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ORIGINAL ARTICLE

Community-onset *Clostridium difficile* infection at a tertiary medical center in southern Taiwan, 2007—2015

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Clostridium difficile infection;
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Abstract *Background: Clostridium difficile* infection (CDI) is well-known as the major cause of infectious diarrhea in hospitalized patients. Community-onset CDI (CO-CDI) is an emerging threat. However, clinical information of CO-CDI in Taiwan remains scarce.
Methods: A retrospective study was conducted at a medical center in southern Taiwan. Symptomatic patients between 2007 and 2015 with *C. difficile* toxin or *tcdB* detected in stool were identified as CDI, and were classified as CO-CDI [including community-associated CDI (CA-CDI) and community-onset health care facility-associated CDI (CO-HCFA-CDI)] and health care facility-onset CDI (HCFO-CDI).
Results: Of 427 patients, 15 (3.5%) were CA-CDI, 49 (11.5%) CO-HCFA-CDI, and 363 (85.0%) HCFO-CDI. Despite major involvement of the elderly (mean age: 66.1 years vs. 69.9 years, $p = 0.46$), no significant differences were noted between CA-CDI and CO-HCFA-CDI groups, except that solid organ cancer was more common in the CO-HCFA-CDI group. The CO-CDI group more often presented with abdominal pain but had shorter hospital stays and less exposure of proton-pump inhibitors or broad-spectrum antibiotics than the HCFO-CDI group did. The mortality rate related to CDI was 4.7% (3 patients) in the CO-CDI group. Despite a lower in-hospital mortality rate in the CO-CDI group (10.9% vs. 22.0%; $p = 0.04$), the recurrence rate was similar (10.9% vs. 7.2%; $p = 0.3$).

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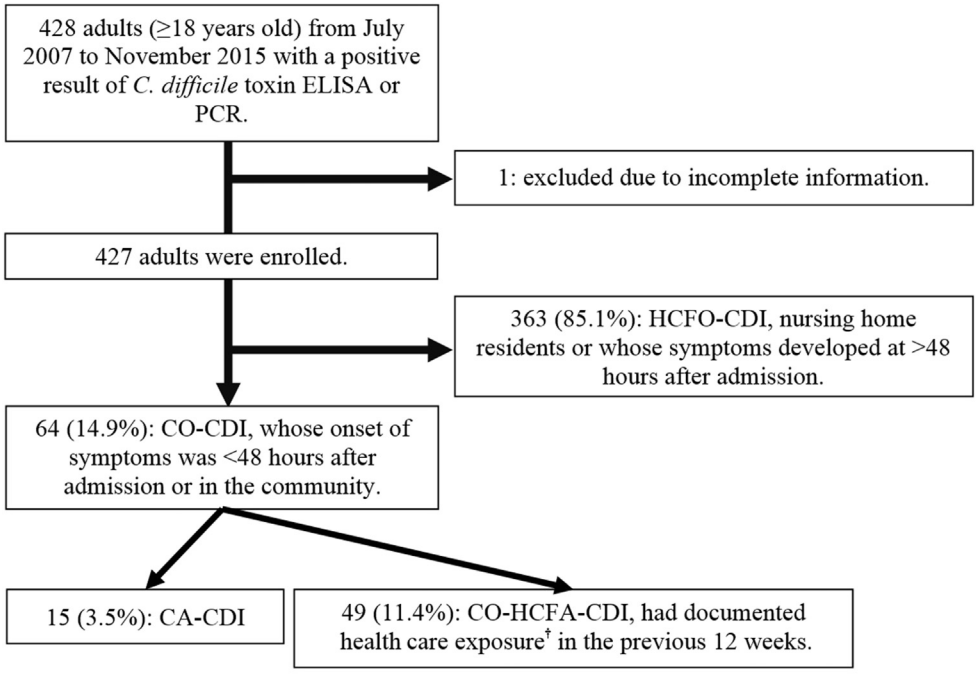
Conclusions: CO-CDI is not common but associated with substantial morbidity and mortality. Physicians should put CDI into consideration among patients who present community-onset fever, diarrhea, or abdominal pain alone or in combination.

Introduction

Clostridium difficile is an anaerobic Gram-positive, spore-forming, toxin-producing bacillus,[1] and has been the major cause of antibiotic-associated diarrhea, or pseudomembranous colitis.[2] *C. difficile* infection (CDI) or *C. difficile*-associated disease is defined by the presence of symptoms (usually diarrhea) and either a stool sample with *C. difficile* toxins or toxigenic *C. difficile*, or the finding of pseudomembranous colitis in colonoscopic studies.[3] CDI has been considered as one of the most common health care-associated infections,[4,5] and was associated with significant morbidity and mortality among hospitalized patients, especially in elderly, patients exposed to antibiotics, cancer patients receiving chemotherapy, and long-term care facility residents.[6–10] The concept that CDI is mainly acquired in the environment of health care facility (HCF) has been challenged by the increasing trend in community-onset (CO) or even community-associated (CA) infections, which have become a potential threat around the world.[11–16] CDI can be classified into three categories, based on the timing of symptom onset: CA-CDI, CO-HCF-associated CDI (CO-HCFA-CDI), and HCFA-CDI.[3,17] The incidence of CA-CDI varies substantially by different definitions and populations, ranging from less than 0.1‰ to 41%.[18,19] To our knowledge, clinical information about CA-CDI and CO-HCFA-CDI was limited in Taiwan. Therefore, we performed a retrospective study to investigate clinical characteristics of CO-CDI.

Materials and methods

A retrospective study was conducted in the National Cheng-Kung University Hospital (NCKUH), a 1300-bed tertiary medical center in southern Taiwan. Symptomatic adults who were aged more than 18 years and hospitalized or visited the clinics of NCKUH between July 2007 and November 2015, if their stool samples had a positive result of qualitative enzyme immunoassay (EIA: Premier toxin



*CO-CDI = community-onset CDI; CA-CDI = community-associated CDI; CO-HCFA-CDI = community-onset, health care facility-associated CDI; HCFO-CDI = health care facility-onset CDI.

†Health care exposure: having a more than 24-hour stay in hospital, being a resident in long-term care facility, receiving dialysis therapy, or regular hospital visits for intravenous infusion.

Figure 1. The study design for the patients with community-onset *Clostridium difficile* infection (CDI).

A&B; Meridian Bioscience Inc., Cincinnati, OH, USA) from July 2007 to March 2014 or *tcdB* detection by polymerase chain reaction (PCR: GeneOhm Cdiff Assay; BD Diagnostics, San Diego, CA, USA) from April 2014 to November 2015, were identified. CDI-associated symptoms included fever, diarrhea, abdominal pain or tenderness, abdominal distention, or nausea/vomiting alone or in combination. Diarrhea was defined as three or more loose stools in a 24-hour period.[3,17] Inpatient and outpatient medical records of the patients with CDI were reviewed in the electronic laboratory information system in NCKUH, and clinical information was recorded in a standardized data collection form.

Collected clinical data included age, sex, dates of admission, discharge, clinical diagnosis of CDI, and outpatient clinic visit (if the patient was identified as having CDI in the outpatient setting), initial clinical manifestations, duration of diarrhea before clinical diagnosis, underlying disease (such as diabetes mellitus, liver cirrhosis, end-stage renal disease, solid-organ or hematologic malignancies, and human immunodeficiency virus infection), and clinical outcome (such as in-hospital mortality and hospital stay after CDI treatment). Laboratory data with the greatest deviation from normal values at 2 days before or 1 day after CDI diagnosis were recorded. Recent medications within the past 30 days before symptom onset of CDI, including antibiotics, chemotherapy, steroid (prednisolone >10 mg/d or equivalent dosage), and proton-pump inhibitors, were abstracted. The patients with incomplete clinical information would be excluded.

Severe CDI was defined as the presence of leukocytosis with a white blood cell count of 15×10^6 cells/L or higher, or a serum creatinine level ≥1.5 times the premorbid level.[3] Recurrent CDI was diagnosed, if CDI-associated symptoms and additional positive results of *C. difficile* toxin EIA or PCR tests were found after discontinuing CDI therapy for at least 48 hours. However, if the above events were noted in the same hospitalization, they were regarded as the same episode of CDI in our study. Specific CDI therapy included oral or parenteral metronidazole, or oral vancomycin alone or in combination. Fidaxomicin was not available in Taiwan during the study period.

Nursing home residents or those developing associated symptoms of CDI at >48 hours after hospital admission were defined as having HCFO-CDI. CA-CDI was defined as associated symptoms onset at <48 hours after hospital admission or in the outpatient setting, if such a patient had no recent health care exposure within prior 12 weeks, including visiting emergency department for >24 hours, hospitalization, or regular dialysis therapy or hospital visits for

Table 1 Clinical characters of 15 patients with community-acquired *Clostridium difficile* infection (CA-CDI) and 49 patients with community-onset, health care facility-associated *C. difficile* infection (CO-HCFA-CDI)

Clinical characteristics	CA-CDI (n = 15)	CO-HCFA-CDI (n = 49)	p
Age (y)	66.13 ± 19.52	69.90 ± 16.42	0.460
Male	9 (60.0)	31 (63.3)	0.819
Comorbidity			
Hypertension	9 (60.0)	29 (59.2)	0.955
Diabetes mellitus	4 (26.7)	15 (30.6)	>0.999
Chronic kidney disease	3 (20.0)	12 (24.5)	>0.999
Solid organ malignancy	2 (13.3)	22 (44.9)	0.027
Old cerebrovascular accident	2 (13.3)	9 (18.4)	0.651
Liver cirrhosis	2 (13.3)	1 (2.0)	0.134
Hematologic malignancy	2 (13.3)	1 (2.0)	0.134
Coronary artery disease	1 (6.7)	3 (6.1)	>0.999
Congestive heart failure	0 (0.0)	6 (12.2)	0.322
Long-term dialysis therapy	0 (0.0)	4 (8.2)	0.565
Human immunodeficiency virus infection	0 (0.0)	1 (2.0)	>0.999
Clinical manifestations			
Fever	9 (60.0)	21 (42.9)	0.244
Diarrhea >2 days before diagnosis	9 (60.0)	33 (68.8)	0.530
Abdominal pain	6 (40.0)	19 (38.8)	0.932
Nausea	2 (13.3)	5 (10.2)	0.662
Vomiting	2 (13.3)	9 (18.4)	>0.999
Abdominal distension	0 (0.0)	7 (14.3)	0.185
Laboratory data			
White blood cells ($\times 10^9$/L)	12.14 ± 8.16	12.30 ± 10.00	0.960
Clinical outcome			
Duration of CDI treatment (d)	11.60 ± 9.66	11.46 ± 7.74	0.954
CDI treatment-to-discharge (d)	16.27 ± 30.96	12.79 ± 14.06	0.679
Severe CDI	3 (20.0)	10 (20.4)	>0.999
In-hospital mortality	1 (6.7)	6 (12.2)	>0.999
Recurrence	1 (6.7)	2 (4.1)	0.558

Data are expressed as patient number (%) or mean ± standard deviation.

intravenous therapy. Otherwise they would be classified as CO-HCFA-CDI.[3,15–17]

All statistical analyses were performed in the statistical software SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA). The Chi-square test and Fisher exact analysis were used to compare categorical variables. Independent Student *t* test was applied to compare continuous variables between groups. A two-tailed *p* value of less than 0.05 was considered to be statistically significant.

Results

In the study hospital, the self-pay *C. difficile* toxin EIA test was electively ordered before April 2014 and thereafter the insurance-covered *tcdB* PCR test was widely used by clinicians for suspected patients with CDI. Since the toxin EIA tests were selected for highly suspected patients with CDI, as evidenced by a high positive rate of 20–40% (data not shown), the incidence of CDI in this period was likely to be underestimated. Thus, the incidence of positive *tcdB* PCR results from April 2014 to November 2015 was 42.3 per 100,000 patient-days (272/642,539).

During the study period (from July 2007 to November 2015), 428 adult patients were confirmed as CDI. One was excluded because of incomplete clinical information. Of 427 patients, five nursing home residents and 358 with CDI-associated symptoms developing at >48 hours after admission were both classified as HCFO-CDI (Figure 1). Sixty-four (15%) patients had CO-CDI, in which CDI-associated symptoms developed at <48 hours after admission or were diagnosed as well as treated in the outpatient setting. Of the 64 patients with CO-CDI, 49 had documented health care exposure in the recent 12 weeks before the onset of CDI-associated symptoms and were classified as CO-HCFA-CDI. The other 15 patients had CA-CDI. By univariate analysis, no significant differences were noted between two groups, except for fewer solid-organ malignancies in the CO-HCFA-CDI groups (13.3% vs. 44.9%, $p = 0.027$; Table 1). Thus, the CA-CDI and CO-HCFA-CDI patients were grouped together as the CO-CDI group, for further comparison with the HCFO-CDI group (Table 2). The CO-CDI group was more likely to have the symptoms of abdominal pain alone (39.1% vs. 19.3%, $p < 0.001$) or in combination with fever (20.3% vs. 8.3%, $p = 0.003$) than HCFO-CDI the group. Notably, the CO-CDI group had a lower in-hospital mortality rate (10.9% vs. 22.0%, $p = 0.04$) and a shorter hospital stay after initiating CDI therapy (13.62 ± 19.20 vs. 20.83 ± 22.73 days, $p = 0.018$) than the HCFO-CDI group. There was no significant difference

Table 2 Clinical characters of 64 patients with community-onset *Clostridium difficile* infection (CO-CDI) and 363 patients with health care facility-onset *C. difficile* infection (HCFO-CDI)

Clinical characteristics	CO-CDI ($n = 64$)	HCFO-CDI ($n = 363$)	*p*
Age (y)	69.02 ± 17.11	66.25 ± 16.37	0.217
Male	40 (62.5)	209 (57.6)	0.461
Comorbidity			
Hypertension	38 (59.4)	172 (47.4)	0.077
Solid-organ malignancy	24 (37.5)	132 (36.4)	0.862
Diabetes mellitus	19 (29.7)	133 (36.6)	0.284
Chronic kidney disease	15 (23.4)	114 (31.4)	0.201
Old cerebrovascular accident	11 (17.2)	51 (14.0)	0.511
Congestive heart failure	6 (9.4)	54 (14.9)	0.243
Long-term dialysis therapy	4 (6.3)	54 (14.9)	0.063
Coronary artery disease	4 (6.3)	30 (8.3)	0.583
Liver cirrhosis	3 (4.7)	21 (5.8)	0.725
Hematologic malignancies	3 (4.7)	34 (9.4)	0.220
Human immunodeficiency virus infection	1 (1.6)	2 (0.6)	0.386
Clinical manifestations			
Diarrhea >2 days before diagnosis	42 (66.7)	261 (72.1)	0.379
Fever	30 (46.9)	179 (49.3)	0.719
Abdominal pain	25 (39.1)	70 (19.3)	<0.001
Vomiting	11 (17.2)	40 (11.0)	0.161
Nausea	7 (10.9)	18 (5.0)	0.079
Abdominal distension	7 (10.9)	26 (7.2)	0.309
Laboratory data			
White blood cells ($\times 10^9$/L)	12.27 ± 9.57	11.37 ± 8.64	0.482
Clinical outcome			
Duration of CDI treatment (d)	11.49 ± 8.15	10.99 ± 5.98	0.567
CDI treatment-to-discharge (d)	13.62 ± 19.20	20.83 ± 22.73	0.018
Severe CDI	16 (25.0)	84 (23.1)	0.746
In-hospital mortality	7 (10.9)	80 (22.0)	0.042
Recurrence	3 (4.7)	11 (3.0)	0.492

Data are expressed as patient number (%) or mean ± standard deviation.

between two groups in terms of severe CDI and recurrence. Medication review demonstrated that the HCFO-CDI group was more often ever treated by broad-spectrum antibiotics, including third- and fourth-generation cephalosporins, carbapenems, or glycopeptides, than the CO-CDI group (Table 3). A similar trend in prior prescriptions of proton-pump inhibitors was noted (63.1% vs. 40.6%, $p = 0.001$). As for the treatment of CO-CDI, 37 patients (57.8%) were treated by orally or intravenously metronidazole averagely for 10.4 days and had symptomatic relief after 5.7 days of metronidazole treatment. Three patients receiving metronidazole had CDI recurrence. Two (3.1%) patients were treated by oral vancomycin and diarrheal symptom in one of them treated for 6 days resolved 6 days later. Clinical information of the other patient with oral vancomycin therapy in the outpatient clinic was incomplete. The antimicrobial regimens for the other 24 patients changed frequently during the treatment course and were difficult to be summarized. One patient was not treated but resolved spontaneously within 3 days.

The patients with CO-CDI were divided into two groups: those with diarrhea for at least 2 days, and those with diarrhea for less than 2 days (Table 4). Those with diarrhea for at least 2 days tended to have a worse outcome (mortality rate: 15.9% vs. 0%, $p = 0.09$) and more severe clinical condition (31.8% vs. 10.0%, $p = 0.06$). All seven CO-CDI patients with in-hospital mortality had diarrhea for at least 2 days before diagnosis. In contrast, those with diarrhea for less than 2 days had no recurrence or in-hospital mortality.

Seven CO-CDI patients with in-hospital mortality were further investigated (Table 5). Six (85.7%) of these seven patients had active cancer in advanced stage or diabetes mellitus. Three (42.9%) patients died of severe CDI and profound shock and the other four died of health care-associated pneumonia, empyema, or bacteremia. Thus, the CDI-related mortality rate was 4.7% (3/64) in the patients with CO-CDI patients.

Discussion

In 2007, McDonald et al issued the recommendations for CDI surveillance and proposed the clinical definitions of CA-CDI, CO-HCFA-CDI, and HCFO-CDI. The patients with CA-CDI were strictly defined as having no overnight stay in any health care facility within 12 weeks prior to symptom onset.[17] Moreover, some studies in the USA strictly defined the patients with CA-CDI as those without recent health care exposure, such as overnight stay in acute care setting, regular dialysis, hospital visits for intravenous therapy, or hospital admission, in the 12 weeks prior to the onset of CDI-associated symptoms.[13,15,16] Following the above strict definitions of CA-CDI, the *indeterminate* patients defined by McDonald et al[17] (i.e. those with recent discharge from health care facilities at 4—12 weeks before the community onset of CDI-associated symptoms) were classified as CO-HCFA-CDI in our study to simplify the classification of CO-CDI.

In our study, CA-CDI accounts for 3.5% of CDI patients, a lower figure than that of another CDI study, which reported that, among 122 CDI patients from 2000 to 2010 at a tertiary medical center in northern Taiwan, more than 20% of patients were CA-CDI.[20] However, this study did not mention

Table 3 Prior medications within 1 month prior to symptom onset among the patients with community-onset *Clostridium difficile* infection (CO-CDI) and health care facility-onset *C. difficile* infection (HCFO-CDI)

Clinical characteristics	CO-CDI ($n = 64$)	HCFO-CDI ($n = 363$)	p
Medication			
Proton-pump inhibitors	26 (40.6)	229 (63.1)	0.001
Steroids (>10 mg prednisolone or equivalent/day)	13 (20.3)	96 (26.4)	0.299
Chemotherapy	6 (9.4)	52 (14.4)	0.283
Antimicrobial therapy			
Penicillins	19 (29.7)	165 (45.5)	0.019
First-generation cephalosporins	5 (7.8)	48 (13.2)	0.226
Second-generation cephalosporins	14 (21.9)	43 (11.8)	0.03
Third-generation cephalosporins	11 (17.2)	126 (34.7)	0.006
Fourth-generation cephalosporins	7 (10.9)	114 (31.4)	0.001
Flomoxef	1 (1.6)	8 (2.2)	0.742
Metronidazole	3 (4.7)	16 (4.4)	0.924
Trimethoprim—sulfamethoxazole	0 (0.0)	7 (1.9)	0.601
Fluoroquinolones	14 (21.9)	95 (26.2)	0.467
Carbapenems	4 (6.3)	111 (30.6)	<0.001
Macrolides	0 (0.0)	9 (2.5)	0.203
Glycopeptides	1 (1.6)	82 (22.6)	<0.001
Tetracyclines	0 (0.0)	17 (4.7)	0.077
Aminoglycosides	1 (1.6)	17 (4.7)	0.252
Antifungal agents	6 (9.4)	61 (16.8)	0.132
Antivirals[a]	2 (3.1)	14 (3.9)	0.776

[a] Includes acyclovir, valaciclovir, ganciclovir, valganciclovir, zanamivir, or oseltamivir.
Data are expressed as patient number (%). N/A, not available.

the exact data of CA-CDI and the definition of CA-CDI did not exclude those with recent health care exposure. It is likely that more patients with CA-CDI would be included in that study.

In spite of similar age and underlying medical illness among the patients with HCFO-CDI and CD-CDI, the former were more often to receive proton-pump inhibitors, which had been mentioned as a predisposing factor of CDI,[21–24] and their hospital stay after initiation of CDI therapy was longer. In addition, the HCFO-CDI group was more often ever treated by broad-spectrum antibiotics, such as cephalosporins, carbapenems, or glycopeptides. These findings indicated more complex medical conditions in the HCFO-CDI group than the CO-CDI group. For the issue of CDI, the proportion of severe CDI, nearly 25%, and the duration of specific antimicrobial therapy for CDI, approximately

Table 4 Clinical features of adults with community-onset *Clostridium difficile* infection (CDI), stratified by diarrhea duration before CDI diagnosis

Variables	Diarrhea ≥2 days, $n = 44$	Diarrhea <2 days, $n = 20$
Clinical presentations		
Fever	21 (47.7)	9 (45.0)
Abdominal pain	19 (43.2)	6 (30.0)
Abdominal distention	5 (11.4)	2 (10.0)
Nausea	6 (13.6)	1 (5.0)
Vomiting	9 (20.5)	2 (10.0)
Admission-to-CDI treatment (d)	2.02 ± 2.19	2.00 ± 2.13
Clinical outcomes		
CDI treatment-to-discharge (d)	14.70 ± 19.72	11.11 ± 18.19
Severe CDI	14 (31.8)	2 (10.0)
Recurrence	3 (6.8)	0 (0.0)
In-hospital mortality	7 (15.9)	0 (0.0)

Data are expressed as patient number (%) or mean ± standard deviation.

Table 5 Causes of in-hospital mortality and comorbidities in seven patients with community-onset *Clostridium difficile* infection (CDI)

Patient No.	Age (y)/sex	Severe CDI	Hospital stay (d)	Cause of mortality	Comorbidities
1	84/M	No	40	Health care-associated pneumonia with respiratory failure	Lung cancer with brain metastasis and steroid therapy; colon cancer with chemotherapy; reflux esophagitis with proton pump inhibitors
2	87/F	Yes	27	Health care-associated pneumonia with respiratory failure	Oral cancer stage IV with palliative chemotherapy; diabetes mellitus
3	51/M	Yes	41	Oxacillin-resistant *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* bacteremia	Acute myeloid leukemia with relapse; diabetes mellitus
4	39/F	No	20	ESBL-producing *Escherichia coli* and *Enterococcus gallinarum* bacteremia, empyema, acute kidney injury	Acute myeloid leukemia after peripheral blood stem cell transplant with relapse; esophageal candidiasis
5	68/M	Yes	3	Severe CDI with septic shock	Adult-onset Still's disease with steroid therapy; diabetes mellitus
6	41/M	Yes	7	Severe CDI with septic shock	Esophageal cancer with bone metastasis; diabetes mellitus
7	88/M	Yes	4	Severe CDI with septic shock	Traumatic subdural hemorrhage; diabetes mellitus

ESBL = extended-spectrum β-lactamase; F = female; M = male.

11 days, both indicated the severity of CDI, was similar in both groups. Therefore, the worse prognosis in the HCFO-CDI may be related to current active medical illness, but not to CDI itself.

In the present study, seven patients with CO-CDI died in the hospital. Although most of these fatal patients had advanced cancer or diabetes mellitus, three died within days due to severe CDI with profound shock and multiple organ failure. Here, the fact that CO-CDI can present as fulminant disease with a grave outcome should be noted and the importance of early diagnosis and therapy of CDI in the primary care clinicians should be emphasized.

Some specific virulent *C. difficile* strains have been known to display severe clinical presentations, such as fulminant sepsis or toxic megacolon, and antimicrobial resistance.[25–28] These hypervirulent *C. difficile* clones, including ribotypes 027 and 078, recognized to be emerging threats in Europe and North America, have been recently reported in Taiwan.[29,30] More studies about the molecular epidemiology of indigenous clinical isolates are essential to reveal clinical role of hypervirulent strains in Taiwan.

In conclusion, although *C. difficile* infection was noted mostly among hospitalized patients, it can cause substantial morbidity and mortality among the elderly outside the hospitals. Physicians should put CDI in the list of differential diagnoses among patients who present community-onset fever, diarrhea, or abdominal pain alone or in combination.

Conflicts of interest

There is no conflict of interests in this study.

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