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ORIGINAL ARTICLE

Clostridium difficile Infection: Clinico-Epidemiological Perspective

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ABSTRAK

Jangkitan Clostridium difficile (CDI) menyebabkan cirit-birit ringan hingga tenat dan kolitis pseudomembran di kalangan pesakit yang mempunyai pendedahan antibiotik terdahulu. Walaupun CDI berleluasa di seluruh dunia, data epidemiologi berkaitan CDI secara relatifnya adalah sedikit di Malaysia. Kajian ini bertujuan menentukan prevalen dan insiden CDI di Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM). Spesimen tinja tidak berbentuk daripada 147 pesakit yang disyaki menghidap CDI dari 1 November 2011 hingga 31 Oktober 2012 telah digunakan dalam kajian ini. Kehadiran toksin A dan/atau B C. difficile dikesan dengan menggunakan kit imunokromatografi komersial (Wampole™ Tox A/B QuikChek). Data pengamatan dikumpul daripada rekod kesihatan pesakit bagi mendapatkan ciri-ciri demografi dan klinikal. Keseluruhan prevalen dan insiden CDI di PPUKM masing-masing adalah 6.1% dan 5.2 kes per 10 000 hari-pesakit. Di kalangan sembilan orang pesakit CDI, 77.8% adalah lelaki dan 55.6% berbangsa Cina. CDI paling kerap berlaku di wad perubatan (88.9%). Median umur adalah 60 tahun dan median tempoh inap di hospital adalah 13 hari. Majoriti (88.9%) pesakit CDI telah menerima antibiotik lapan minggu sebelum mendapat CDI. Penisilin-perencat-beta-laktamase merupakan antibiotik yang paling kerap digunakan. Lima (55.6%) pesakit CDI telah menerima ubatan penindas asid. Kadar kematian di hospital adalah 22.2%. Kesimpulannya, prevalen dan insiden CDI dalam institusi ini secara relatifnya adalah rendah dan berlaku secara sporadik.

Kata kunci: jangkitan Clostridium difficile, ciri-ciri demografi, prevalen, insiden, Malaysia

ABSTRACT

Clostridium difficile infection (CDI) causes mild to severe diarrhoea and

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pseudomembranous colitis in patients who had prior antibiotic exposure. Despite CDI being prevalent worldwide, its epidemiological data is scanty in Malaysia. This study aimed to determine the prevalence and incidence of CDI at Universiti Kebangsaan Malaysia Medical Centre (UKMMC). Stool specimens from 147-suspected CDI patients were obtained from 1 November 2011 until 31 October 2012. The presence of *C. difficile* toxin A and/or B were detected using a commercial immunochromatographic kit (*Wampole™ Tox A/B Quik Chek*). Surveillance data was collected from patients' medical records to establish the demographic and clinical characteristics. The overall prevalence and incidence of CDI in UKMMC was 6.1% and 5.2 cases per 10 000 patient-days, respectively. Among nine CDI patients, 77.8% were males and 55.6% were Chinese. CDI was most common in medical wards (88.9%). The median age was 60 years and the median length of hospital stay was 13 days. Majority (88.9%) of CDI patients received antibiotics eight weeks prior to CDI. Penicillin-beta-lactamase inhibitors were the most common antecedent antibiotics. Five (55.6%) CDI patients received acid suppressant medications. The in-hospital mortality rate was 22.2%. In conclusion, the prevalence and incidence of CDI at UKMMC is relatively low and occurs sporadically.

Keywords: *Clostridium difficile* infection, demographic characteristics, prevalence, incidence, Malaysia

INTRODUCTION

Clostridium difficile is recognized as a significant nosocomial pathogen responsible for antibiotic-associated diarrhoea in most hospitals worldwide (Bartlett 1996; Hall & O'Toole 1935; McFarland 1998). It is an opportunistic, gram-positive, rod-shaped, spore-forming anaerobic bacterium known to be one of the minor colonic floras. The diagnosis of *Clostridium difficile* infection (CDI) is based on the presence of diarrhoea and stool test positive for toxigenic *C. difficile* or its toxin or colonoscopy or hisptopathologic findings demonstrating pseudomembranous colitis (Cohen et al. 2010).

The prevalence of CDI varies with hospital populations. In the United States, it affects over three million diarrhoeal and colitis patients, annually (Schroeder 2005). In Asia Pacific region, CDI prevalence had increased over the years. In Singapore for instance, the prevalence increased from 1.49 cases per 10,000 patient-days in year 2001 to 6.64 cases per 10,000 patient-days in year 2006 (Lim et al. 2008). In Malaysia, three out of seven CDI cases resulted in death from pseudomembranous colitis (Parasakthi et al.1988). Recently, it has been observed that incidence of CDI cases in northern eastern coast of Malaysia is 13.7% (Hassan et al. 2012).

Although CDI had been extensively investigated in most western and Asia Pacific region, there has been no established data on it at Universiti Kebangsaan Malaysia Medical Centre (UKMMC). The aim of the present study was to determine the incidence,

prevalence and epidemiological and clinical characteristics of CDI among hospitalized patients at UKMMC.

MATERIALS AND METHODS

STUDY DESIGN

The cross-sectional study was carried out in Bacteriology Laboratory, Department of Diagnostic Laboratory Services from November 2011 until October 2012. All unformed stool specimens from patients suspected with CDI as sent by clinicians were included. Duplicate specimens from the same patient within a 10-day period were excluded from this study (Peterson & Robicsek 2009). The diagnosis of CDI was confirmed by presence of *C. difficile* toxins in stool.

CLOSTRIDIUM DIFFICILE TOXIN DETECTION

Clostridium difficile toxins A and/or B were detected by a commercial kit (Wampole™ Tox A/B QuikChek, Techlab, USA), having 90.2% sensitivity and 99.7% specificity (manufacturer's insert). This rapid membrane enzyme immunoassay uses specific antibodies to detect toxins A and/or B of *C. difficile* in stool. The procedure steps were followed as directed. Presence of blue line in control and test reaction window within a 10-minute reading time was interpreted as positive result; indicating the presence of *C. difficile* A and/or B toxin.

DEMOGRAPHIC AND CLINICAL DATA

Data of *C. difficile* toxin-positive cases that were collected from patients' medical records included length of hospitalization, onset of diarrhoea, antibiotics used two months prior to diarrhoeal onset, nasogastric tube usage, immunosuppressive therapy, recent surgical intervention, underlying disease and others.

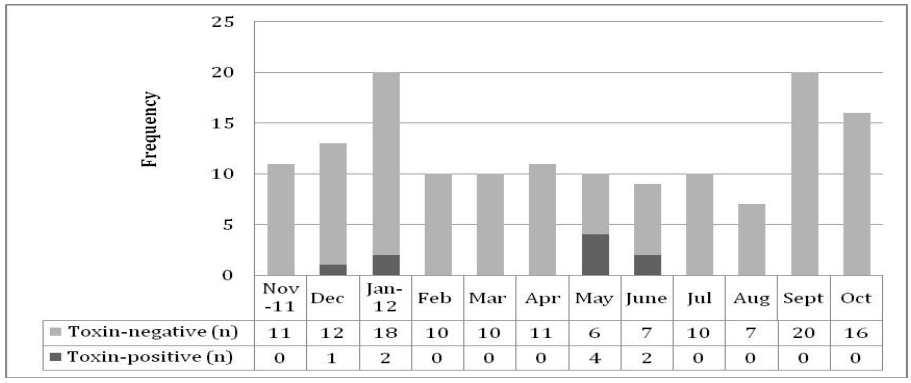
Monthly data on inpatient-days were obtained from Medical Informatics Department to calculate the incidence of CDI. The study received approval from the Research and Ethics Committee of Universiti Kebangsaan Malaysia (ERGS/1/2011/SKK/UKM/03/29).

STATISTICAL ANALYSIS

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 15.0 (SPSS, Inc, USA). Categorical variables and continuous variables were described as number (percentage) and median (IQR or range), respectively.

RESULTS

A total of 147 stool specimens were collected throughout the one-year study period. Nine of the 147 specimens were *C. difficile* toxin-positive and categorized as CDI (Figure 1). The overall prevalence of CDI was 6.1%. Monthly incidence of CDI was presented (Figure 2). Cases of CDI occurred sporadically during December-January and May-June. However, there were no CDI in the remaining months. The overall incidence throughout the study period was 5.2 cases per 10 000 patient-days. The average monthly incidence rate was 0.4 per 10 000 patient-days.



	Nov -11	Dec	Jan-12	Feb	Mar	Apr	May	June	Jul	Aug	Sept	Oct
Toxin-negative (n)	11	12	18	10	10	11	6	7	10	7	20	16
Toxin-positive (n)	0	1	2	0	0	0	4	2	0	0	0	0

Figure 1: Prevalence of *Clostridium difficile* infection at UKMMC

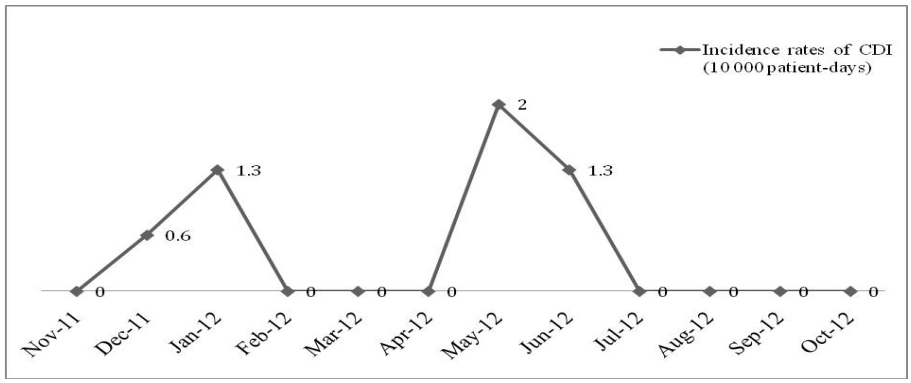


Figure 2: Monthly incidence rates of *Clostridium difficile* infection at UKMMC

Demographic and clinical characteristics of nine CDI cases were summarized (Table 1). It was revealed from the table that male to female ratio is 7:2, and affects both Chinese and Malay. The median patient age is 60 years (IQR: 57-67.5 years, range: 25-74). Majority of cases are from medical wards.

Two (22.2%) of the diarrhoeal cases occurred prior to the hospitalisation and confirmed CDI within 48 hours of admission. The remaining seven cases acquired CDI during hospitalisation. Median duration between admissions to CDI onset was six days (IQR: 6-12 days, range: 5-29 days). Median time to CDI detection was nine days (IQR 6-13 days, range: 6-32 days).

One (11.1%) of the nine cases did not have antibiotics therapy eight weeks prior to diarrhoea onset. In the remaining eight cases, a combined total of 22 courses of antibiotics (median: 2, range: 1-5 courses) and 106 days of antibiotic therapy (median: 13.5, range: 5-21 days) were implicated. Penicillin-beta lactamase inhibitors group (Table 2) was the most common antibiotics used; accounting for 49 out of 106 days. Cephalosporins and carbapenems accounted for seven and six out of 106 days, respectively.

Table 1: Demographic and clinical characteristics of *Clostridium difficile* infection at UKMMC

Characteristics		Frequency (%)
Sex	Male	7 (77.8)
	Female	2 (22.2)
	Male:Female	3.5:1
Race	Chinese	5 (55.6)
	Malay	4 (44.4)
	Indian & others	0 (0)
Age (years)	Median (IQR)	60 (57-67.5)
	Range	25-74
	> 65 years	6 (66.7)
Location	Medical	8 (88.9)
	Intensive Care Unit	1 (11.1)
Diarrheal Onset	Before hospitalisation	2 (22.2)
	During hospitalisation	7 (77.8)
Admission to CDI Onset (days)	Median (IQR)	6 (6-12)
	Range	5-29
Admission to CDI Detection (days)	Median (IQR)	9 (6-13)
	Range	6-32
Recent Antibiotics (courses)	0	1(11.1)
	1	3 (33.3)
	2	5 (55.5)
	Median (Range)	2 (1-5)
Duration of Antibiotic Therapy (days)	Median (Range)	13.5 (5-21)
Prior Hospitalisation	Yes	4 (44.4)
	No	3 (33.3)
	No data	2 (22.2)
Length of Current Hospitalisation (days)	Median (IQR)	13 (8-18)
	Range	7-39
Comorbidity	1 underlying disease	1 (11.1)
	≥2 underlying diseases	8 (88.9)
Acid-suppressing Medications	Yes	5 (55.6)
	No	4 (44.4)
Recent Therapeutic Intervention	Nasogastric tube	4 (44.4)
	OGDS	1 (11.1)
	Chemotherapy	0 (0)
	Colonoscopy	0 (0)
	GIT surgery	0 (0)
	In-hospital Mortality Rate	2 (22.2)

IQR: Interquartile Range

OGDS: Oesophagogastroduodenoscopy

GIT: Gastrointestinal

Table 2: Antibiotics implicated in *Clostridium difficile* infection

Antibiotic Class	Days
Penicillin-Beta-Lactamase Inhibitor	49
Macrolide	14
Quinolone	8
Sulphonamide	8
Glycopeptide	8
Cephalosporin	7
Carbapenem	6
Nitroimidazole	4
Penicillin	2

Records on prior hospitalisation were available in seven CDI cases. Four (57.1%) of these cases had hospitalization 12 weeks prior to the current admission. There were no recurrent CDI found in this study. The median length of hospitalisation for CDI was 13 days (IQR: 8-18 days, range: 7-39 days). Most cases had two or more underlying diseases. Five (55.6%) of the cases were on acid-suppressing medication. Throughout this period, majority of CDI was mild to moderate. None of the cases was treated with oral metronidazole or oral vancomycin. Hospital mortality rate among CDI cases was 22.2%.

DISCUSSION

The overall prevalence of CDI at UKMMC was 6.1% and the overall incidence was 5.2 cases per 10 000 patient-days. This data is comparable with the data from southern Taiwan and Singapore (Chung et al. 2010; Lim et al. 2008). Our prevalence was substantially lower than that of Canadian hospitals (Simor et al. 2013) and northeastern part of Peninsular Malaysia (Hassan et al. 2012). The monthly incidence rate indicates that CDI is not endemic in our institution.

The difference in prevalence and incidence can be explained by (1) difference in hospital categories (2) diversity in study population (3) variable study designs and sampling methods and (4) prior medications and therapeutic intervention (Chung et al. 2010). In our institution, low prevalence of CDI could be due to lack of awareness to CDI (Jamal et al. 2010). Lack of suspicion affects the yield of sampling and reduces the chances to diagnose CDI. In addition, the use of less sensitive technique instead of tissue culture cytotoxin assay and toxigenic *C. difficile* culture (Alcalá et al. 2008) may also explain for this finding. Hence, we started with another study involving several sensitive techniques to validate the current findings.

Major risk factors for CDI are hospitalisation, older age and history of antibiotic usage (Bartlett 2008). Underlying disease has been reported as another major risk factor for nosocomial CDI (Kyne et al. 2002). In our study, we observed that majority of CDI cases had diarrhoea onset during hospitalisation and six

(66.7%) of these cases were patients older than 65 years old. In addition, eight (88.9%) patients had antibiotics therapy within eight weeks before diarrhoea onset and all nine cases had at least one underlying disease. Unlike in other studies, tube feeding and oesophagogastroduodenoscopy (OGDS) were not common therapeutic interventions among CDI cases in our institution (Bliss et al. 1998; Thibault et al. 1991). More than half of CDI cases had received acid-suppressing medications within 8 weeks before the diarrhoeal onset. This finding is similar to that reported by Aslam & Musher (2006). Our study did not demonstrate significant association between CDI and the established risk factors (data not shown) because of small number of cases studied over a short period. To identify the risk factors in our institution, a case-control study involving larger samples would be appropriate.

For hospital-acquired CDI the median duration of diarrhoea onset was six days and median time to detection was nine days. Our study had shorter median time for detection as majority of the cases had earlier diarrhoea-onset between five to six days. Previous study by Forster et al. (2012) showed a longer time for detection of hospital-acquired CDI as the study focused on cases occurring after day-7 hospitalisation.

It was observed that penicillin-beta-lactamase inhibitors were the most common antibiotics received prior to CDI onset. This finding is similar to the previous study by Lee et al. (2012). Unlike in other studies, cephalosporins were not the common antecedent antibiotics (Kim et al. 2014; Lai et al. 2013). We also found that most of the cases were not on 'low risk' antibiotics prior to CDI onset. To reduce CDI incidence, Talpaert et al. (2011) recommended the usage of 'low risk' antibiotics for empirical treatment of common infections among hospitalized patients.

The median length of hospitalization for CDI cases was 13 days. Our finding is consistent with other studies. Few studies found that CDI is more likely to occur among patients who are hospitalized for seven days or more (Dumyati et al. 2012; Lee et al. 2012; Manian et al. 2007). We found that majority of the cases were mild to moderate and did not require oral metronidazole or oral vancomycin. Two cases that succumbed to death were related to their underlying primary diseases. However, in one case, the patient died one day after CDI was diagnosed. The death could be attributed to the complications associated with CDI.

A continuous CDI surveillance is useful to illustrate future incidence trend, disease recurrence and changes in our local clinico-epidemiology pattern. Based on this observational study, physicians should keep CDI in consideration in all cases of diarrhoea that had antibiotic therapy and/or acid suppressing medications in the preceding eight weeks.

CONCLUSION

In conclusion, the incidence and prevalence of CDI in our institution were relatively low. The cases occurred sporadically and were mild to moderate

in severity. Our preliminary data has important clinical significance that conveys strong message: community and hospital-acquired CDI do exist at our institution. A continuous surveillance and regular antibiotic audit may help curb CDI from spreading further.

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