A Review of *Clostridium difficile* Infection at the University Hospital of the West Indies, Jamaica

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ABSTRACT

Objectives: *This study examined the frequency of* Clostridium difficile *infection (CDI) among hospital admission and diarrhoeal stool samples over a six-year period.*

Methods: *A review of all suspected cases of* C difficile *positive patients from 2007 to 2012 at the University Hospital of the West Indies (UHWI), Jamaica, was performed.* Clostridium difficile *infection was confirmed by clinical features and a positive enzyme-linked immunosorbent assay (ELISA) stool test for Clostridium Toxins A and B. The demographics, clinical features, risk factors, treatment and outcomes were also collated.*

Results: *There were 56 patients reviewed. The most commonly affected age group was 40−59 years of age. The proportion of CDI cases per total stool samples increased from 0.5% in 2007 to 5.9% in 2010 then fell to 2.2% in 2011 but increased again to 4.3% in 2012. The proportion of cases per total UHWI admissions also increased from 0.12 cases per 1000 admissions in 2007 to 1.16 in 2010 and 1.36 in 2012 (*p < 0.001)*. Most CDI cases were nosocomial (76% males, 48.6% females). Co-morbidities included hypertension and end-stage renal disease. Ceftazidime was the most common antibiotic associated with the development of CDI. Resolution occurred in 62.5% of patients. Duration of hospital stay was longer in males than females (≥ 21 versus < 7 days) and males had more adverse outcomes, with death in 23.8% versus 11.4%.*

Conclusion: *There has been an increase in the frequency of CDI at UHWI with a greater than expected frequency of community acquired CDI. Increased awareness is needed of the increasing risk for CDI and measures must be taken to prevent the disease, especially in hospitalized patients.*

Keywords: *C difficile* infection, ceftazidime, diarrhoea, nosocomial

Revisión de la Infección por *Clostridium difficile* en el Hospital Universitario de West Indies, Jamaica

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RESUMEN

Objetivos: *Este estudio examinó la frecuencia de la infección por* Clostridium difficile *(ICD) entre los ingresos al hospital y las muestras de heces diarreicas durante un período de seis años.*

Métodos: *Se realizó una revisión de todos los presuntos casos de pacientes* C difficile *positivos desde 2007 a 2012 en el Hospital Universitario de West Indies (HUWI), Jamaica. La infección por* Clostridium difficile *fue confirmada por las características clínicas y un análisis de heces fecales positivo mediante ensayo por inmunoabsorción ligado a enzimas ELISA para detectar las toxinas A y B de Clostridium. También se recopilaron datos demográficos, características clínicas, factores de riesgo, tratamiento y resultados.*

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Resultados: *Se revisaron 56 pacientes. El grupo etario más comúnmente afectado fue el de 40−59 años de edad. La proporción de casos de ICD por total de muestras de heces aumentó de 0.5% en 2007 a 5.9% en 2010, luego cayó a 2.2% en 2011, pero aumentó nuevamente a 4.3% en 2012. La proporción de casos por total de ingresos al HUWI también aumentó de 0.12 casos por cada 1000 ingresos en 2007 a 1.16 en el 2010 y 1.36 en 2012 (p < 0.001). La mayor parte de los casos de ICD fueron nosocomiales (76% varones, 48.6% mujeres). Las comorbilidades incluyeron hipertensión y enfermedad renal en fase terminal. La ceftazidima fue el antibiótico más comúnmente asociado con el desarrollo de la ICD. La resolución ocurrió en el 62.5% de los pacientes. La duración de la estancia hospitalaria fue mayor en los varones que en las hembras (≥ 21 versus < 7 días), y los varones tuvieron resultados más adversos, con la muerte en 23.8% frente a 11.4%.*

Conclusión: *Ha habido un aumento en la frecuencia de la ICD en el HUWI con una frecuencia mayor que la esperada de ICD adquirido por la comunidad. Es necesario tomar mayor conciencia del creciente riesgo creciente de ICD, e implantar medidas para prevenir la enfermedad, especialmente en pacientes hospitalizados.*

INTRODUCTION

The association between antibiotic-associated diarrhoea and colitis was established shortly after antibiotics became widely available. In 1978, *Clostridium difficile* was recognized as the major causative pathogen, and the earliest cases were attributed mainly to clindamycin (1, 2). Greater use of cephalosporins and penicillins subsequently led to the implication of these antibiotic classes with *Clostridium difficile* infection (C DI). Antibiotic therapy promotes overgrowth of *Clostridium difficile* within the colon by disrupting the normal intestinal flora. *Clostridium difficile* infection is the most common cause of nosocomial diarrhoea among adults in the developed world and its incidence appears to be increasing (3). An increase in the frequency and severity of CDI was observed in the early 2000s in developed countries and cases were also more serious and refractory to therapy (4). *Clostridium difficile* exist in two forms: one form produces spores that are resistant to antibiotics, heat and acid and the second is a vegetative form within the colon. The vegetative form is toxin-producing and is susceptible to killing by antimicrobial agents. Toxins A and B are two dominant exotoxins that mediate diarrhoea and colitis. Toxin A causes inflammation leading to intestinal fluid secretion and mucosal injury and also directly activates neutrophils, while Toxin B is a cytotoxin (5, 6). Both toxins A and B can promote neutrophil chemotaxis to localize in pseudomembranes and the underlying intestinal mucosal layer.

The most common antibiotics that predispose to *C difficile* infection are fluoroquinolones, clindamycin, cephalosporins and penicillins; however, this problem has been documented to occur with almost all families of antibiotics. Metronidazole and vancomycin remain the treatments of choice for patients with CDI (7).

In the past two decades, CDI has become more widespread, occurring more frequently and cases are increasingly more severe. The disease burden is on the rise, posing the possibility of further increases in morbidity and mortality. Jamaica currently has minimal data on CDI. This study examined the frequency of CDI among hospital admissions and diarrhoeal stool samples over a six-year period at the University Hospital of the West Indies (UHWI) and describes the demographic characteristics, clinical features, treatment and outcomes among patients with CDI.

SUBJECTS AND METHODS

All cases of CDI which were diagnosed at the UHWI, Jamaica, over the six-year period 2007 to 2012 were identified. Laboratory records from the UHWI Department of Microbiology were reviewed to identify patients with positive stool test for *C difficile* for the study period. The corresponding medical records of all positive patients were retrieved and reviewed.

The inclusion criteria for the diagnosis of CDI included the following: a history of diarrhoea, fever or abdominal pain from the medical records and Clostridium Toxin A and B positivity from diarrhoeal stool samples sent in a sterile container and tested with an immunoassay for Clostridium Toxin A and B.

The data collected included demographic characteristics: age and gender; clinical features including signs, symptoms, the presence of leukocytosis and pre-renal azotaemia; risk factors including co-morbidities and previous antibiotics; place of acquisition; wards on which patients were admitted; treatment (both empirical and definitive) and outcomes.

Ethical approval was granted for the study by the Ethics Committee of the University Hospital of the West Indies/University of the West Indies/Faculty of Medical Sciences, Mona, Jamaica.

Statistical analyses

Data collected were analysed using Stata statistical software version 12 (College Station, Texas). Means and proportions were obtained for clinical characteristics by gender. The difference in proportions was compared using Fisher's exact test. Hospital admission rates and proportion of CDI cases per stool

samples were computed using data on the total number of admissions obtained from the UHWI Medical Records Department and total number of stool samples received by the Microbiology Department. The Chi-squared test for trends was used to see if there was an increase in the proportion of *Clostridium difficile* cases over the study period. A *p*-value less than 0.05 was used to indicate statistical significance.

RESULTS

Seventy-one stool samples were positive for Clostridium toxins A and B over the period 2007–2012; however, 56 medical records were available for review and the relevant patient information was therefore extracted from these records.

There were 35 females and 21 males. The most commonly affected age group was 40–59 years of age, consisting of 23.8% males and 28.6% females. Elderly patients (age ≥ 80 years) comprised 14.3% males and 25.7% females.

There was only one admission with CDI for 2007 and none for 2008. From 2009 to 2010, the number of CDI cases increased from 8 to 21. However in 2011, the number of cases decreased to 6 and rose to 20 in 2012. The proportions of *C difficile*-associated diarrhoea cases to total diarrhoeal stool samples increased from 0.5% in 2007 to 5.9% in 2010 (Table 1).

Table 1: Proportion of *Clostridium difficile* infection (CDI) cases per total diarrhoeal stool samples from 2007–2012

Year	Proportion of CDI cases/total diarrhoeal stool samples (%)	95% Confidence interval
2007	0.53	0.21, 1.27
2009	2.32	0.96, 3.68
2010	5.90	3.39, 8.41
2011	2.18	1.01, 3.36
2012	4.28	2.63, 5.92

*Note: There was no result for 2008 as information for CDI cases was not available. $p < 0.001$, p for trend = 0.007

There was also another increase from 2011 to 2012 from 2.2% to 4.3%. The proportions of CDI cases to total UHWI admissions increased from 0.12 case per 1000 admissions in 2007 to 1.16 in 2010 (Table 2). There was also another increase from 2011 to 2012 from 0.78 to 1.36 case per 1000 admissions.

Table 2: Proportion of *Clostridium difficile* infection (CDI) cases per total University Hospital of the West Indies (UHWI) admissions from 2007–2012

Year	Proportion of CDI cases/total UHWI admissions (case per 1000 admissions)	95% Confidence interval
2007	0.12	0.04, 0.29
2009	0.66	0.27, 1.05
2010	1.16	0.65, 1.66
2011	0.78	0.36, 1.21
2012	1.36	0.83, 1.90

*Note: There was no result for 2008 as information for CDI cases was not available. $p < 0.001$, p for trend < 0.001

The majority of patients (62.5%) with CDI were on the medicine wards whilst the surgical wards and the private wards accounted for 7.1% each. The percentage of patients from the Accident and Emergency Department and the Intensive Care Unit was 5.4% and 3.6%, respectively. The paediatric ward accounted for only 1.8% of cases.

The majority of CDI cases were hospital acquired: 76.2% of males and 48.6% of females. Some 19.1% of males and 34.3% of females acquired CDI in the community.

Diarrhoea alone or in combination with other symptoms such as fever or abdominal pain, occurred in 91.1% of patients with CDI while 48.2% of patients had fever alone or in combination with other symptoms and 30.4% had abdominal pain alone or in combination with other symptoms (Table 3).

Table 3: Clinical symptoms in patients with *Clostridium difficile* infection (CDI)

Clinical symptoms	Frequency (n)	Per cent (%)
Individual symptoms		
Diarrhoea	51	91.1
Fever	27	48.2
Abdominal pain	17	30.4
Symptom patterns		
Diarrhoea only	20	35.7
Fever and diarrhoea	13	23.2
Fever, diarrhoea and abdominal pain	9	16.1
Abdominal pain and diarrhoea	8	14.3
Fever only	4	7.1

The most frequent symptom pattern was diarrhoea only accounting for 35.7% of patients followed by diarrhoea and fever accounting for 23.2% of cases. Fever, diarrhoea and abdominal pain, abdominal pain and diarrhoea, and fever only accounted for 16.1%, 14.3% and 7.1% of cases, respectively. Leukocytosis was present in 46% of patients.

Hypertension was present in 19 patients (34%), endstage renal disease in 17 (30%), lower respiratory tract infection in 14 (25%) and diabetes mellitus in 8 (14.3%).

Previous antibiotic therapy for various indications was used in 45 patients (80%). Previous antibiotic therapy indicates the receipt of oral or parenteral antibiotic agent for > 72 hours in the preceding two months. Ceftazidime was the most common antibiotic used prior to a diagnosis of CDI in 14 patients (25%), ceftriaxone in eight and amoxillin-clavulanate in six (Figure). There was no history of prior antibiotic use in 11 patients.

Empirical antibiotic therapy for diarrhoea was given to 27% of patients and of these, metronidazole was given in 14.3%, followed by ciprofloxacin, 8.9%. Definitive treatment for CDI was given to 50% of patients while 27% of patients did not receive any definitive antibiotic treatment. Definitive treatment included metronidazole, metronidazole then vancomycin or metronidazole and vancomycin.
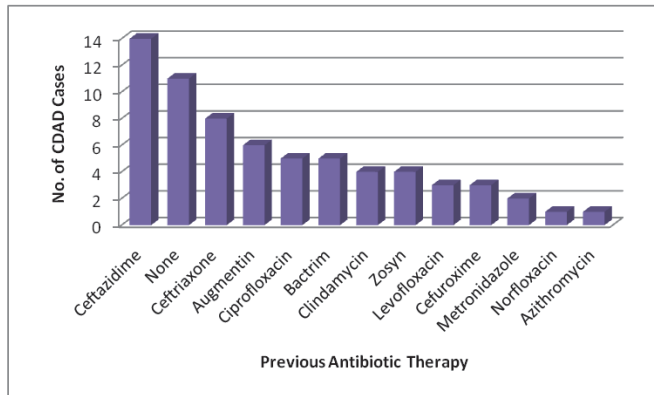
Figure: Number of *Clostridium difficile* infection cases and previous antibi-
          otic therapy.
*Previous antibiotic therapy implies the receipt of oral or parenteral antibiotic
agent for > 72 hours in the preceding two months.

Improvement without resolution occurred in 41.1% of CDI patients, 21.4% had complete resolution, 16.1% died and 21.4% had an unknown outcome.

The median length of hospital stay was 13 days and the interquartile range was 6–34.5 days. Approximately 56% of male patients had prolonged hospital stay (21 days or longer) compared to 31% of females (not significant). Similarly, a higher proportion of males had pre-renal azotaemia (23.8% *vs* 17.1%) and a higher proportion of males died, 23.8% *vs* 11.4% (NS).

DISCUSSION

There was an increase in the frequency of CDI cases over the six years studied and this was expressed as an upward trend for CDI cases per diarrhoeal stool samples and cases per hospital admissions. This increase in incidence is in keeping with trends in other countries. A 2003 outbreak in Quebec, Canada, was notable for its scope and impact; the incidence of CDI was stable from 1991 to 2002 but quadrupled in 2003 (8). A study in the United States of America (USA) revealed the number and rate of short-stay hospital discharges with a diagnosis of CDI significantly increased from 2000 to 2003 and another study in Minnesota revealed a 19.3-fold increase from two per 100 000 person-years in 1991–93 to 40.2 per 100 000 person-years in 2003–05 (9, 10).

In the present study, the most commonly affected age group was 40–59 years of age. However, in recent reports, the majority of patients with CDI were elderly. In a study in the USA, the overall rate was several-fold higher in patients over 65 years of age than the second highest group affected which was the 45–64-year group (9). Also, in a previous study, the frequency of CDI among elderly persons (≥ 65 years) was 10-fold higher than observed in younger adults (11). Of interest, the incidence of CDI in the paediatric population appears to be increasing in hospitals in the USA (12).

There was a higher number of females diagnosed with CDI in this study. This may reflect the general attitude of females to health whereby females tend to display more health-seeking behaviours and would therefore account for more hospital admissions in Jamaica. In a report of a large outbreak of CDI in Canada, there was also a female predominance (4). Additionally, a review of CDI cases in Minnesota revealed that 65.7% patients were female and a prospective study in Israel revealed a predominance of females (3, 10).

The UHWI medicine wards accounted for 62.5% of the patients diagnosed with CDI. This may indicate that the medicine wards have more critically ill patients which is a known risk factor for CDI. In the present study, 19.6% of patients with CDI did not use antibiotics prior to developing CDI. These patients may represent persons who were infected by CDI patients who were on the ward or from colonized healthcare workers. In institutions that have multiple beds, with shared toilets, transmission of infection may be facilitated (4). An infection control programme that emphasizes contact isolation precautions for diarrhoeal cases, placement of infected patients on one ward or in private rooms, using gloves and gowns for all patient contact, good hand hygiene, restriction of workers and patient movement and ward closure with the recognition of an outbreak are important measures. Limited data support enhanced environmental cleaning, especially of heavily contaminated patient care equipment (9). For many years, CDI was deemed to be almost always hospital acquired, however, one study showed that 41% of 381 definite CDI cases were community acquired and patients were more likely to be female and younger (10). In the present study, 19% of males and 34% of females acquired CDI in the community.

The most frequent clinical feature of CDI is diarrhoea (3). In this study, most patients with CDI had diarrhoea (91% of patients) and 35.7% of patients had diarrhoea only. Leukocytosis was present in 46% of patients. A previous study concluded that infection with *C difficile* should be considered in hospitalized patients with leukocytosis preceding, coinciding or worsening with diarrhoea who were previously or concurrently treated with antibiotics (13). Another study found that most patients with unexplained leukocytosis had *C difficile* infection as compared with controls in a tertiary care hospital setting (14). In a third report, leukocytosis and a high creatinine level were strong and independent factors associated with an increased risk of complicated CDI (8).

Hypertension was the most common co-morbidity which likely reflects the relatively high prevalence of this condition in the general population. End-stage renal disease was the second most common co-morbidity which may be the result of repeated hospitalizations, repeated infections and subsequent antibiotic usage due to relative immunosuppression or dialysis catheter use. In a recent report, patients with a high Charlson co-morbidity index and low serum albumin level were associated with an increased risk of CDI among an outpatient dialysis cohort (15, 16). Future studies are needed to determine if dialysis delivery method influences the prevalence of CDI in end-stage renal disease patients.

Previous antibiotic use is the most common risk factor for CDI (4). The present study highlighted the common use of cephalosporin agents prior to diagnosis of CDI. In a previous study, the most common classes of antibiotic administered were cephalosporins followed by fluoroquinolones (4). Another study revealed that more than two-thirds of cases had received cephalosporins in the two months before diagnosis of CDI. Also, the proportion of patients who had received quinolones increased progressively (8). In the present study, the proportion of patients that received ciprofloxacin in hospital was relatively high in comparison to those who received metronidazole for acute diarrhoea. Ciprofloxacin is a risk factor for the development of CDI and fluoroquinolones have been associated with an increased risk of *C difficile*-associated diarrhoea (4). Future studies to better differentiate signs of various infectious colitis should be undertaken to prevent hazardous empirical treatment.

An important initial step in the treatment of CDI is discontinuing the offending antibiotic and implementation of infection control policies. Metronidazole and vancomycin are standard definitive pharmacological agents used to treat CDI and were used accordingly in this study. Faecal microbiota transplantation may be useful for treatment of patients with recurrent CDI (17). Another very important aspect of management is implementation of infection control policies. Contact precautions are necessary for patients with *C difficile* infection and it is therefore vital that healthcare workers wash their hands with soap and water prior to and after attending to patients. This is one of the few situations where the use of soap and water is preferred above alcohol-based hand sanitizers. Limited data suggest that probiotics may play a role for treatment of CDI, as an adjunct to antibiotic therapy. There is no evidence to support the use of probiotics alone in treatment (18).

The present study revealed that nine (16.1%) patients died, five of whom were males. Males also tended to have more of the other adverse outcomes such as prolonged length of stay (56.3% of males *versus* 31.25% of females) and pre-renal azotaemia (23.81% of males *versus* 17.14% of females). In a Canadian study, the mortality at 30 days was 23% (11). In a USA study, the overall mortality rate was 8.5% which remained stable over a four-year interval (9). In a review of 24 studies of CDI from North America and the United Kingdom, all-cause 30-day mortality appeared to be high, with 15 studies indicating a mortality of 15% or more (19).

There were limitations in this study. Not all medical records were available for review and a minority did not have all the information required by the study. Resource challenges by the diagnostic laboratory were also a limitation.

The results of the present study should form the basis of further surveys. This study indicates an increase in CDI cases per diarrhoea stool samples and cases per admission, greater than expected frequency of community acquired CDI and a suggestion of greater morbidity and mortality in male patients. Awareness is needed of the increasing risk for CDI and measures taken to prevent the disease, especially in hospitalized patients.

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