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Clostridioides difficile Infection: Clinical Practice and Health Outcomes in 6 Large Tertiary Hospitals in Eastern Australia

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Background. *Clostridioides difficile* infection (CDI) is associated with significant morbidity and mortality in both healthcare and community settings. We aimed to define the predisposing factors, risks for severe disease, and mortality determinants of CDI in eastern Australia over a 1-year period.

Methods. This is an observational retrospective study of CDI in hospitalized patients aged ≥18 years in 6 tertiary institutions from 1 January 2016 to 31 December 2016. Patients were identified through laboratory databases and medical records of participating institutions. Clinical, imaging, and laboratory data were input into an electronic database hosted at a central site.

Results. A total of 578 patients (578 CDI episodes) were included. Median age was 65 (range, 18–99) years and 48.2% were male. Hospital-onset CDI occurred in 64.0%. Recent antimicrobial use (41.9%) and proton pump inhibitor use (35.8%) were common. Significant risk factors for severe CDI were age <65 years ($P < .001$), malignancy within the last 5 years ($P < .001$), and surgery within the previous 30 days ($P < .001$). Significant risk factors for first recurrence included severe CDI ($P = .03$) and inflammatory bowel disease ($P = .04$). Metronidazole was the most common regimen for first episodes of CDI with 65.2% being concordant with Australian treatment guidelines overall. Determinants for death at 60 days included age ≥65 years ($P = .01$), severe CDI ($P < .001$), and antibiotic use within the prior 30 days ($P = .02$). Of those who received metronidazole as first-line therapy, 10.1% died in the 60-day follow-up period, compared to 9.8% of those who received vancomycin ($P = .86$).

Conclusions. Patients who experience CDI are vulnerable and require early diagnosis, clinical surveillance, and effective therapy to prevent complications and improve outcomes.

Keywords. Australia; *Clostridioides difficile*; CDI; hospital epidemiology.

Clostridioides difficile infection (CDI) is a leading cause of healthcare-associated infection with a huge burden on health resources. In Australia, CDI is recognized with rise in frequency in 2012 [1], yet estimates of CDI burdens at individual institutions or even at regional levels are not well defined. Most data are derived from Western Australia [1–3]. In eastern Australia, Worth et al estimated a CDI rate of 2.49 per 10 000 bed-days with >1500 CDI events per year in Victoria; 18%–28% of cases were community onset [4]. In Queensland, a population-based survey identified various geographic "hot spots" of disease in various patient age groups, and residential and hospital facilities [5]. Despite these studies, there are few data from systematic surveillance for CDI and its complications using common denominators and comparable diagnostic tests in the eastern jurisdictions. Furthermore, disease burden in specific populations (eg, immunocompromised patients, elderly), or whether there are differences in characteristics between community-onset and hospital-onset disease is not well described in the Australian context. Determining where infection occurs in the community is also undefined.

Studies outside of Australia have noted predictors of mortality in specific populations. Leibovici-Weissman et al noted diabetes

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mellitus, low albumin, and therapy other than metronidazole monotherapy to be associated with 30-day mortality in hospitalized patients ≥80 years old with CDI [6]. Yoon et al demonstrated that neutropenia was an independent predictor of CDI-related mortality (odds ratio [OR], 5.17) in cancer patients [7]. Whether these findings are generalizable to the Australian setting is uncertain. Moreover, data on the frequency of recurrence of CDI (first recurrence, 25%–33% of patients, with 38%–45% chance of a second recurrence) [8] are also incompletely defined. Delineating the size of these individual burdens is essential to healthcare planning in Australia, including that of drug therapies.

To address the relative paucity of data from eastern Australia, the present study sought to describe the epidemiology, treatment, and outcomes of CDI in Australia over a 1-year period. In particular, we determined patient demographics; comorbidities and predisposing factors for CDI; and risk factors for severe disease, recurrence, and mortality at 60 days post-diagnosis. Differences in disease characteristics of hospital-onset versus community-onset CDI were also analyzed.

METHODS

Study Design

This was a retrospective, noninterventional observational study of CDI in hospitalized patients ≥18 years of age in 6 large tertiary institutions in the jurisdictions of New South Wales, Queensland, and Victoria, Australia. Patients with a diagnosis of CDI (see "Definitions" section below) from 1 January through 31 December 2016 were enrolled on the basis of the first (approximately) 100 consecutive patients at each site who had at least 1 stool sample sent routinely to the microbiology laboratory for detection of *C difficile,* and who had *C difficile* identified. Patients were identified through search of the laboratory information databases and hospital medical records of participating institutions. Eligible patients were assigned a unique study number. No additional clinical specimens were collected for microbiological or for pathological examination. Patients underwent treatment for CDI with antibacterial agents and other management (eg, surgery) at the discretion of the treating physician and according to the institutions' standard protocols.

Patient Consent Statement

The patient's written consent was obtained. The design of the work has been approved by the human ethics research committees (HRECs) at all sites (Western Sydney Local Health District HREC; HREC/17/WMEASD/270).

Data Collection

For each case of CDI, the following data were extracted using a dedicated case report form: patient demographics, date of hospital admission and discharge, readmission dates if relevant, hospital length of stay (LOS), ward type, intensive care unit (ICU) admission, and whether the infection was deemed community onset or not. Underlying medical conditions (eg, diabetes mellitus, malignancy, organ transplantation, inflammatory bowel disease, chronic obstructive pulmonary disease) were noted as were predisposing factors (eg, major surgery, use of antimicrobial agents, immunosuppressive agents, and proton pump inhibitors [PPIs], all within 30 days). Clinical features were recorded. Laboratory (eg, baseline renal function, neutrophil count) and microbiological test results (including tests to detect presence of *C difficile* and its toxins) and imaging data were also recorded. Severity of disease, antimicrobial treatment (type of antimicrobial, number of courses given) and other management approaches (eg, colectomy) of CDI were assessed, as well as clinical outcome at 14 days and 60 days. When evaluating risk factors for recurrence and mortality, the outcome at end of follow-up (60 days) was used.

Data were entered into the REDCap electronic data tools hosted at the University of Sydney at a central site (Westmead Hospital) [9]. Data were audited every 6 months for consistency, accuracy, and completeness with regular discussion among the site investigators.

Definitions

An episode of CDI was defined as (1) diarrhea and related symptoms in the absence of another cause for the diarrhea; and (2) detection of either *C difficile* toxin A/B enzyme immunoassay (EIA) or polymerase chain reaction (PCR) assay targeting the toxin B gene of *C difficile*. The type of toxin A/B EIA and PCR tests varied between study sites.

Community-onset disease was symptom onset that occurred while the patient was in the community prior to or <48 hours after admission to hospital [10]. Severe disease was defined by the presence of at least 1 of 5 factors: requirement for ICU admission; presence of pseudomembranes on colonoscopy (if performed); ileus or megacolon on abdominal radiograph or pancolitis on computed tomography scan; surgery (eg, colectomy); and clinical and laboratory criteria including fever of >38.5°C and white blood cell (WBC) count of $>20 \times 10^9$ cells/L [11]. Recurrence was defined as recurrence of diarrhea, a positive test for CDI (see above), and recommencement of CDI treatment occurring within 2 months of the initial positive laboratory test [12]. Clinical cure (or complete response to treatment) was defined by the resolution of diarrhea with maintenance of resolution for duration of treatment and no further requirement for treatment after the end of the treatment course [13]. Clinical failure was defined by the persistence of diarrhea, the need for additional treatment for CDI, or both, in the opinion of the investigator [13]. Partial response was defined as those who experienced some improvement in diarrhea but did not meet criteria for complete response.

Statistical Analysis

Descriptive statistics were carried out for patient demographics, location in hospital, comorbidities, risk factors, baseline laboratory findings, and outcomes. Categorical data are described using absolute and relative frequencies. Where data points were left blank or unknown, these were not included in the corresponding analysis. Risk factors for severe disease, first recurrence, and all-cause mortality were examined by calculating ORs on univariate analysis using the Pearson χ^2 test and Fisher exact test. If the P value was <.10 on univariate analysis, the adjusted ORs and 95% confidence intervals (CIs) were obtained by multinomial logistic regression analysis. Kaplan-Meier survival curves and log-rank test values were generated to compare survival between different patient groups as appropriate. All analyses were performed using Stata version 15 software (StataCorp, College Station, Texas).

RESULTS

Demographics

A total of 578 patients (accounting for 578 CDI episodes) from 6 hospitals fulfilled the study inclusion criteria: Westmead Hospital (183 [31.7%]), Monash Hospital (100 [17.3%]), Royal North Shore Hospital (92 [15.9%]), Royal Melbourne Hospital (91 [15.7%]), Royal Brisbane and Women's Hospital (86 [14.9%]), and Peter MacCallum Cancer Centre (26 [4.5%]). Females accounted for 299 (51.7%) and males for 279 (48.3%) patients. For microbiological testing methods used, see the Supplementary Material. Median age was 65 years (interquartile range, 51–79 years). Patient location at time of symptom onset included hospital (370 [64.0%]), residential aged care facilities (7 [1.2%]), and the community (197 [34.1%]), with 4 (0.7%) unknown. Of the 370 with symptom onset in hospital, 295 (79.7%) were in those hospitalized for at least 48 hours before symptom onset.

Comorbidities and Predisposing Factors

Immunocompromise was common in the study population of 578 patients. This included use of immunosuppressant agents in 106 (18.3%), transplant recipients in 56 (9.7%), hematologic malignancy in 109 (18.9%), connective tissue disease in 20 (3.5%), and neutrophil count <0.5 $\times 10^9$ cells/L in 35 (6%). With regard to the 56 transplant recipients, they were made up of stem cell transplant (31 patients), kidney (18), lung (1), heart (1), kidney-pancreas (3), liver-kidney (1), and liver-pancreas (1) recipients. Chronic renal failure was present in 111 (19.2%), chronic obstructive respiratory disease in 48 (8.3%), and cirrhosis in 12 (2.1%) patients. Diabetes mellitus was present in 148 (25.6%), inflammatory bowel disease in 30 (5.2%), PPI use in 207 (35.8%), and prior antibiotic use in the last 30 days in 242 (41.9%). Other patient characteristics and comorbidities stratified according to hospital- or community-onset CDI are summarized in Table 1.

Table 1. Characteristics of Patients With *Clostridioides difficile* Infection

Characteristic	Community-Onset	Hospital-Onset
Age, y, median (IQR)	64 (50–78)	66 (53–79)
Male sex	85 (42)	193 (52)
Diabetes mellitus	49 (24)	99 (27)
COPD	18 (9)	30 (8)
Cardiovascular disease	46 (23)	72 (19)
Aortic aneurysm	4 (2)	2 (<1)
Cerebrovascular disease	13 (6)	40 (11)
Peptic ulcer disease	1 (<1)	13 (4)
Liver disease	11 (6)	11 (3)
Hepatitis B	7 (3)	14 (4)
Hepatitis C	4 (2)	6 (2)
Chronic renal failure	36 (18)	75 (20)
Connective tissue disease	6 (3)	14 (4)
Inflammatory bowel disease	17 (8)	13 (4)
Dementia	6 (3)	18 (5)
HIV infection	0 (<1)	4 (1)
Malignancy <5 y	66 (32)	154 (42)
Transplant recipient	19 (9)	37 (10)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IQR, interquartile range.

Severe Disease

Of 578 patients, 175 (30.2%) fulfilled at least 1 criterion for severe disease: ICU admission (80 patients [13.8%]), fever >38.5° C (57 [9.9%]), WBC count >20 $\times 10^9$ cells/L (51 [8.8%]), pancolitis on computed tomography scan (21 [3.6%]), ileus or megacolon radiologically (8 [1.4%]), pseudomembranes on colonoscopy/sigmoidoscopy (5 [0.9%]), and need for colectomy (2 [0.3%]). Fifty-nine patients met >1 criteria for severe disease. Significant risk factors for severe CDI on univariate analysis (Table 2) included age <65 years ($P < .001$), malignancy within the last 5 years ($P < .001$), and surgery within the previous 30 days ($P < .001$). Hospital-onset CDI patients did not experience more severe disease compared with those with community-onset disease ($P = .51$). Adjusted ORs (aORs) and CIs obtained by multinomial logistic regression analysis were as follows: age <65 years (aOR, 0.55 [95% CI, .38–.78]), malignancy within the last 5 years (aOR, 1.87 [95% CI, 1.29–2.70]), and surgery within the previous 30 days (aOR, 1.90 [95% CI, 1.20–3.00]).

CDI Recurrence

At enrollment, the majority of CDI cases were classified as first episodes (516 [92%]), with 47 (8%) experiencing an episode of CDI within the preceding 2 months; recurrence status was unknown in 15 patients (2.6%). Of 516 patients with a first episode of CDI, 101 (19.6%) experienced a first recurrence and 20

Table 2. Risk Factors for Severe Disease in *Clostridioides difficile* Infection on Enrollment

Characteristic	Nonsevere	Severe	Total	OR (95% CI)	*P* Value
Age, y				0.53 (.36–.77)	.001
≥65	223	69	292		
<65	180	106	286		
Sex				1.02 (.70–1.47)	.92
Male	194	85	279		
Female	209	90	299		
Location at episode				1.14 (.76–1.70)	.51
Hospital	255	115	370		
Community	141	56	197		
Diabetes mellitus				1.04 (.68–1.58)	.85
Yes	103	46	149		
No	300	129	429		
Cardiovascular disease				0.81 (.50–1.30)	.37
Yes	87	32	119		
No	316	143	459		
Peptic ulcer disease				1.29 (.33–4.35)	.65
Yes	9	5	14		
No	394	170	564		
Proton pump inhibitor use				1.01 (.69–1.47)	.96
Yes	158	69	227		
No	245	106	351		
Liver disease				1.63 (.60–4.20)	.27
Yes	13	9	22		
No	390	166	556		
Chronic kidney disease				1.13 (.70–1.80)	.58
Yes	75	36	111		
No	328	139	467		
Inflammatory bowel disease				1.16 (.47–2.67)	.71
Yes	20	10	30		
No	383	165	548		
Malignancy within last 5 y				1.90 (1.30–2.77)	<.001
Yes	136	86	222		
No	267	89	356		
Prior antibiotic use in previous 30 d				0.84 (.56–1.22)	.34
Yes	197	78	275		
No	206	97	303		
Prior surgery within previous 30 d				1.78 (1.11–2.85)	.01
Yes	59	41	100		
No	344	134	478		

Data are presented as No. unless otherwise indicated.

Abbreviations: CI, confidence interval; OR, odds ratio.

(3.9%) experienced a second recurrence during the 60-day follow-up period. Risks for first recurrence, in those individuals enrolled into the study with a first episode of CDI, on univariate analysis (Table 3) were severe CDI ($P = .03$) and inflammatory bowel disease ($P = .04$). A higher proportion of patients with community-onset CDI experienced recurrence when compared to hospital-onset disease (25% vs 17%, $P = .08$). Adjusted ORs and CIs obtained by multinomial logistic regression analysis were as follows: location of CDI onset (aOR, 1.50 [95% CI, .99–2.28]), severe CDI (aOR, 2.06 [95% CI, 1.36–3.13]), and inflammatory bowel disease (aOR, 0.34 [95% CI, .99–1.15]).

Treatment Regimens

Metronidazole was overwhelmingly the most common regimen for first episodes of CDI, being used in 450 patients (77.6%). Orally administered metronidazole was used in 414 patients (71.6%) and intravenous metronidazole in 36 patients (6.2%). Oral vancomycin was used as treatment of the first episode in 76 patients (13.1%). Rifaxamin was used in 1 patient, treatment was unknown in 19 patients (3.3%), and 32 (5.5%) received no treatment. Concordance with Australian Therapeutic Guidelines occurred in 65.2% of patients with regards to initial treatment.

Of the 101 (19.6%) patients experiencing a first recurrence, orally administered vancomycin was the most used agent in 92 patients (91.1%). Of those receiving oral vancomycin to treat the first recurrence, 9 of 92 (9.8%) had a vancomycin taper. The vancomycin dose utilized varied significantly between patients. Metronidazole was used in 28 patients (27.7%), some in combination with oral vancomycin, and fidaxomicin was used in 2 patients (2%). Of the 20 (3.9%) patients experiencing a second recurrence, treatment regimens were more varied with 12 (60%). receiving vancomycin, 8 (40%) receiving metronidazole, 4 (20%) receiving fidaxomicin, and 3 (15%) receiving fecal microbiota transplantation. Of note, some patients received multiple therapies for their recurrent episode.

Outcomes

At 14 days, 308 of 578 (53%) had clinical cure and 89 (15%) were considered clinical failures while 80 patients (14%) were deemed to have had a partial response to therapy. In addition, 24 (4%) patients died, with the remaining 77 patients (13%) having an unknown status at 14 days. Hence at 14 days, of 554 patients alive, the cure rate was 56%.

At 60 days, 293 of 578 (51%) had clinical cure, 26 patients (5%) had partial response, and 37 (6%) patients had clinical failure with 48 (8%) deaths (150 patients of 578 [30%] had an unknown status at 60 days). Of 48 deaths, 2 were deemed to be secondary to CDI. Median hospital LOS was 14 days (range, 0–339 days). Of those 79 patients who were admitted to ICU, median LOS in ICU was 4 days (range, 0–59 days). Of those who did not receive treatment for their first episode (32 [5.5%]), when compared to those who did receive treatment, CDI recurrence (0% vs 19.6%, $P = .002$), clinical cure at 14

Table 3. Risk Factors for Recurrence in First-Episode *Clostridioides difficile* Infection During 60-Day Follow-up

Characteristic	Nonrecurrence	Recurrence	Total	OR (95% CI)	*P* Value
Age, y				1.41 (.82–2.43)	.19
≥65	149	43	192		
<65	156	32	188		
Sex				1.21 (.71–2.08)	.46
Male	148	40	188		
Female	157	35	192		
Location at episode				0.63 (.36–1.11)	.08
Hospital	216	45	261		
Community	84	28	112		
Severity				1.75 (1.00–3.03)	.03
Severe	91	32	123		
Nonsevere	214	43	257		
First treatment				1.7 (.71–4.68)	.21
Metronidazole	240	68	308		
Vancomycin	42	7	49		
Transplant recipient				1.06 (.40–2.48)	.90
Yes	31	8	39		
No	274	67	341		
Diabetes mellitus				1.54 (.86–2.73)	.11
Yes	78	26	104		
No	227	49	276		
Neutropenia within 7 d prior to enrollment				1.99 (.66–5.42)	.14
Yes	15	7	22		
No	290	68	358		
Immunosuppressant medication (inc. prednisolone)				1.00 (.50–1.91)	.99
Yes	65	16	81		
No	240	59	299		
Proton pump inhibitor use				1.37 (.79–2.36)	.22
Yes	111	33	144		
No	194	42	236		
Liver disease				0.67 (.07–3.11)	.60
Yes	12	2	14		
No	293	73	366		
Chronic kidney disease				0.93 (.48–1.75)	.82
Yes	73	17	90		
No	232	58	290		
Inflammatory bowel disease				0.24 (.01–.93)	.04
Yes	16	0	16		
No	289	75	364		
Malignancy within last 5 y				1.26 (.73–2.16)	.37
Yes	121	34	155		
No	184	41	225		
Prior antibiotic use in previous 30 d				1.19 (.70–2.05)	.49
Yes	141	38	179		
No	164	37	201		
Prior surgery within previous 30 d				1.38 (.69–2.68)	.31
Yes	50	16	66		
No	255	59	314		

Data are presented as No. unless otherwise indicated.

Abbreviations: CI, confidence interval; OR, odds ratio.

days (26% vs 53%, $P < .001$), and clinical cure at 60 days (26% vs 51%, $P < .001$) were determined. Clinical cure in those who received metronidazole as first treatment (64.9%), when compared to vancomycin (47.2%), was significantly different on subgroup analysis ($P = .002$). Of note, more patients receiving vancomycin experienced severe disease (32.9%) compared with those receiving metronidazole (27.3%).

Significant risk factors for all-cause death at day 60 on univariate analysis (Table 4) included age ≥65 years ($P = .01$), severe CDI ($P < .001$), and antibiotic use within the prior 30 days

Table 4. Risk Factors for Death in *Clostridioides difficile* Infection at 60-Day Follow-up

Characteristic	Survived	Death	Total	OR (95% CI)	*P* Value
Age, y				1.94 (1.11–3.41)	.01
≥65	170	46	216		
<65	186	26	212		
Sex				0.96 (.56–1.64)	.87
Male	172	34	206		
Female	184	38	222		
Location at episode				0.66 (.34–1.22)	.16
Hospital	115	17	132		
Community	236	53	289		
Severity				2.60 (1.50–4.49)	<.001
Severe	103	37	140		
Nonsevere	253	35	288		
First treatment				1.09 (.42–3.33)	.86
Metronidazole	284	32	316		
Vancomycin	58	6	64		
Transplant recipient				0.57 (.17–1.53)	.25
Yes	41	5	46		
No	315	67	382		
Diabetes mellitus				1.12 (.60–2.03)	.70
Yes	91	20	111		
No	265	52	317		
Serum albumin <25 g/L				5.60 (3.19–10.01)	<.001
Yes	146	50	196		
No	360	22	382		
Neutropenia within 7 d prior to enrollment				0.69 (.17–2.06)	.50
Yes	28	4	32		
No	328	68	396		
Immunosuppressant medication (inc. prednisolone)				1.10 (.57–2.06)	.75
Yes	78	17	95		
No	278	55	333		
Liver disease				1.55 (.36–5.22)	.45
Yes	13	4	17		
No	343	68	411		
Chronic kidney disease				1.34 (.71–2.47)	.32
Yes	75	19	94		
No	281	53	334		
Inflammatory bowel disease				0.30 (.01–1.99)	.22
Yes	16	1	17		
No	340	71	411		
Malignancy within last 5 y				1.41 (.82–2.42)	.19
Yes	143	35	178		
No	213	37	250		
Prior antibiotic use in previous 30 d				1.86 (1.08–3.25)	.02
Yes	163	44	207		
No	193	28	221		
Prior surgery within previous 30 d				0.72 (.30–1.56)	.39
Yes	59	9	68		
No	297	63	360		

Data are presented as No. unless otherwise indicated.

Abbreviations: CI, confidence interval; OR, odds ratio.

($P = .02$). Serum albumin was <25 g/L in 196 of 578 (33.9%) and was also associated with death at 60 days ($P < .001$). Figure 1 represents survival analysis when comparing antibiotic use within the prior 30 days and onset of first CDI episode. Of patients receiving first treatment with metronidazole, 32 of 316 (10.1%) died during the 60-day follow-up period, compared with 6 of 64 (9.8%) of those receiving vancomycin as first treatment ($P = .86$). Adjusted ORs and CIs obtained by multinomial

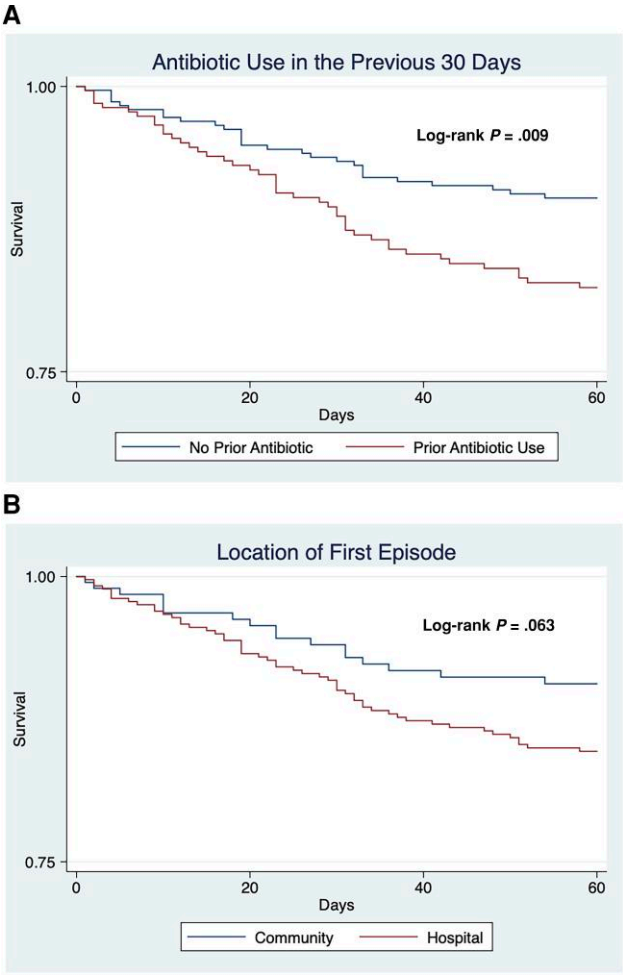

Figure 1. Kaplan-Meier survival graph comparing groups based on antibiotic use in the previous 30 days (*A*) and location of first episode of *Clostridioides difficile* infection (*B*).

logistic regression analysis were as follows: age ≥65 years (aOR, 1.64 [95% CI, .85–3.15]), severe CDI (aOR, 1.62 [95% CI, .84–3.10]), albumin <25 g/L (aOR, 3.07 [95% CI, 1.62–5.81]), and prior antibiotic use in previous 30 days (aOR, 1.72 [95% CI, .92–3.25]).

DISCUSSION

CDI causes significant inpatient and outpatient morbidity and has been identified as an urgent antibiotic resistance threat by the Centers for Disease Control and Prevention in 2019 [14]. A changing epidemiology requires accurate characterization of risk factors for disease and poor outcomes (eg, recurrence, death). Our study identified noteworthy findings, which include age <65 years being a risk factor for severe disease, but no association between PPI and prior antibiotic use with recurrence of CDI.

Many risk factors for severe CDI have been identified, some of which have been included in severity scoring systems. These largely depend on the population being studied (eg, adult vs children, community vs hospital associated) as well as the definition used to for severe CDI [11, 15]. In a recent systematic review of 31 studies on the definition and predictors of severe CDI, there was no commonly agreed-upon definition [11]. Most definitions require meeting 1 of several clinical, radiological, or biochemical factors associated with severity [16]. These may include ileus, megacolon, peritonitis or intestinal perforation, pseudomembranous colitis, colectomy, death, fever, septic shock, serum creatinine concentration >50% above baseline, and leukocytosis (WBC count $>15 \times 10^9$ cells/L). For our definition, we chose 5 established clinical, radiological, and biochemical markers of severity that correlate positively with severity of colitis in the absence of another explanation of findings [17].

Advanced age has been consistently associated with severe CDI previously [11, 16, 18]. Unexpectedly in our study, age <65 years was associated with increased risk of severe CDI ($P = .001$). Possible explanations for this include high comorbidity status in the younger cohort, too low of an age cutoff for dichotomous age comparison, and overall population characteristics (eg, patient selection). Interestingly, a reliable and accurate clinical prediction tool was developed that included age >65 years as 1 of only 3 variables [19]. One retrospective study identified a high Acute Physiology and Chronic Health Evaluation (APACHE) II score, onset in the ICU setting, low albumin, high C-reactive protein (CRP), and concurrent antibiotic use as independent risk factors for severe CDI [20]. CRP has been emphasized as a risk factor in other studies [21] but remains absent from conventional scoring systems. Similarly, a Charlson Comorbidity Index score >3 is strongly associated with severe disease [22]. Prior antibiotic use does not appear to be linked with severe CDI as was the finding in our study [22]. Another study identified immunosuppression as being protective for severe disease [18]. The same study noted no association between malignancy and development of severe CDI. Data on the association of severe CDI with immunosuppression and malignancy have yielded conflicting results [21]. In a cohort of hospitalized adults, impaired functional status (ie, ability to perform activities of daily living) was an independent risk factor for severe CDI [23]. Body mass index >35 kg/m^2 was associated with almost a 2-fold greater rate of severe CDI in a single-center cohort study [24]. Just over 30% of our cohort fulfilled at least 1 criterion for severity. This contrasts with other hospital cohort studies, which report much higher rates (up to 84.5%) [22].

Risk of death overlaps heavily with risk of severe disease. In a single-center retrospective cohort study of 401 patients, malignancy, blood urea nitrogen–to–serum creatinine ratio, and increased glucose were significant predictors for 30-day all-cause

mortality [25]. Another study including 128 restriction endonuclease–typed cases noted that ischemic heart disease and hypoalbuminemia predicted death [26]. A systematic review of 30 studies assessing the risk factors for mortality in CDI identified increased age, diabetes mellitus, immunosuppression (including prior corticosteroid use), leukocytosis, increased serum urea, increased serum creatinine, elevated CRP, hyponatremia, and hypoalbuminemia [27]. Ribotype 027 was also associated with 30-day mortality (relative risk [RR], 1.3–10.4) [27]. As such, the *Clostridium difficile* Associated Risk of Death Score (CARDS) has been developed from 374 747 hospitalized cases of CDI (overall in-hospital mortality 8%) where 8 predictors of mortality were identified [28]. These included age, cardiopulmonary disease, malignancy, diabetes, inflammatory bowel disease, acute renal failure, liver disease, and ICU admission. Other prediction tools for mortality using machine learning have been created and validated using large cohorts [29]. These have also identified nonconventional risk factors such as free calcium, bicarbonate, platelet level, and mean blood pressure. Although we did not undertake ribotyping on all isolates, nor any other analysis of bacteria for virulence factors in our study. Laboratory surveillance in Australia has shown that ribotype 027 is uncommon [30].

In our study, the only factors significantly associated with death at 60 days were age <65 years, severe disease, serum albumin <25 g/L, and antibiotic use within the prior 30 days. In addition, there was a slight excess mortality in those receiving metronidazole as first treatment when compared to vancomycin, consistent with the findings of a systematic review and meta-analysis comparing the efficacy of treatments for CDI, and which found metronidazole to be the worst regimen with regard to sustained symptomatic cure [31]. Importantly in our study malignancy and immunosuppression was not associated with 60-day mortality. This may be due to improved early detection and treatment, and optimized supportive care of these high-risk patients.

In Australia, metronidazole remains the most common first-line therapy for CDI, and for serious/recurrent illness oral vancomycin and fidaxomicin are indicated [32, 33]. In our study, patients treated with metronidazole for their first episode of CDI, when compared to vancomycin, experienced numerically more recurrence (22% vs 14%, $P = .21$) and death at 60 days (10.1% vs 9.8%, $P = .86$). Vancomycin has demonstrated more favorable outcomes, when compared to metronidazole, particularly for severe CDI [34]. Of note, only 30% of our cohort met criteria for severe CDI. Metronidazole for treatment of mild to moderate CDI in hospitalized patients has been identified as an independent predictor of treatment failure [35]. Other studies support metronidazole use and the finding of noninferiority to vancomycin for mild CDI [36]. Current international guidelines do not support the use of metronidazole for first-line therapy for CDI [37]. Given our study findings, discussion of aligning local guidelines with international guidelines may be required.

Additionally, fecal microbiota transplantation is increasingly performed for refractory CDI [38]. While our study was not designed to compare the effectiveness of different treatment regimens, it identified compliance with treatment guidelines in 66% of cases. Further studies examining the position of newer agents in the management algorithm of CDI and their cost effectiveness are warranted.

Recurrence causes significant morbidity for patients. The first recurrence rate in our study was 19.6%, which is consistent with other data [12]. We also identified severe CDI and inflammatory bowel disease as risk factors for recurrence, and although not statistically significant, patients with community-onset disease had a higher rate of recurrence (33.3%) when compared to hospital-onset (20.1%). CDI is now recognized as an important cause of community-onset diarrhea, especially in younger individuals [39]. Although community-onset CDI has been described as a mild illness, poor outcomes including recurrence have been noted. Established predictors of recurrence are advanced age, receipt of concomitantly administered non–*C difficile* antibiotics following a diagnosis of CDI, gastric acid–suppressing medication, impaired immune response, prolonged hospital stay, severe CDI, and specific comorbidities (chronic kidney disease and inflammatory bowel disease) [8]. Our findings were largely consistent with this. We did not observe a correlation with age ≥65 years, initial treatment regimen, immunosuppression, or administration of gastric acid–suppressing medication. This may be due to differences in patient population characteristics.

There are several limitations to this study. First, this was a retrospective study where focused data were only collected on the first 100 consecutive patients per recruiting site during a single year. In addition, recruitment only included adults and was performed at tertiary hospitals, which provide care for high-acuity and complex patients, leading to selection bias. Second, clinical follow-up data from medical records was incomplete, with outcome data unavailable for a portion of patients. Third, a lack of consensus definitions for both severe CDI and recurrence (including time intervals) required that a pragmatic approach be taken to define study outcomes. This highlights the great need for harmonization of definitions for CDI to correctly interpret intervention clinical trials and to compare data between centers. Fourth, an additional dataset was not collected to identify new nonclassical risk factors for severity, death, and recurrence. Also, our case definition for CDI included both toxin EIA and/or PCR positivity. The significance of a positive PCR alone has been questioned and European guidelines have recommended EIA in addition to PCR [40]. Last, in some cases we could not fully determine whether a community-onset case had had no hospital or healthcare contact prior to their CDI. This is important as

new patient populations and therapeutics evolve and possibly change the landscape of a disease.

CONCLUSIONS

The burden of disease caused by CDI is a continued and growing concern. As the delivery and mode of healthcare continues to change, hospital and community surveillance is paramount to refining our understanding of this disease. Patients who experience CDI continue to be our most vulnerable, with a high representation of those immunosuppressed or with multiple comorbidities, and on multiple medications. Risk factors for severe CDI include active malignancy, recent surgery, and hypoalbuminemia. Risk factors for recurrence were CDI and inflammatory bowel disease. Roughly two-thirds of first-line therapy in our cohort was guideline concordant.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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