology ward	29/66.7 (33.7)
Infection ward	10/105.0 (11.6)
Nephrology ward	8/59.4 (9.3)
Gastrointestinal ward	6/25.1 (7.0)
Other medical wards	10/12.0 (11.6)
Comorbidity	
Malignancy	37 (43.0)
Diabetes mellitus	28 (32.6)
Chronic kidney disease	24 (27.9)
Hemodialysis	13 (15.1)
Liver cirrhosis	13 (15.1)
HIV infection	2 (2.3)
Recent therapeutic intervention[c]	
Tube feeding	42 (48.8)
Chemotherapy	23 (26.7)
Endotracheal tube or tracheostomy	20 (23.3)
Mechanical ventilation	17 (19.7)
Immunosuppression	9 (10.5)
Recent medications[c,d]	
Antimicrobial therapy	
1st generation cephalosporin	4 (5.0)
2nd generation cephalosporin	5 (6.3)
3rd generation cephalosporin	32 (40.0)
4th generation cephalosporin	27 (33.8)
Penicillin/β-lactamase inhibitor	26 (32.5)
Fluoroquinolones	26 (32.5)
Glycopeptides	23 (28.8)
Carbapenem	21 (26.3)
Penicillins	13 (16.3)
Macrolides	8 (10.0)
Aminoglycosides	4 (5.0)
Clindamycin	3 (3.8)
Proton-pump inhibitors	41 (51.3)
Antifungal agents	14 (17.5)
Histamine H2-blockers	3 (3.8)

[a]Data presented as *n* (%) or case/100,000 patient-days (%); [b]number/incidence (case/100,000 patient-days); [c]recent medications and interventions were given within 30 days prior to the diagnosis of *Clostridium difficile* infections; [d]only 80 patients received recent medication. ICU=Intensive care unit.

Table 2. Clinical presentations, laboratory parameters, treatment, and outcome of 86 hospitalized patients with *Clostridium difficile* infections

Clinical features[a] (case number with specific data)	Case
Diarrhea	82 (95.3)
Watery	44 (53.7)
Loose	34 (41.5)
Mucus	4 (4.8)
Fever	47 (54.7)
Abdominal distension	29 (33.7)
Abdominal pain	18 (20.9)
Vague discomfort	8 (9.3)
Laboratory data at diagnosis	
Leukocyte count ($\times 10^9$ cell/mL; $n=84$)	
Neutropenia[b] ($n=13$)	362±25 (100–900)
Non-neutropenia ($n=71$)	12,335±102 (800–70,700)
Creatinine[c] (mg/dL; $n=72$)	1.81±2.47 (0.3–12.2)
CRP (mg/L; $n=73$)	106.4±100.3 (7.0–448.4)
Albumin (g/dL; $n=70$)	2.8±0.6 (1.3–4.6)
Antimicrobial therapy	
Metronidazole only	83 (96.5)
Metronidazole+vancomycin	9 (10.5)
Clinical outcome	
Time to recovery (d; $n=82$)	6.0±6.2 (1–29)
Time to defeverence (d; $n=47$)	6.5±4.8 (1–20)
Prolonged diarrhea after metronidazole therapy	31 (36.4)
Recurrence	7 (8.1)
Vancomycin-resistant *Enterococcus* colonization	3 (3.5)
In-hospital mortality rate	32 (37.2)

[a]Data presented as *n* (%) or mean±standard deviation (range); [b]neutropenia related to chemotherapy is defined as less than 0.5×10^9/L of neutrophil count; [c]excluding those with end-stage renal stage requiring hemodialysis or peritoneal dialysis. CRP=C-reactive protein.

responses to metronidazole therapy. The mean duration of treatment was 12.5 days (range, 3–44 days). Prolonged diarrhea (≥7 days) was found in 31/82 (37.8%) patients. Univariate analysis revealed that patients with prolonged diarrhea were likely to receive hemodialysis therapy (29.0% *vs.* 7.8%, $p=0.026$), and had higher Charlson scores (7.9 *vs.* 6.0,

Table 3. Univariate analysis of factors associated with prolonged diarrhea with *Clostridium difficile* infections

Variable[a]	Mild diarrhea ($n=51$)	Prolonged diarrhea ($n=31$)	p
Sex, male	25 (49.0)	15 (48.4)	0.654
Age	59.9±19.7	62.7±18.0	0.513
Recent hospitalization	24 (47.1)	14 (45.2)	1.000
ICU admission	13 (25.5)	13 (41.9)	0.146
Comorbidity			
Diabetes mellitus	14 (27.5)	12 (38.7)	0.333
Chronic kidney disease	11 (21.6)	13 (41.9)	0.079
Hemodialysis	4 (7.8)	9 (29.0)	0.026
Malignancy	21 (41.2)	12 (38.7)	0.589
Neutropenia[b]	9 (17.6)	4 (12.9)	0.757
Charlson score	6.0±3.6	7.9±3.6	0.024
Clinical Outcomes			
Recurrence	3 (5.9)	4 (12.9)	0.417
30-day mortality	12 (23.5)	8 (25.8)	1.000
In-hospital mortality	15 (29.4)	17 (54.8)	0.035

[a]Data presented as *n* (%) or mean±standard deviation; [b]neutropenia is defined as less than 0.5×10^9/L of neutrophil count. ICU=Intensive care unit.

$p=0.024$) than those without prolonged diarrhea (Table 3). Recurrence of CDI occurred in seven (8.1%) patients.

VRE colonization was found in five (5.8%) patients, and three VRE isolates were discovered after the initialization of antimicrobial therapy for CDI. The mean hospital stay after diagnosis of CDI was 25.7 days (range, 2–176 days). The crude 30-day mortality was 23.3%, and all-cause in-hospital mortality was 37.2%. There was no difference in crude 30-day mortality between patients with and without prolonged diarrhea (23.5% *vs.* 25.8%, $p=1.000$). However, in-hospital mortality rates were higher in those patients with prolonged diarrhea (29% *vs.* 54.8%, $p=0.035$; Table 3).

Discussion

In this study, the incidence of CDI was 42.6 cases per 100,000 patient-days, or 3.4 cases per 1,000 discharges, which is compatible with the data from the Canadian nosocomial surveillance between November 2004 and April 2005 (i.e. 65 cases per 100,000 patient-days, or 4.6 cases per 1,000 admissions),[12] and the recorded 3.3 patients per 1,000 hospital discharges in Oregon, USA from 1995 to 2002.[5] With regard to Southeast Asia, the incidence in Singapore was 3.2 cases per 1,000 admissions, or 53.8 cases per 100,000 patient-days, between October 2002 and February 2003.[13] A recent study of patients in two infection wards and six medical ICUs in a tertiary hospital in Northern Taiwan revealed an incidence of 120 cases per 100,000 patient-days.[14] However, increasing incidence rates were noted during the surveillance, and variable incidences among medical wards were noted, which may be partly related to the different clinical characteristics of the hospitalized patients in the different units, such as underlying illnesses, and antibiotics or PPIs exposure. The familiarity with CDI among the attending physicians in these units might also influence the attempts to diagnose CDI, and thereafter its incidence. Also, it was a retrospective study in which clinical data were retrieved from symptomatic patients with *C. difficile* toxin in feces, and the *C. difficile* toxin test was not covered by health insurance. The incidence of patients with CDI was, therefore, likely to be underestimated.

Not surprisingly, diarrhea was common in patients with CDI. Previous guidelines for *C. difficile*-associated diarrhea recommended that tests for *C. difficile* should be

done in patients with diarrhea.[8] However, some patients may present with abdominal distension and pain without diarrhea, which can be the case in 8–50% of CDI complicated with fulminant colitis, or in postoperative cases with ileus.[15] In the present series, four (4.7%) patients did not have diarrhea, but presented with fever (4 patients), abdominal pain (2 patients) or distention (2 patients). Three of the four patients had concurrent leukocytosis. Wanahita et al analyzed 60 patients with unexplained leukocytosis, and 35 (58.3%) patients were diagnosed with CDI; 7/35 (20.0%) of these patients did not report diarrhea.[16] Therefore, in hospitalized patients with unexplained abdominal discomfort and leukocytosis, CDI should be considered as a differential diagnosis. However, another common test given to hospitalized patients with diarrhea, the fecal leukocyte test, was performed in 66/86 patients with CDI, and positive results were noted in 15 (22.7%) patients. Due to the low sensitivity rate of 30%,[17] the routine use of the fecal leukocyte test is not necessary for CDI patients.

CT scans are not routinely performed for CDI. In our patients, only 8/18 (44.4%) who underwent abdominal CT examination were found to have bowel wall thickening. None had the uncommon, but specific, CT finding for *C. difficile* colitis, nodular fold thickening, or so called "accordion sign".[18] A previous study reported abnormal wall thickening in 50–76% of patients with CDI by abdominal CT scanning.[19] Despite CT scanning not being a diagnostic tool for CDI, it can be useful in distinguishing severe diseases from mild-to-moderate infections, and to evaluate the need for surgical intervention.

PPIs have been proposed as risk factors for CDI.[3] In this study, PPIs were given to 41/86 (47.7%) patients within the 30 days before diagnosis of CDI. However, this was not a case-control study, so we cannot plot the association between CDI and PPI use. Further case-control studies will be performed.

Oral metronidazole has been recommended as the first line treatment for mild and moderate CDI, in part due to cost effectiveness and, in part due to the concern that oral vancomycin may be more likely to promote colonization by VRE.[20] In this study, VRE colonization was detected in 5/86 (5.8%) patients. Previous studies suggest that metronidazole and extended-spectrum cephalosporins will increase the risk of VRE acquisition.[21] Moreover, in a prospective observational study, Al-Nassir et al found that oral metronidazole and vancomycin therapy specific for CDI could promote VRE overgrowth, and both were recognized as risk factors for fecal VRE colonization.[22] With the increasing threat of VRE in modern medicine, new agents with less effect on intestinal microflora are desperately needed for the treatment of CDI.

The clinical resolution of diarrhea associated with CDI was always noted within 2–3 days after antimicrobial therapy, and complete resolution ensued within 7–10 days.[23] The mean duration of diarrhea after the start of treatment was 6 days in the present study, which was comparable to that of an Israeli study of nosocomial diarrhea (mean, 6 days; range, 1–40 days).[24] However, after appropriate metronidazole treatment for 1 week, more than one-third (36.4%) of patients still had diarrhea, similar to the results of Hardt et al (37%).[25] The crude mortality rate at 30 days in this series was 23.3%. The in-hospital mortality rate in our study was significantly higher in those patients with prolonged diarrhea, up to 54.8%. It is speculated that the death of patients with prolonged diarrhea could be attributed to underlying morbidity rather than to the complications associated with CDI.

In conclusion, CDI was increasingly recognized during this study, especially in ICU patients. Although diarrhea was the most common symptom, CDI should be considered in hospitalized adults with diarrhea, fever, or abdominal distension alone, or in combination.

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