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Clostridium difficile Infection in Immuno-compromised and Non-immunocompromised Hosts – A Single-center Experience

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Authors' contributions

This work was carried out in collaboration between all authors. Author SWC served as the principal investigator, and was responsible for the study and protocol design, statistical analysis, literature searches, analyses of study and manuscript writing. Authors WMY, LSWL and KKL participated in the study design and manuscript editing. All authors read and approved the final manuscript.

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ABSTRACT

Background: *Clostridium difficile* infection (CDI) is the most common nosocomial and antibiotic-associated diarrheal disease of different severity. Patients of immunocompromised status were observed to be particularly at risk of complications and severe disease in the Western culture; however, local clinical data in tropical or subtropical region is scarce.
Methods: We performed a retrospective review of 220 cases at the Tuen Mun Hospital in Hong Kong from May 2010 to April 2012. Independent predictors for 30-day mortality and 60-day recurrence were determined by multivariate logistic regression analysis.

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Results: The mortality and recurrence were more prevalent in the immunocompromised group accounting for 36.1% (n=44) and 18.9% (n=23) respectively. We found independent associations between death and the hostel residency (odds ratio [OR], 2.33; 95% confidence interval [CI], 0.99-5.5), chronic kidney disease (OR, 2.74; 95% CI, 1.12-6.7), metronidazole treatment <10 days (OR, 2.31; 95% CI, 1.04-5.11), albumin level <30 g/L (OR, 2.31; 95% CI, 1.04-5.14) and proton pump inhibitor exposure (OR, 2.4, 95% CI 1.03-5.54). The hostel residency (OR, 2.56; 95% CI, 1.07-6.1) and duration of disease ≥ 10 days (OR, 2.55; 95% CI, 0.997-6.52) were associated with increased odds of recurrence.

Conclusions: CDI is a disease with significant morbidities, complications and mortality whereas the severity is significantly higher in the immunocompromised hosts. Shorter duration of metronidazole as an independent poor prognostic predictor was rarely reported before this paper.

Keywords: Clostridium difficile; immunocompromised; pseudomembranous colitis; proton pump inhibitor; albumin.

1. INTRODUCTION

Clostridium difficile (CD) is an anerobic gram-positive spore-forming organism and its incidence appeared stable since the discovery in the 1970's until the 20th century, when it became a principal pathogen of nosocomial infection with increasing incidence, severity, rate of recurrence, mortality and more refractoriness to treatment [1-6]. In 2002, an outbreak in Quebec, Canada, the emergence of the virulent strain BI/NAP1/027 demonstrated a trend towards a fulminant disease [2,3] and the 30-day mortality was up to 30.9% in the inpatient population [3]. CDI has surged as the first major contributor to gastroenteritis-associated deaths in the United States [6].

The immunocompromised individuals have been frequently reported to be at risk for severe CDI diseases or recurrence. The common conditions associated with adverse clinical outcomes include human immunodeficiency virus (HIV) infection, solid organ transplant and bone marrow transplant, malignancy, chemotherapy, use of immunosuppressant particularly corticosteroid, diabetes mellitus (DM), liver cirrhosis, chronic kidney disease (CKD) and these associations have been recently documented in the latest guideline published by the American Journal of Gastroenterology (AJG) in April 2013 [7-19]. However, conflicting results were reported in several studies and many of which were limited by their varied definitions of immunocompromised status and outcomes [9,17,20-22].

In Hong Kong, a large cohort study of 300 patients was done by the local microbiologists, in which a predominant clone of *C. difficile* PCR ribotype 002 was identified and that was related to a significant increase in both the incidence of toxigenic *C. difficile* and the rate of positive detection [23]. Another small scale outbreak of 15 cases was reported in 2011 in a local rehabilitative unit [24]. Currently, there is no large-scale study focusing on the clinical aspects of CDI from the perspective of a regional hospital. Therefore, this study aimed to compare the clinical characteristics and outcomes of immunocompromised and non-immunocompromised patients who presented with CD-associated diarrhea and to identify potential predictors for severe disease.

2. METHODS

2.1 Study Population

This was a retrospective, cohort study conducted within the inpatient population from the Department of Medicine and Geriatrics of the Tuen Mun Hospital which is a regional tertiary hospital serving one million population. Patients who tested positive for *Clostridium difficile* (toxigenic) PCR between May 2010 and April 2012 were identified from the computer database of the microbiology laboratory of the Department of Clinical Pathology in Tuen Mun Hospital. Approval for the study was granted by the local ethics committee of the institution.

2.2 Data Source and Collection

The case notes of eligible patients were reviewed and patients' demographic characteristics and relevant clinical data were recorded into a specially designed case report form.

2.3 Inclusion and Exclusion Criteria

The inclusion criteria were patients aged ≥18 years, a positive test for toxigenic

Clostridium difficile PCR and diarrhea with loose or watery stool ≥ 3x/day, or ileus.

The patients with the following conditions which may suggest a carrier status or alter the presentation of the infection were excluded: well-formed stool <3 bowel movement/day, alternative diagnosis for gastroenteritis within 4 weeks, active lower gastrointestinal (GI) pathologies such as inflammatory bowel disease (IBD) or colonic malignancy, abnormal anatomy such as ileostomy or colostomy, chronic diarrhea ≥ 4 weeks and recent abdominal surgery within 4 weeks.

For patients who had more than one episode of recurrence during the study period, only the first episode was counted and included in the analysis.

2.4 Definition

A CDI was defined as diarrhea with passage of unformed stool > 3x/day in a patient and a positive test for toxigenic *Clostridium difficile* PCR in any stool sample. With ileus, a positive test for *Clostridium difficile* (toxigenic) PCR in stool was adequate in the absence of diarrhea. The same criteria were used to define recurrent CDI when the symptoms recurred within 60 days after complete resolution of the symptoms. Treatment failure was defined as the persistence of symptoms > 6 days after the initiation of antibiotic treatment, and cases that no antibiotic treatment for CDI was given or died within six days of treatment were not included in the study.

A CDI was defined as healthcare facility-related and hospital-acquired if its symptom onset was > 48 hours after admission or within 4 weeks of hospital discharge, others were considered as community-acquired infection. The number of hospital-days in the last 60 days before the illness and the number of days to symptom onset since the index admission were recorded. Hostel resident was defined as a patient living in a long-term care facility such as an aged home for elderly or a permanent hostel for mentally-handicapped patients.

The following were defined as immunocompromised conditions: active malignancy, DM, transplant recipients, regular immunosuppresants ≥ 1 month, recent chemotherapy within 1 month, stage 4 and 5 CKD, defined as estimated glomerular filtration rate (eGFR) <30ml/min by the Modification of Diet in Renal Disease (MDRD) Study equation.

2.5 Clinical Outcomes

The primary outcomes included the rate of treatment failure, the rate of complicated CDI and the recurrent rate. Complicated CDI were defined as the occurrence of renal deterioration (creatinine increased by 1.5x from the baseline), septic shock, ileus, toxic megacolon, bowel perforation, surgical intervention and 30-day all-cause mortality.

Secondary outcomes were the duration of the disease, the number of days from the symptom onset to diagnosis and the number of days from the treatment initiation to the resolution of diarrhoea. Relevant clinical predictors for the 30-day mortality and the 60-day recurrence would be analyzed as well.

2.6 Laboratory Assay

The laboratory assay used was a commercial kit named 'LightMix® Kit *Clostridium difficile*' (TIB MOLBIOL, Berlin, Germany) which targeted on the toxin regulator gene tcdC gene. It detected as low as 10 copies of *Clostridium difficile* DNA with a linear measuring range of 10^2 to 10^6 copies. The laboratory analysis was performed by the laboratory technicians of the Department of Clinical Pathology of the hospital.

2.7 Sample Size Estimation

For complicated CDI, the rate was about 10% in the general population [1,21,22,25] and it ranged from 7-50% in different reports in the immunocompromised patients (25% used as the most commonly quoted figure) [14].

Using the formula for comparing two sample proportions:

$$n_1 = \frac{\left(z_{\alpha/2} + z_{\beta}\right)^2 \left[r\theta_1\left(1-\theta_1\right) + \theta_2\left(1-\theta_2\right)\right]}{\left(\theta_1 - \theta_2\right)^2}$$

$$n_2 = rn_1$$

α: the probability of rejecting the true null hypothesis.

β: 1 –β =power of the test θ: Expected outcome proportions of the sample.

Assuming that an equal allocation of n1 (immunocompromised) and n2

(immunocompetent) (R=1), and α=0.05, β=0.2 (giving a power of 0.8), with θ1=0.1 and θ2=0.25, the estimated sample number would be n1=n2=97 and the total sample (N)=194. Therefore, a minimum of 194 patients would be recruited.

2.8 Statistical Analysis

Demographic data and quantitative variables were presented as percentages and mean with standard deviation (SD) respectively. Chi-square test and student T test were used for categorical variables and the continuous variables accordingly. Specific parameters such as white cell count, albumin, age, duration of disease and other clinical relevant information were dichotomized for easy analysis. To identify potential risk factors, relevant clinical data were analyzed by univariate analysis whereas factors with P≤0.2 were subsequently analyzed by the logistic multivariate regression to identify the independent clinical predictors of the 30-day mortality or 60-day recurrence. All results were significant at P≤0.05. Computer Software SPSS version 16.0 was used for the processing of the above statistic methods.

3. RESULTS

A total of 280 patients were noted to have tested positive for *C. difficile* (toxigenic) by PCR lab test from the period of 1st May 2010 to 1st April 2012 in our database. Seventeen patients were excluded due to unavailable case notes, and another 43 were excluded according to the aforementioned exclusion criteria (17 absence of diarrhea, 8 positive for norovirus, 5 chronic diarrhea, 4 lower GI malignancy, 3 IBD, 3 incomplete record or data, 2 ileostomy, 1 recent abdominal surgery). Two hundred and twenty patients were eligible for analysis.

3.1 Demographic Data

Table 1 shows the demographic data, co-morbidities, history of medication exposure and baseline biochemistry results of the patients between the immunocompromised and non-immunocompromised groups. All patients were Asians and the non-immunocompromised group had an older mean age (79 years vs 71 years, P<0.001) than its counterpart. Eighty-nine percent (n= 195) of the CDI were hospital-acquired. The mean hospital stay within the last 60 days was 21 days and number of days to symptom onset from the index admission was 15-20 days which did not differ significantly in the two groups. However, more long-term hostel residents were found in the non-immunocompromised arm (50%) compared to the immunocompromised arm (36%). Significantly more patients used proton-pump inhibitor (PPI) and suffered from chronic obstructive airways disease (COAD) and neurological disease in the non-immunocompromised group, but no difference was seen in the antibiotic exposure. Biochemically, patients with compromised immune conditions presented the disease with a higher mean white cell count and a higher serum creatinine level due to the inclusion of the patients with chronic kidney disease (CKD).

Table 2 shows the percentage of conditions associated with altered immune status, more than half of the patients had CKD and DM, twenty-two percent of patients had malignancy and small proportions were treated with regular immunosuppressants, chemotherapy in the last 30 days or a transplant surgery.

3.2 Treatment

Antibiotic treatment was not given in 13% of the patients in either group (Table 3). Majority (85% of patients in both groups) were prescribed with metronidazole (oral or intravenous) for the management of clostridium-associated diarrhea. Only 5 patients (2.27%) received oral vancomycin as the first line treatment of choice. Three patients (1.36%) were treated with both vancomycin and metronidazole due to critical illness. The rate of treatment failure was 26.7% (27/101) in the patients in the immunocompromised group, which was significantly higher than the rate in the patients without immunocompromised status [9/83 (10.8%), P=0.007] (Table 3).

3.3 Disease Outcomes

The detailed outcomes are listed in Table 3. For the primary outcomes, the immunocompromised group of patient had generally more clinically severe diseases, with a higher rate of complicated CDI (63.9% vs 23.5%, P<0.001). Among those patients, there were also significant higher rates of ileus (7.4%), renal deterioration (25.4%) and septic shock (23.8%). Only one patient was found to have bowel perforation in this study and suffered from diabetes mellitus (DM). The 30-Day all-cause mortality was observed in 36.1% (n= 44) of the

immunocompromised individuals suffering from clostridium-associated diarrheal disease, compared to only 17.3% (n= 17) in the control group. Recurrent disease within 60 days also developed at a double rate in the immunocompromised group versus the non-immunocompromised group (18.9% vs 9.2%, P=0.043).

In reference to the secondary outcomes, clinicians took longer to diagnose CDI in the immunocompromised patients compared to the patient without immune deficiency (6.2 days vs 5.1 days, P=0.038). The duration of CDI was also longer in the immunocompromised group compared to the non-immunocompromised group (10.1 days vs 7.6 days, P=0.002). The time for the disease to response to the antibiotic treatment also showed a slight longer trend in the immunocompromised group but it did not reach a statistically significance (4.3 days vs 3.1 days, P=0.068).

Table 1. Demographic data and clinical characteristics

	Immunocompromised group (N= 122)	Non-immunocompromised group (N= 98)	P-value
Age (mean ± SD)	70.94±16.6	79.32±13.96	<0.001*
Gender			
Female: Male	1.18	1.39	0.54
Smoking			0.41
Ex-smoker	30 (30.6%)	28 (23.0%)	
Active smoker	7 (7.1%)	8 (6.5%)	
Health-care facility			
Hostel resident	44 (30.1%)	49 (50%)	0.041*
Hospital acquired disease	105 (87.5)	90 (91.8%)	0.3
Number of Hospital-days in the last 60 days	21.03±17.24	21.18±18.20	0.95
Number of days to symptoms onset since the index admission	15.25±32.96	20.71±44.72	0.299
The use of medications			
Antibiotics with 60 days	105 (86.1%)	85 (86.7%)	0.886
PPI use within 90 days	49 (40.2%)	18 (18.4%)	<0.001*
H2RB use	40 (32.8%)	35 (35.6%)	0.649
Co-morbidities			
Cardiovascular disease	35 (28.5%)	23 (23.5%)	0.383
Chronic liver disease/liver failure	4 (3.3%)	0 (0%)	0.07
COAD	7 (5.7%)	23 (23.5%)	<0.001*
Neurological disease	26 (21.3%)	40 (40.8%)	0.002*
Laboratory results			
White cell count (x 10^9/L)	13.36±11.54	9.90±4.27	0.005*
Neutrophil count (x 10^9/L)	9.56±6.39	9.68±15.02	0.935
Lymphocyte count (x 10^9/L)	1.40±1.64	1.25±0.71	0.397
Creatinine (umol/L)	315.83±304.00	76.43±57.88	<0.001*
Protein (g/L)	59.29±9.00	63.0±8.25	0.002*
Albumin (g/L)	30.40±9.23	31.69±7.69	0.265
Bilirubin (umol/L)	8.16±5.59	10.83±11.15	0.022*
Spot glucose (mmol/L)	8.16±5.59	7.38±5.09	0.054
C-reactive protein (mg/L)	69.05±73	52±69	0.385
ESR (mm/hr)	61.38±35.7	56.59±34.30	0.52
Colonoscopy done †	11 (9%)	5 (5.1%)	0.266

Abbreviations: PPI, Proton-pump inhibitor; H2RB, histamine-2-receptor blocker; COAD, chronic obstructive airway disease; ESR, erythrocyte sedimentation rate

† No pseudomembrane appearance was present among the patients with colonoscopy done.

** Significant differences (P≤0.05)*

Table 2. The composition of different conditions in the immunocompromised group

Background conditions	Immunocompromised group (N= 122)
Chronic kidney disease	70 (57.4%)
Diabetes mellitus †	67 (54.9%)
Malignancy	27 (22.1%)
Regular immunosuppressants	8 (6.6%)
Chemotherapy within 30 days	8 (6.6%)
Transplant recipients	3 (2.5%)

† (Mean of glycosylated haemoglobin A1c (HbA1c) within 3 months of the patients with diabetes mellitus: 7.75%±1.82%

Table 3. Diseases outcomes of the patients

	Immunocompromised group (N= 122)	Non-immunocompromised group (N= 98)	P value
No antibiotics treatment given†	17 (13.9%)	13 (13.3%)	0.886
Diseases outcomes			
Treatment failure	27/101 (26.7%)	9/83 (10.8%)	0.007*
Complicated CDI	78 (63.9%)	23 (23.5%)	<0.001*
60-Day recurrence	23 (18.9%)	9 (9.2%)	0.043*
Number of days from symptoms onset to diagnosis	6.18±3.83	5.10±3.78	0.038*
Duration of disease, days	10.10±6.57	7.57±5.18	0.002*
Number of days from treatment initiation to symptom resolution	4.26±4.47	3.07±4.21	0.068
Details of the complicated CDI			
Ileus	9 (7.4%)	0 (0%)	0.006*
Renal deterioration	31 (25.4%)	7 (7.1%)	<0.001*
Bowel perforation/ Surgical intervention	1 (0.8%)	0 (0%)	0.369
Septic shock	29 (23.8%)	8 (8.2%)	0.002*
30-day all-cause mortality	44 (36.1%)	17 (17.3%)	0.002*

Abbreviation: CDI, Clostridium difficile infection.

† 11 patients had symptoms resolved with supportive care, 6 patients died before the treatment initiation in the immunocompromised group and 10 patients had symptoms resolved with supportive care, 3 patients died before the treatment initiation in the non-immunocompromised group.

**Significant differences (P≤0.05)*

3.4 Clinical Predictors

The potential risk factors for 30-day all-cause mortality and 60-day recurrence are tabulated in Tables 4 and 5. The following clinical factors were associated with 30-day all-cause mortality with P value ≤0.05 by the univariate analysis: age ≥65 years, DM, CKD, continuation of the causative antibiotics, PPI exposure within 90 days, duration of disease ≥10 days, requiring the use of intravenous fluid, hemodynamic instability, fever, a low serum albumin level and renal deterioration. The CKD, metronidazole treatment <10 days, PPI exposure within 90 days and a low serum albumin level <30 g/L were found to have independent associations with 30- day mortality (Table 4). The clinical variables associated with 60-day recurrence with significance after univariate analysis included DM, CKD, exposure to ≥2 groups of antibiotics in the last 60 days and duration of disease ≥10 days. Only the hostel resident and the duration of the disease ≥10 days were statistically significant as the independent predictors for recurrence while exposure to ≥2 groups of antibiotics and metronidazole treatment <10 days displayed a trend towards a recurrent disease but failed to reach statistical significance (Table 5).

Table 4. Results of clinical predictors of 30-day mortality

	Univariate analysis unadjusted OR (95% CI)	Multivariate analysis adjusted OR (95% CI)
Background characteristics		
Age ≥ 65 years old	2.43* (1.11-5.32)	
Hostel resident	1.77 (0.98-3.22)	2.33* (0.99-5.49)
Hospital-acquired disease	1.45 (0.51-4.10)	
Co-morbidities		
Diabetes mellitus	2.14* (1.15-3.97)	
Chronic kidney disease	2.36* (1.28-4.37)	2.74* (1.12-6.70)
Malignancy	1.36 (0.57-3.20)	
Chemotherapy in the last 30 days	0.36 (0.04-3.01)	
Regular immunosuppressants	0.86 (0.17-4.40)	
Chronic obstructive airways disease	1.14 (0.49-2.64)	
Cardiovascular disease	1.55 (0.81-2.97)	
Neurological disease	0.78 (0.40-1.50)	
Antibiotic history & treatment		
Exposure to ≥ 2 groups of antibiotics in the last 60 days	1.10 (0.61-2.01)	
Causative antibiotic stopped	0.58* (0.35-0.98)	
No antibiotic treatment given	1.62 (0.72-3.64)	
Metronidazole treatment < 10 days	1.54 (0.80-2.97)	2.31* (1.04-5.11)
PPI use within 90 days	2.14* (1.15-3.97)	2.39* (1.03-5.54)
Clinical features		
Duration of disease ≥ 10 days	2.02* (1.10-3.71)	
Intravenous fluid used	1.98* (1.05-3.72)	
SBP drop > 40 mmHg	2.14* (1.02-4.50)	
SBP < 90 mmHg	2.72* (1.26-5.88)	
Heart rate > 100 BPM	3.49** (1.82-6.68)	
Fever > 38 degree celsius	2.21* (1.92-4.10)	
White cell count > 13 x 10^9/L	1.51 (0.80-2.86)	
Albumin < 30 g/L	2.99* (1.61-5.52)	2.31* (1.04-5.14)
Renal deterioration	2.54* (1.23-5.24)	

Abbreviations: OR, Odds ratio; CI, confidence interval; PPI, Proton-pump inhibitor; SBP, systolic blood pressure.
** Significant differences (P≤0.05); ** Significant differences (P<0.001)*

4. DISCUSSION

This retrospective cohort study, being the first one characterizing the clinical presentations of CDI in Hong Kong, has demonstrated the consistency of the disease features compared with the literature from the Caucasian populations and shed light on the limited experience in the Asian patients about this disease with increasing prevalence and severity. Clinical data on CDI is inadequate in Hong Kong or even in the Asians, our cohort illustrated that CDI is not trivial in our locality with complication rates of 63.9% and 23.5% in the immunocompromised and non-compromised groups, respectively, and the overall 30-day mortality rate was 27.7% (61/220), which is similar to mortality rates reported in other countries [1,2,3].

Conditions such as DM, CKD, HIV, and malignancy have been consistently reported to result in a depressed T-cell function and thus an inadequate adaptive immune response [26-30]. Immunosuppressive agents such as glucocorticoids, cytotoxic drugs, or chemotherapy iatrogenically down regulate the immune response and may alter the normal commensal flora of the bowel, thereby worsening the susceptibility to CDI. Therefore, it is logical to anticipate generally more severe clinical presentations in the patients suffering from these immunity-related conditions.

Table 5. Results of clinical predictors of 60-day recurrence

	Univariate analysis unadjusted OR (95% CI)	Mulitvariate analysis OR (95% CI)
Background characteristics		
Age ≥ 65 years old	0.85 (0.37-1.97)	
Hostel resident	1.93 (0.91-4.13)	2.56* (1.07-6.09)
Hospital-acquired disease	3.84 (0.53-29.63)	
Co-morbidities		
Diabetes mellitus	2.31* (1.08-4.96)	
Chronic kidney disease	2.13* (1.00-4.59)	
Malignancy	0.71 (0.20-2.50)	
Chemotherapy in the last 30 days	2.02 (0.39-10.49)	
Regular immunosuppressants	N/A	
Chronic obstructive airways disease	0.62 (0.18-2.17)	
Cardiovascular disease	0.92 (0.39-2.18)	
Neurological disease	0.90 (0.39-2.06)	
Antibiotic history & treatment		
Exposure to ≥ 2 groups of antibiotics in the last 60 days	2.41* (1.12-5.17)	2.29† (0.92-5.66)
Causative antibiotic stopped	1.17 (0.65-2.20)	
No antibiotic treatment given	0.18 (0.02-1.35)	
Metronidazole treatment < 10 days	1.49 (0.69-3.23)	2.117† (0.85-5.26)
PPI use within 90 days	1.24 (0.56-2.73)	
Clinical features		
Duration of disease ≥ 10 days	2.96* (1.38-6.35)	2.55* (1.00-6.52)
Intravenous fluid used	1.63 (0.73-3.63)	
SBP drop > 40 mmHg	0.94 (0.34-2.63)	
SBP < 90 mmHg	1.10 (0.39-3.12)	
Heart rate > 100 BPM	0.88 (0.42-1.86)	
Fever > 38 degree celsius	0.69 (0.30-1.63)	
White cell count > 13 x 10^9/L	0.10 (0.43-2.29)	
Albumin < 30 g/L	0.88 (0.42-1.88)	
Renal deterioration	0.87 (0.31-2.43)	

Abbreviations: OR, Odds ratio; CI, confidence interval; PPI, Proton-pump inhibitor; SBP, systolic blood pressure.
**Significant differences (P≤0.05).*
† Exposure to antibiotic ≥2 groups and metronidazole use <10 days showed a trend towards significance as a predictor for a recurrence disease (P = 0.074 and P = 0.107 respectively)

The patents with DM and CKD were clearly defined groups and they illustrated a significantly more severe disease in both 30-day mortality and 60-day recurrence by univariate analysis. In the multivariate analysis model, CKD was identified as an independent predictor for 30-day mortality, which was compatible with our pathophysiological postulation. Although the diabetes mellitus did not show any predictive role from the analysis, we can notice that our diabetic patients were under relatively good diabetic control with a mean glycosylated hemoglobin A1c (HbA1c) level of 7.75%±1.82%) and the impact of DM on their immunity was probably mild. The patients who had malignancy and regular immunosuppressive agents were probably representing the more heterogeneous clusters of patients varying from having solid organ malignancy to hematological malignancy, and from using glucocorticoids, to cytotoxic agents or even intensive chemotherapy. Significant difference in outcomes could not be detected in these combinations of patients.

Increasing age, particularly over 65 years of age, is associated with poor prognosis in terms of the treatment refractoriness, complications and recurrence in many reports [2,3,13,17,31,32]. Contradictorily, in our cohort, patients in the non-immunocompromised group, who had a better general clinical outcome, were of significantly older age than those in immunocompromised group (mean age 79.32±13.96 vs 70.94±16.6, P<0.001). Although being an adverse factor for 30-day mortality in the univariate analysis, old age (≥ 65 years) was not a risk factor once other co-founding factors were adjusted for in the multivariate analysis.

Significant difference in treatment failure was found between the two major groups of patients (26.7% vs 10.8%, P=0.007). Treatment failure rate in the literature varies from 2% to 37.8% [4,15,32,25] and we recognized a potential group of patients having immunocompromised diseases at an increased risk of treatment failure. The guideline published by the Infectious Diseases Society of America in 2010 recommends the use of oral metronidazole 500mg 3 times per day for 10 to 14 days for the initial episode of mild to moderate CDI [13] based on the design of certain prospective randomized controlled trials [33,34], using 10-day course of metronidazole as the standard regime with a successful rate >90%. The outcomes of patient received a shorter duration of treatment has seldom been investigated and we identified the metronidazole treatment <10 days being a significant predictor in 30-day mortality and having a trend towards a recurrent disease within the 60-day period. Few Studies focused on the effect of PPI use on the severity or complication rate of the disease. Morrison et al. retrospectively reviewed 485 CDI patients and found a prior acid suppression positively correlated to the total complication and CDI-associated mortality rate, with adjusted OR of 2.4 and 4.74, respectively [16]. We report a higher mortality rate from CDI in patients with recent exposure to PPI, in terms of an OR of 2.4 after adjusting the potential cofounders. This offers supplementary evidence for the clinicians to reserve the administration of potent acid suppressive agents to those clinically indicated patients and to advise against the current trend of liberate use of PPI.

Health-care facility resident and hospitalization increases the chance of colonization of CD at a steady rate after hospitalization implying a cumulative risk of exposure to the spores in the healthcare setting [13,25]. Our data suggested the immunocompromised patients were less likely to be long-term hostel residents (36.1% vs 50%, P=0.041, Table 1) and this inferred that more community-acquired infection happened in this vulnerable group of patients. Long-term hostel residency was an independent risk factor for both mortality and recurrence and this could be a reflection of an increased exposure to spores in the health-care facility. A low albumin level was commonly quoted as a feature found in severe CDI and it could be both a causative factor for complicated diseases and a consequence resulted from protein-losing enteropathy [25,35-37]. The association of hypoalbuminemia with the 30-day mortality reinforces the crucial role of the pre-morbid nutritional status during the immune defense against CDI.

Several limitations should be noted in our study. Firstly, this was a retrospective study and certain variables were subject to reporting and documentation bias. An attempt to set clear definitions of disease and clinical complications was made and the clinical predictors were analyzed using objective data such as the laboratory results and duration in days to minimize this problem. Second, it was a single-center study. Thirdly, the *C. difficile* culture and ribotyping were not available in our study. Nevertheless, the uniform use of the sensitive PCR assay could reduce the heterogeneity of the diagnosis. Finally, we had small sample sizes of chemotherapy, organ transplant recipient and immunosuppressant and no known HIV-seropositive patient.

Albeit all the discussed limitations, this cohort study is the first study with adequate sample size focusing on the clinical aspects and management on the CDI in Hong Kong.

5. CONCLUSION

In conclusion, the CDI is a disease with remarkable morbidities, complications and mortality whereas the severity is significantly higher in the immunocompromised hosts. The independent clinical predictors for mortality include chronic kidney disease, hypoalbuminemia, a shorter duration of metronidazole treatment, use of PPI, while hostel residency and a longer duration of disease are the risk factors for disease recurrence. Further prospective controlled studies concerning the clinical impacts of these risk factors on CDI are advocated to resolve the controversies in this intestinal disease with rising importance.

CONSENT

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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