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Brief communication (Original)

The burden of *Clostridium difficile* infection in Thais: nationwide survey

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Background: Data on the incidence and burden of *Clostridium difficile* infection (CDI) in Asia is limited.

Objectives: To evaluate the incidence and burden of CDI in Thailand.

Methods: We used 2010 Nationwide Hospital Admission Data, which included the diagnosis of digestive disorders from various causes coded using the ICD-10. Patients with a diagnosis of *Clostridium difficile* (ICD10-A07) aged >18 years, were included. Their baseline characteristics, clinical outcomes, and risk factors for CDI were analyzed. Length of hospital stay (LOS), mortality rate, and hospital expenses were used as indicators to evaluate the burden of CDI in Thailand.

Results: Of 4,863,935 admissions in 2010, 554 patients in 570 admissions (0.01%) were diagnosed with CDI. Of these, 106 (19.1%) died during the index hospitalization, and 98.1% had at least one comorbidity. The mean LOS for patients with CDI was longer than with other colitis ($P < 0.001$) and was also significantly longer for those who died during the index admission, compared with those who survived during the index admission ($P = 0.04$). The hospital expense for those who died was significantly higher than for those who survived ($P < 0.001$). From a multivariate analysis, age ≥85 years old, comorbidity, and sepsis were risk factors for mortality during admission with adjusted odds ratios of 2.40, 7.4, and 5.14, respectively.

Conclusions: The calculated burden of CDI in Thais is high; although the incidence of CDI is lower in Thailand than in Western countries. The mortality relates to the elderly age-group and comorbidity, especially sepsis.

Keywords: Burden, *Clostridium difficile* infection, nationwide study, Southeast Asia, Thailand, epidemiology

Clostridium difficile infection (CDI) is a well-known leading cause of hospital associated gastrointestinal disease [1]. CDI has become the most common infectious cause of nosocomial diarrhea in North America [2, 3] and the incidence of CDI has increased least 2–3-fold during the past decade, as according to U.S. and European nationwide databases [4-7]. For instance, in the U.S. the rate of hospital discharges with CDI listed as any diagnosis increased from 3.82 per 1000 discharges in 2000 to 8.75 per 1000 discharges in 2008 [4]. CDI is included among diseases with a high burden affecting people in Western countries. The annual cost of hospital care for patients was 3.2 billion dollars in the U.S. health-care system [8, 9]. Unfortunately, data on the incidence and burden of CDI in Asia and Southeast Asia, including Thailand, is limited [10, 11].

The first case of CDI in Southeast Asia was reported in 1985 [10] and in Thailand in 1990 [12]. Since then, some studies have indicated the various incidence of CDI in small populations and over various periods [13-15]. However, the previous data are inhomogeneous and do not represent the overall incidence and burden of CDI in Southeast Asia including Thailand. To address this, we sought to evaluate the incidence, burden, and risk factors for CDI in Thailand by using the nationwide database from 2010. Findings from this study will help to explore the importance of CDI in Thailand, representing Southeast Asia, and help to plan future health policies.

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Methods

We retrieved in-patient medical data, including the expense of hospitalization, from the 2010 Thailand

Nationwide Hospital Admission Database available from the National Health Security Office. The diagnosis of digestive diseases with any form of colitis listed as causes, either as principal diagnosis or comorbidity, coded by the International Classification of Disease and Related Health Problems, 10th Revision (ICD10) was recorded. The inclusion criteria were: (1) diagnosis of enterocolitis because of *Clostridium difficile* (ICD10-A07); and (2) age >18 years. If the data were incomplete, the case was excluded. The criteria for diagnosing CDI included clinical suspicion and therapeutic treatment with or without standard laboratory techniques such as *C. difficile* toxin A, B, or polymerase chain reaction. The baseline characteristics, including age, sex, comorbid disease, and history of endoscopy or surgery, were recorded. The burden of CDI was evaluated by length of hospital stay (LOS), mortality rate, and hospital cost. The study protocol was approved by the Chulalongkorn University Institutional Review Board (No. 464/57).

Statistical analyses

Values are expressed as mean ± standard deviation (SD) in normally distributed data. Continuous variables were compared using a Student *t* test. Discontinuous variables were compared using a c^2 test. Multivariate analyses were calculated and are presented as adjusted odd ratios (OR) and 95% confidence intervals (CIs). PASW Statistics for Windows (version 18.0, SPSS Inc. Chicago, IL, USA) was used for statistical analysis. Differences were considered significant at the level of 0.05.

Results

Of 4,863,935 admissions in the year 2010, 554 patients in 570 admissions (0.01%) were diagnosed with CDI (ICD10-A07), whereas 214,810 admissions of 204,126 patients (4.4%) were diagnosed with colitis (ICD10-A09). Eighty-eight of the 570 admissions (15.4%) were because of CDI as a principle diagnosis, whereas the remaining cases of CDI were diagnosed later as comorbidity. The highest proportion of CDI cases were found in patients 85 years (40 patients among 7,164 admitted with colitis) (**Figure 1**).

Cases of CDI were equally distributed between men and women (50% each). Of 554 patients with CDI, 493 (89%) had at least one comorbidity, including chronic renal failure, diabetes mellitus, cerebral vascular disease, cardiovascular disease, sepsis, human immunodeficiency virus infection, and/or inflammatory bowel disease. Of these, sepsis (at 30%) was the most common comorbidity among patients with CDI. In addition, 1.2% of patients with CDI underwent surgery or endoscopy during admission (**Table 1**).

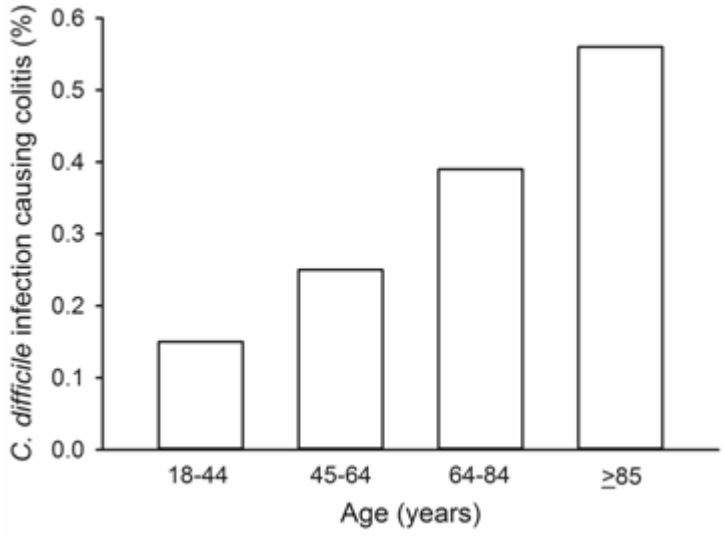

Figure 1. The proportion of all admissions with colitis in each age-group with *C. difficile* infection.

Table 1. Baseline characteristic of patients with colitis and CDI (554 patients in 570 admissions)

Variables	Number (%), n = 570
Sex; male	284 (49.8)
Age (years old)	
18-44	112 (19.6)
45-64	172 (30.2)
65-84	246(43.2)
≥85	40 (7.0)
Comorbidity	508 (89.1)
Sepsis	170 (29.8)
Cerebrovascular disease	49 (8.6)
Ischemic heart disease	46 (8.1)
End-stage renal disease	23 (4)
Inflammatory bowel disease	7 (1.2)
Diabetes mellitus	5 (0.9)
Human immunodeficiency virus	3 (0.5)
Surgery or endoscopy during the index admission	40 (7)
Length of hospital stay (mean ± standard deviation)	32.4 ± 36.7 days

Twenty-two of 554 patients with CDI (4%) were admitted more than once because of recurrence or relapsed CDI. The death rate of patients with CDI was 30% and 17.7% for those that were older and younger than 85 years, respectively. Moreover, 106 (19.1%) patients with CDI died during admission (all within 6 days); 98.1% of these had at least one comorbidity. The rate of comorbidity in CDI patients who died during the index hospitalization was significantly higher than those that survived (98.1% vs 87.1%; $P = 0.006$). Furthermore, patients with CDI had to stay in the hospital significantly longer than patients with colitis from another cause (32.4 ± 36.7 vs 2.5 ± 3.0 days; $P < 0.001$). The length of hospital stay (LOS) of patients with CDI who died during admission was significant longer than those who survived (38.8 ± 33.2 vs 31.4 ± 33 days; $P = 0.04$). The total hospital cost in the group that died was significantly higher than in the surviving group (9,683 ± 9,033 vs 5,293 ± 7,792 U.S. dollars; $P < 0.001$). From multivariate analysis, we found that the factors associated with mortality rate were age of ≥85 years and presence of at least one comorbidity, especially sepsis (**Table 2**).

Discussion

Clostridium difficile is a well-known toxin-producing, gram-positive, rod-shaped anaerobic bacterium with subterminal endospores [16, 17]. To our knowledge, this is the first study published of the nationwide incidence and burden of CDI in Southeast Asia, and only the second such study in Asia [10]. From 2004–2008, Korea reported a nationwide incidence of CDI infection in adults at approximately 0.2% among overall admissions [18]. Although not covering the same period, the Korean incidence of CDI was higher than that reported for Thailand. From the present study, the incidence of CDI in Thailand in

Table 2. Multivariate analysis for mortality in CDI patients

Factors	Adjusted OR (95%CI)	*P*
Age ≥85 years old	2.40 (1.09, 5.27)	0.03
Length of hospital stay	1.00 (0.99, 1.00)	0.86
Per additional comorbidity	7.47 (1.78, 31.36)	0.006
Sepsis	5.41 (3.40, 8.62)	<0.001
Surgery or endoscopy	0.28 (0.08, 0.98)	0.04

OR, odds ratio; CI, confidence interval.

2010 was estimated at only 0.01%. By contrast, the U.S. Center for Disease Control and Prevention surveyed across 10 U.S. geographical regions in 2011 and calculated that the estimated CDI prevalence was 0.14% (95%CI; 0.12%-0.16%) among overall population [19]. Both studies in Asia (Korea and Thailand) retrieved the data from overall admissions (incidence), whereas the U.S. study calculated the results from the population overall (prevalence). Although the prevalence of CDI in the U.S. cannot be compared with the incidence in Korea and Thailand directly, it can be assumed that the incidence in the U.S. should be much higher than in either Asian country [18, 19]. In 2014, an analysis of the U.S. Nationwide Inpatient Sample Healthcare Cost and Utilization Project database reported the epidemiology of CDI in patients after cardiac surgery, which had low risk of CDI, at 0.75% over 5 years [20]. From these findings, we propose that the incidence of CDI is lower in Eastern countries than in Western countries.

There are many reasons why the incidence of CDI may differ regionally. Diet is known as an important factor causing modification of gut microbiota, and a normal flora may be associated with CDI [21]. Consequently, Asian populations may have different microbiota than populations in Western countries and this may account for the lower rate of CDI in Thai and Korean people. A study in China [22] found that Chinese *Fen-Daqu* (a starter for liquor and vinegar fermentation) can alter the microbial species of its environment. In Chinese food, these microbial environments may not be compatible with the *C. difficile*, thus reducing the degree of *C. difficile* proliferation and contamination. Moreover, over production of *Bacillus* species may inhibit the growth rate of *C. difficile*. However, there has been no nationwide CDI study conducted in China to support these hypotheses. In the present study, one might presume that Southeast Asian food may offer protective factors against CDI; preserving healthy microbiota that can combat the *C. difficile* organism and reduce the CDI rate. Prospective studies need to be conducted to prove this hypothesis. Furthermore, Thais do not often take antibiotics, and even less so in rural areas, despite the availability of these medications as over-the-counter drugs. Traditions of rural people may help to protect them against CDI, despite other risk factors.

This study emphasized that old age is an important factor for CDI infection and can predict mortality because of CDI. Although much of the CDI occurred in young to middle-age patients (i.e., <65 years old), the proportion varied within each age group. The highest incidence for CDI was found in the group ≥85 years-old, whereas the proportions in the 18-44, 45-64, and 65-84 year-old age groups were progressively less with age (**Figure 1**). These results were consistent with the findings of an epidemiological study in the U.S. [4].

Comorbidity is an important parameter in the mortality rate of CDI patients. Approximately 90% of CDI patients had comorbidity, and almost all of the patients who died during index admission had comorbidity (98.1%). Comorbidity has been suggested as the precipitating factor of CDI, but the evidence has not been clear [7]. Here we show that comorbidity is an important mortality risk factor with an OR of 7.47 in multivariate analysis. In this study, the most important comorbidity associated with mortality was sepsis. Sepsis is a risk factor that predicts CDI because patients always require antibiotic treatment, which is a well-known risk factor for CDI [7, 23]. LOS was not a predictor of death, because severe CDI was life-threatening, and these patients typically died within a few days after diagnosis.

Our retrospectively data collection is the main limitation of the present study. The authors obtained all information from summary discharge; therefore, the information was limited. This study could not retrieve the result of investigation, criteria for CDI diagnosis, history of antibiotic usage, history of previous admission from other causes, nor other possible associated risk factors, such as proton pump inhibitor prescription. Moreover, this study relied on ICD10 coding for CDI diagnosis, which may be inaccurate. Nevertheless, this is the first large scale study in Thailand that can represent the actual situation and can thus guide future health policy decisions.

Conclusion

From a first nationwide study in Thailand, the burden of CDI infection in Thailand is high, even though the prevalence of CDI is likely to be relatively low. National health policies should improve strategies to prevent CDI.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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