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Hospital-acquired *Clostridium difficile* infection among patients with type 2 diabetes mellitus in acute medical wards

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ABSTRACT

Background: *Clostridum difficile* (*C. difficile*) infection is increasingly seen among hospitalised patients with type 2 diabetes mellitus but its rate and associated risk factors are not known. We aimed to determine the rate and characteristics of hospital-acquired *C. difficile* infection in subjects with type 2 diabetes mellitus admitted into acute medical wards.

Methods: Our prospective cross-sectional study involved 159 patients with established type 2 diabetes mellitus admitted into acute medical wards who developed a hospital-acquired *C. difficile* infection. Stools were tested for *C. difficile* toxins using a toxin A/B kit and a toxin A kit. Clinical features, laboratory findings, types of antibiotics, and use of a proton pump inhibitor were examined for their association with the infection.

Results: Thirteen subjects were positive for toxin A and one for toxin B. Using univariable analysis, we found that patients with type 2 diabetes mellitus and hospital-acquired *C. difficile* infection were younger (mean 53.8 years, p=0.02), had diarrhoea and abdominal pain (p=0.001) but no fever. Sepsis (p=0.02) and use of a proton pump inhibitor (p=0.01) were more commonly implicated as the cause of the infection. Of the various types of antibiotics prescribed, carbapenem (28.6% vs 4.1%, p=0.01) and metronidazole (42.9% vs 19.3%, p=0.04) were significantly associated with hospital-acquired *C. difficile* infection.

Conclusions: Patients with type 2 diabetes mellitus admitted into acute medical wards and who developed hospital-acquired *C. difficile* infection have distinct characteristics.

KEYWORDS *Clostridium difficile*, type 2 diabetes mellitus, nosocomial, antibiotics, acute medical wards

DECLARATION OF INTERESTS No conflicts of interest declared.

INTRODUCTION

Clostridium difficile (*C. difficile*) is one of the most common nosocomial infections in recent decades, with increasing prevalence, morbidity and mortality being reported worldwide.[1–3] Unfortunately data on the incidence of *C. difficile* infection in Asia in particular are more limited but the available reports suggest an increasing number in countries including Singapore, Taiwan, Korea, India and Japan.[4–8] *C. difficile* is a gram-positive spore-forming bacterium, producing cytotoxin (toxin A, B) and the resulting pathology can vary from being asymptomatic to pseudomembranous colitis, a condition with high morbidity.

Some of the established risk factors for hospital-acquired *C. difficile* infection include exposure to antibiotics, use of a proton pump inhibitor, advancing age, impaired immunity (e.g. haematologic malignancies, chemotherapy) and renal disease.[9,10] Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease related to insulin resistance and it is associated with increased susceptibility to infections as a result of impaired immunological tolerance. Diabetes mellitus has recently been implicated as a risk factor for recurrent *C. difficile* infection.[11]

Type 2 diabetes mellitus is highly prevalent in the North-eastern region of Peninsular Malaysia.[12,13] An increasing number of hospital-acquired *C. difficile* infections have been reported among our patients with T2DM, especially in those admitted into acute medical wards, but its rate and associated risk factors are not known. A literature review found few relevant studies, thus prompting our review. We aimed to determine the characteristics of hospital-acquired *C. difficile* infection in patients with T2DM, admitted into acute medical wards.

MATERIALS AND METHODS

Study population

We conducted a prospective cross-sectional study between August 2009 and May 2010 in a tertiary university hospital (Hospital Universiti Sains Malaysia) serving the North-eastern region of Peninsular Malaysia (State of Kelantan). The region has a population of 1.6 million with a predominance of Malay people of approximately 90%. The university hospital has 700 beds and is the main referral institution within the region for the management of T2DM and its associated complications, with approximately 16 beds in acute medical wards (high dependency unit and critical care unit).

All adult patients over the age of 18-years-old, with established T2DM, consecutively admitted into the acute medical wards of the university hospital during the study period were screened for hospital-acquired *C. difficile* infection. Suspected or unconfirmed cases of T2DM and type 1 diabetes mellitus were excluded. Other exclusion criteria included patients with other co-morbidities known to have an increased susceptibility to *C. difficile* infection including acquired immune deficiency syndrome (AIDS), other immune-compromised states, gastro-intestinal infections and inflammation.

A total of 159 out of 163 screened patients who satisfied the inclusion and exclusion criteria were recruited after providing informed consent. Clinical parameters including age, gender, symptoms, medical illnesses and infective complications associated with T2DM, type of antibiotics and proton pump inhibitor use were carefully documented in a data capture sheet. A sample of venous blood (5 mL) was collected from each patient to test for white cell counts, urea, creatinine level and glycosylated haemoglobin (HBA1c).

Our study was approved by the Human Ethics Committee of the Universiti Sains Malaysia.

Definitions

A diagnosis of T2DM was based on typical symptoms and a casual plasma glucose level of ≥11.1 mmol/L, a fasting plasma glucose level of >7.0 mmol/L or a two-hour postload glucose level of ≥11.1 mmol/L.[14] It is the most common form, and is characterised by insulin resistance and an increased risk for microvascular and macrovascular complications.[14] A patient was considered to have *C. difficile* infection for the purposes of our study when they had a positive cytotoxin assay and diarrhoea.[15] The presence of either toxin A or B in the stools, confirmed using at least two different test kits, was considered positive for the cytotoxin assay.[16] Diarrhoea was defined as passage of more than three loose stools within a 24-hour period with a duration of more than two days.[15] A *C. difficile* infection was considered to be hospital-acquired when it occurred more than 48 hours after hospital admission or less than 48 hours after admission in patients who had been hospitalised for four weeks prior to the current admission.[17] Exposure to any antibiotic treatment was defined as a prescription covering at least 48 hours in the last eight weeks prior to the *C. difficile* infection. Sepsis is a clinical syndrome and was defined by the presence of a systemic inflammatory response and bacteraemia from a positive blood culture.[18]

Stool sample and toxin detection

At least one fresh stool sample was collected from all patients included in the study. They were then stored at temperatures between 2–8°C in a microbiology laboratory with a dedicated storage facility. The samples were tested for the presence of toxin(s) within 72 hours; those not tested during this period were stored at –20°C or below and tested within two months of collection. The presence and type of toxin(s) in the stool samples were first tested using a *C. difficile* toxin A/B test kit. The single-use test kit is a membrane-type of enzyme immunoassay (EIA) allowing results to be read from a membrane, and it detects both toxins A and B.[16] According to the manufacturer, the test kit has a sensitivity of 86.3%, specificity of 96.2% and a negative predictive value of 96.8%, with reading time within 20 minutes. Stool samples tested positive were then re-tested using the *C. difficile* toxin A test to confirm the presence of toxin A in the stool samples. Negative samples were considered to have toxin B present. The toxin A test is also a form of membrane-type EIA, with a sensitivity of 90.4%, specificity of 97.8% and a reading time within 30 minutes.[16]

Statistical analysis

Data analyses were carried out using statistical software. All variables were reported as frequency and percentage unless otherwise stated. Univariable differences were tested using a chi-squared test or a Fisher's exact test for categorical variables and an independent t-test for continuous variables. A p value of <0.05 was considered statistically significant for all analyses.

RESULTS

Of the 159 study patients, there were more females than males (54.1% vs 45.9%) and the mean age (standard deviation [SD]) was 60.7 years old (11.0). In keeping with the demographic pattern within the region, ethnic Malays constituted 94.3% of the recruited patients. Fourteen out of 159 stool samples (8.8%) tested positive for *C. difficile* using the toxin A/B kit. When retested with the toxin A test, 13 tested positive for toxin A.

Patients with T2DM and who tested positive for *C. difficile* infection were significantly younger ($p=0.02$) but no significant difference between genders was noted

TABLE 1 Characteristics of study population with a *Clostridium difficile* infection

Parameters	*Clostridium difficile* status		p value
	Positive (n=14)	Negative (n=145)	
Age, years, mean	53.8 (14.2)	61.1 (10.5)	0.02*
Gender			
Male	5 (35.7%)	68 (46.9%)	0.43
Female	9 (64.3%)	77 (53.1%)	
Clinical features suggestive of CDI			
Fever	5 (35.7%)	55 (37.9%)	0.87
Abdominal pain	8 (57.1%)	23 (15.9%)	0.001*
Asymptomatic	0	26 (17.9%)	0.08
Laboratory features			
White cell counts, x10^9/L, mean	12.6 (7.1)	12.6 (6.2)	0.98
Urea, mmol/L, mean	15.8 (8.2)	14.2 (10.3)	0.56
Creatinine, µmol/L, mean	415.4 (316.5)	318.4 (325.3)	0.29
Albumin, g/L, mean	30.9 (8.1)	31.3 (7.7)	0.87
HBA1c, %, mean	7.0 (1.3)	8.5 (2.96)	0.07
Complications of diabetes mellitus			
Hypertension	11 (78.6%)	96 (66.2%)	0.35
Ischaemic heart disease	3 (21.4%)	44 (30.3%)	0.49
Chronic kidney disease	8 (57.1%)	56 (38.6%)	0.18
Cerebrovascular disease	0	5 (3.4%)	0.48
Infections needing antibiotics			
Abscess	1 (7.1%)	7 (4.8%)	0.71
Infective endocarditis	0	1 (0.7%)	0.75
Intra-abdominal infection	2 (14.3%)	14 (9.7%)	0.58
Infected diabetic foot	1 (7.1%)	9 (6.2%)	0.89
Pneumonia	6 (42.9%)	70 (48.3%)	0.70
Sepsis	5 (35.7%)	19 (13.1%)	0.02*
Skin infection	0	15 (10.3%)	0.21
Other soft tissues infection	0	11 (7.6%)	0.29
Use of proton pump inhibitor	13 (92.9%)	85 (58.6%)	0.01*

n= number of cases; **mean=** standard deviation; *significant p value <0.05 (Fisher's exact test)

(Table 1). Besides diarrhoea, the presence of abdominal pain (p=0.001) but not fever was more common among subjects with T2DM and *C. difficile* infection. None of the laboratory markers were helpful for differentiating either active or inactive infection (Table 1). Of the various types of clinical infections identified during admission, only sepsis was significantly associated with *C. difficile* (p=0.02). There was a significant usage of proton-pump inhibitors among patients tested positive for *C. difficile* infection (p=0.01). Only 44 (27.7%) patients received just one type of antibiotic during admission, with the rest receiving two or more types. Cloxacillin (33.3%) followed by ceftazidime (29.6%) were the most commonly prescribed. The combination of carbapenem (28.6% vs 4.1%, p=0.01) and metronidazole (42.9% vs 19.3%, p=0.04) was significantly associated with *C. difficile* infection in our study (Table 2).

TABLE 2 Type of antibiotics associated with *Clostridium difficile* infection

Antibiotics	*Clostridium difficile* status		p value
	Positive (n=14)	Negative (n=145)	
Cephalosporin	10 (71.4%)	104 (71.7%)	0.6
Penicillin	8 (57.1%)	80 (50.3%)	0.9
Macrolide	3 (21.4%)	38 (26.2%	0.5
Carbapenem	4 (28.6%)	6 (4.1%)	0.01§
Aminoglycoside	0	2 (1.4%)	0.8
Vancomycin	1 (7.1%)	3 (2.1%)	0.2
Metronidazole	6 (42.9%)	28 (19.3%)	0.04§
Ciprofloxacin	2 (14.3%)	16 (11.0%)	0.7
Anti-tuberculosis antibiotics*	0	5 (3.4%)	0.5

n=number of cases; §=p value <0.05 Fisher's exact test; *antituberculosis antibiotics include isoniazid, rifampicin, ethambutol and pyrazinamide in combination

DISCUSSION

We acknowledge from the outset that the study was limited by the small number of positive samples of *C. difficile*, which did not allow further multivariable analysis.

We found that patients with T2DM and hospital-acquired *C. difficile* infection were significantly younger than non-infected patients. In contrast, the majority of studies report that the infection occurs more frequently in older people, but diabetes mellitus was not specifically addressed.[19] The reason for this difference in age is unknown but it might relate to an earlier and longer exposure to antibiotics. Abdominal pain but not fever was more significantly associated with hospital-acquired *C. difficile* infection in patients with T2DM. Besides diarrhoea, other clinical features consistent with *C. difficile* infection include abdominal pain, fever, leukocytosis

and hypoalbuminemia.[15] In general, fever occurs in ~28% cases, abdominal pain in ~22% and leukocytosis in ~50%.[20] In our study, with the presence of other infections and an immune-suppressed state associated with T2DM, it is probably not surprising that fever was not discriminatory for *C. difficile* infection.

White cell counts, urea, creatinine, albumin and HBA1C levels were not discriminatory for *C. difficile* infection in subjects with T2DM. Leukocytosis and hypoalbuminemia, commonly associated with *C. difficile* infection, and the absence of association in our study, is probably a result of their co-presence with T2DM-associated co-morbidities. Similarly, none of the common medical complications of T2DM were shown to make any significant difference between infected and non-infected patients. Contrary to generally accepted belief, chronic kidney disease did not appear to increase the risk of *C. difficile* infection in our study either. However, the risk may not have increased until the glomerular filtration rate decreased to 15 mL/min and below.[21]

Of the different types of severe infections associated with T2DM in acute medical wards, sepsis was the only significant risk factor associated with a hospital-acquired *C. difficile* infection. Sepsis tends to be more severe and hence management often involves use of multiple high-dose broad spectrum antibiotics for a longer duration of time. This inevitably increases the risk for hospital-acquired *C. difficile* infection. Proton-pump inhibitor use was significantly associated with hospital-acquired *C. difficile* infection among the patients in our study, and in keeping with other reported studies, this is an established risk factor.[22]

Clindamycin and cephalosporins are antibiotics commonly implicated in *C. difficile* infection[23] but any connection with diabetes mellitus is unknown. Our study indicates that carbapenem and metronidazole were possibly associated with hospital-acquired *C. difficile* infection in subjects with T2DM admitted into acute medical wards.

Our findings corroborate with a recent case-control study which reported that carbapenem was more commonly implicated with *C. difficile* infection in hospitalised subjects, even though diabetes mellitus was not specifically investigated in this study.[24] The reasons for this are unknown. One early study reported that three out of ten patients were reported to have developed a *C. difficile* infection particularly when a high-dose of imipenem/cilastatin of 1 g was given every six hours.[25] Furthermore, chronic renal disease (which is common in people with diabetes mellitus) can potentially increase the toxicity of antibiotics due to a reduced excretion rate. Evidence suggests that patients with diabetes mellitus are particularly vulnerable to bowel infections as a result of altered gut microbiota composition and volume[26] and this is even more likely with the use of luminal antibiotics. Metronidazole, in oral form, is commonly used in the treatment of *C. difficile*-associated colitis. In our study, however, metronidazole was prescribed before a diagnosis of *C. difficile* infection was made. Recent reports indicate that the resistance of *C. difficile* to metronidazole is increasing,[27] particularly in tropical countries, where it is commonly used as an anti-parasite agent. A recent study indicated that diabetes mellitus and sepsis are significant risk factors which explains the failure of metronidazole treatment in *C. difficile* infection.[28] Based on this information, vancomycin appears to be the better choice for treatment of *C. difficile* infection in patients with T2DM and sepsis.

There were limitations in our study. Sample size was partly limited by recruiting subjects with only T2DM admitted into acute medical wards. Exclusion criteria, an inability to provide consent (due to confusion, severe illness etc.) or stool samples were other limiting factors. As more than 70% of our study patients received two or more antibiotics, it was difficult to fully evaluate the effect of interactions between them. Patients with type 1 diabetes mellitus were not included in the study but the same results might be applicable since both conditions are associated with increased susceptibility to infections.

CONCLUSION

Hospital-acquired *C. difficile* infection was more common in younger subjects with T2DM admitted into acute medical wards, especially in the presence of sepsis and the use of carbapenem and metronidazole were associated with a higher risk of infection.

While we accept that there were some limitations in our study, we still believe that the information we gathered should be used for future research and ultimately improvements in patient care.

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