Recurrent *Clostridium difficile* infection is associated with increased mortality

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Abstract

Clostridium difficile infections (CDI) are associated with decreased survival, and up to 30% of CDI patients may experience a recurrence. Data on the impact of recurrent CDI on mortality are scarce. The purpose of this study was to determine whether recurrent CDI was independently associated with decreased 6-month survival compared with patients with CDI who did not develop a recurrence. We performed a retrospective cohort study at an academic, urban, tertiary care hospital. Data were collected from the electronic medical record and chart review. CDI patients were followed for 180 days from the end of their index hospital discharge or end of index CDI antibiotic treatment, whichever was later, to determine mortality. Kaplan–Meier analysis was used to compare patient mortality by recurrent CDI status. Cox proportional hazards models were used to determine independent risk factors for death within 180 days. In all, 3958 patients aged $\geq$ 18 years who developed an initial CDI episode from 2003 to 2009, including 421 patients with recurrent CDI, were included in the study. Thirty-six per cent of persons with recurrent CDI died within 180 days, compared with 26% of persons without CDI recurrence (log-rank p <0.001). Recurrent CDI was associated with significantly higher hazards of death within 180 days, adjusting for demographics, comorbidities and medications received during the index CDI hospitalization (hazard ratio 1.33; 95% CI 1.12–1.58). Recurrent CDI is associated with significantly increased risk of death within 6 months after completion of their initial CDI treatment compared with CDI patients who do not develop a recurrence.

Keywords: *Clostridium difficile*, cohort, epidemiology, mortality, recurrence, survival
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Introduction

Clostridium difficile infections (CDI) are associated with decreased survival, but CDI mortality estimates vary widely. Crude mortality in CDI patients ranges from <5% to >40% [1–6], and the direct attributable mortality of CDI has been estimated to be from 4 to 7% [1,2,7]. In a review of CDI studies, Karas *et al.* estimated that the attributable mortality associated with CDI was 5.99%; the pooled attributable mortality increased to 8.03% when only studies published since 2000 were included [8]. The publications included in this review included a variety of study designs, patient populations and mortality surveillance periods (30 days to 1 year post-CDI infection). All of these differences probably contribute to the variance in mortality estimates in the published studies.

Up to 30% of patients with CDI experience a recurrence [9,10], but data on mortality after recurrent CDI are scarce. Pepin *et al.* reported that 9.3% of patients who developed recurrent CDI died within 30 days of recurrence [11], and Taori *et al.* reported that 16.4% of patients who developed recurrent CDI died within a year of recurrence with death

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attributable to CDI [12]. To the best of our knowledge, these are the only estimates of mortality in patients with recurrent CDI, and no studies have been published on mortality associated with recurrent CDI from healthcare facilities in the USA. The purpose of this study was to determine whether recurrent CDI was independently associated with increased 6-month mortality in a retrospective cohort of hospitalized patients in the USA.

Materials and methods

Study design

This study was conducted at Barnes-Jewish Hospital (BJH), an academic tertiary care facility in St Louis, MO, USA. CDI patients ≥18 years of age were identified by querying the hospital's Medical Informatics database for all patients with positive *C. difficile* toxin assay results during an inpatient hospitalization from 1 January 2003 to 31 December 2009. Two toxin assays were used during the study period (TechLab *C. difficile* Toxin A/B II before July 2004 and after May 2009; Remel ProSpec T *C. difficile* A/B Assay from July 2004 to May 2009). The BJH laboratory accepts only diarrhoeal stools for *C. difficile* testing. Additional electronic data collected from the Medical Informatics database included demographics, admission and discharge dates, admission type (e.g. inpatient, emergency department), International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes, inpatient medications and laboratory results. ICD-9-CM discharge diagnosis codes from the index admission and any admissions within the previous year were used to identify underlying comorbidities, classified by the Charlson–Deyo algorithm [13,14]. All other variables were included only if they occurred during the patient's index CDI hospitalization. Electronic data were supplemented with medical record review to determine medications upon admission and discharge from the hospital and whether the patient was diagnosed with recurrent CDI as an outpatient or at a separate facility. Death dates were collected from Medical Informatics and the Social Security Death Index (register of all deaths reported to the Social Security Administration). The Washington University Human Research Protection Office approved this study.

CDI case definitions

Each patient's first inpatient hospitalization (with length of stay >0.75 days) with a positive *C. difficile* toxin assay during the study period was defined as the CDI index hospitalization. A patient with recurrent CDI was defined as a patient who had documentation of recurrent CDI within 42 days of the end of index CDI antibiotic treatment or index discharge, either by repeat positive toxin assay or by clinical diagnosis documented in the medical record (history of a positive laboratory test as an outpatient or at an outside healthcare facility and symptoms consistent with CDI). Forty-two days was used as the risk period to develop recurrent CDI based on the current surveillance definition of 8 weeks (i.e. 56 days) between episodes to be considered recurrent CDI [15]. Since the recommended CDI treatment duration is 10–14 days [16], the risk period for recurrent CDI after end of treatment for the surveillance definition is 42–46 days. Patients were followed for 180 days from their index discharge or the end of index CDI antibiotic treatment (whichever occurred later) to determine mortality.

Exclusion criteria

Patients with a documented history of CDI in the 60 days before the study period were excluded to prevent enrolment of any recurrent CDI patients at baseline. Patients who died during the index admission or were discharged to a hospice were excluded.

Statistical analysis

Log-rank tests were used to compare patient mortality by recurrent CDI status. Cox proportional hazards models were used to determine univariate and multivariable risk factors for death within 180 days of index discharge or end of index CDI antibiotic treatment. Variables with $p \leq 0.2$ on univariate analysis or with clinical/biological plausibility were included in initial multivariable models. Multivariable Cox proportional hazards models were developed using backward elimination with $p \leq 0.1$ to retain variables in the model.

The variable albumin had significant missing data; we imputed missing albumin data under the missing at random assumption to generate ten imputation data sets. We then identified risk factors for death at 180 days using univariate and multivariable analyses in each of the ten imputation data sets. The risk factors for death identified were the same in all ten data sets.

We evaluated the appropriate functional form of all continuous variables with a restricted cubic spline function with common knots across the ten data sets. The necessity of the spline in each data set was determined with graphic plots and the likelihood ratio test of the model with spline terms compared with the model without the spline terms. Parameter estimates and their standard errors were pooled over the ten data sets using Rubin's rule [17]. Hazard ratios (HR) and 95% confidence intervals were based on the pooled estimates. The Kaplan–Meier curves of mortality probability for recurrent versus non-recurrent CDI were produced using the pooled (averaged) baseline hazard function across the ten imputation data sets and Rubin's rule-pooled Cox proportional hazards

model parameter estimates of recurrent versus non-recurrent CDI.

Statistical analyses were performed with SPSS version 21 (IBM Corporation, Armonk, NY, USA), SAS version 9.3 (SAS Institute, Cary, NC, USA), and R (R Foundation, Vienna, Austria), with the R mice package. All statistical testing was two-tailed with significance at the α level $\leq$0.05.

Results

The retrospective cohort included 3958 patients with CDI during an index hospitalization from 2003 to 2009, 421 (11%) of whom developed recurrent CDI within 42 days of index hospitalization discharge or the end of index CDI therapy. Sixty-two (15%) of the recurrent CDI patients were diagnosed and treated as outpatients; 119 (28%) recurrent CDI cases did not have a repeat positive toxin at BJH but had documentation in their medical record of recurrent CDI diagnosed as an outpatient or another healthcare facility. Of these, 86 (72%) had record of a positive toxin assay (or other laboratory test) with diagnosis date available. All of the recurrent CDI cases identified without a positive toxin at BJH had clinical symptoms compatible with CDI and response to treatment documented in the medical record.

Factors associated with mortality within 180 days in univariate Cox analysis are given in Table 1, and these included numerous demographic characteristics, comorbidities, infections, and medications received during the patient's index CDI admission. Duration and type of index CDI antibiotic treatment were not associated with mortality ($p > 0.05$). Overall mean survival among the population was 149 days. The mean survival time for recurrent CDI cases was 140 days versus 150 days for non-recurrent CDI case patients (log-rank $p < 0.001$). Mortality rates at 30, 60, 90 and 180 days are given in Table 2. The Kaplan–Meier curves for death within 180 days for patients with recurrent CDI versus patients without a recurrence of their CDI are presented in Fig. 1. Overall, 26.8% (n = 1062) of the patients died within 180 days of their index CDI discharge date/end of index antibiotic therapy. There was no significant difference in the percentage of recurrent versus non-recurrent CDI patients alive at 30 days, but mortality was of borderline significance at 60 days and was significantly higher among patients with recurrent CDI at 90 and 180 days (Table 2). By 180 days, 36% of patients with recurrent CDI had died, compared with 26% of patients who did not have recurrence ($p < 0.001$).

Factors significantly associated with mortality within 180 days in multivariable analysis are given in Table 3. Recurrent CDI was associated with 33% higher hazards of death compared with no recurrence within 42 days after completion of index CDI treatment (95% CI 1.12–1.58), controlling for demographic characteristics, comorbidities and medications received during the index hospitalization. The characteristics most strongly associated with mortality in the multivariable model were comorbidities, including leukaemia or lymphoma (HR = 2.36), metastatic solid tumour (HR = 2.47) and HIV/AIDS (HR = 2.36). Patients whose index CDI hospitalization was classified as surgical had significantly lower hazards of death (HR = 0.78; 95% CI 0.68–0.90) than patients whose index hospitalization was classified as a medical admission.

Discussion

To our knowledge, this is only the third published study examining mortality associated with recurrent CDI, and the first from a healthcare facility in the USA. Pepin *et al.* reported that 9.3% of patients with at least one CDI recurrence died within 30 days of recurrence [11]. Their estimate of 9.3% crude mortality at 30 days after recurrence is comparable to our finding of 7.8% mortality in patients with recurrent CDI within 30 days of index discharge or the end of index antibiotic treatment. In a study from Scotland, Taori *et al.* reported that 16.4% of the patients with recurrent CDI died within 1 year of recurrence with CDI listed on the death certificate as a cause of death [12]. Taori et al.'s estimate is lower than the 36.3% of patients with recurrent CDI in our current study who died within 180 days, but this is not surprising, because we identified all-cause mortality rather than death specifically attributed to CDI.

In a previous study of outcomes associated with CDI at our hospital, we observed that CDI had a delayed association with death. In a matched-pairs analysis, mortality in persons with or without CDI did not begin to diverge until 60 days after CDI (or hospital discharge for non-CDI patients) [1]. Mitchell *et al.* reported similar results in Australia, with survival rates between CDI and non-CDI patients diverging at 60 days [18]. The results of our current study show a similar relationship between mortality in patients with and without recurrent CDI. The percentage of patients with and without recurrent CDI who died was similar at 30 days (7.8% vs 8.7%, respectively) but diverged thereafter. At 60 days, 17.8% of patients with recurrent CDI had died versus 14.3% of patients without recurrence, and the differences in mortality between the two groups increased incrementally at 90 days and 180 days. Just as CDI may contribute to a general decline in patient function over time compared with patients without CDI, recurrent CDI may precipitate a decline in patient function over time when compared with patients who do not develop a recurrence.

TABLE 1. Univariate Cox analysis of risk factors for death at 180 days after index discharge or end of *Clostridium difficile* infections (CDI) index antibiotic treatment

Variable	Alive at 180 days (n = 2896) n (%) or median (range)	Died within 180 days (n = 1062) n (%) or median (range)	p
Recurrent CDI	268 (9)	153 (14)	<0.001
Residence in St Louis metro area	1977 (68)	753 (71)	0.090
Female	1397 (48)	518 (49)	0.701
Non-white race	910 (31)	327 (31)	0.780
Case status[a]			
HCFO/HCFA	1725 (60)	643 (61)	Ref
CA	505 (17)	123 (12)	<0.001
CO/HCFA or non-BJH HCFA	666 (23)	296 (28)	0.022
Age	60 (18–102)	67 (18–102)	<0.001
Index CDI hospitalization length of stay	11 (1–144)	14 (1–137)	<0.001
Index CDI admission from healthcare facility	724 (25)	337 (32)	<0.001
Index CDI discharged to healthcare facility	711 (25)	432 (41)	<0.001
Index CDI surgical admission	1203 (42)	394 (37)	0.005
ICU admission during index hospitalization	937 (32)	333 (31)	0.291
Median income ($) by zip code (quartiles)			
≥45 582	714 (25)	255 (24)	Ref
35 946–45 582	723 (25)	242 (23)	0.554
28 737–35 946	738 (26)	262 (25)	0.943
≤28 737	721 (25)	303 (29)	0.093
Inpatient hospitalizations in 60 days before index CDI hospitalization			
0	1822 (63)	556 (52)	Ref
1	759 (26)	339 (32)	<0.001
≥ 2	315 (11)	167 (16)	<0.001
Duration of index CDI antibiotic treatment	13 (1–91)	13 (1–86)	0.926
Index CDI antibiotic treatment			
Metronidzole alone	2229 (77)	804 (76)	Ref
Metronidazole and oral vancomycin	574 (20)	234 (22)	0.157
Oral vancomycin alone	93 (3)	24 (2)	0.163
Comorbidities/Infections			
Myocardial infarction	226 (8)	108 (10)	0.018
Congestive heart failure	557 (19)	326 (31)	<0.001
Peripheral vascular disease	190 (7)	100 (9)	0.002
Cerebrovascular disease	180 (6)	98 (9)	<0.001
Chronic renal failure	126 (4)	76 (7)	<0.001
Dementia	16 (1)	12 (1)	0.013
Chronic obstructive pulmonary disease	662 (23)	305 (29)	<0.001
Rheumatological disease	103 (4)	53 (5)	0.039
Peptic ulcer disease	105 (4)	55 (5)	0.022
Liver disease	141 (5)	84 (8)	<0.001
Diabetes	746 (26)	302 (28)	0.099
Paraplegia / hemiplegia	69 (2)	17 (2)	0.217
Cancer	503 (17)	296 (28)	<0.001
Leukaemia or lymphoma	472 (16)	216 (20)	0.007
Metastatic solid tumour	256 (9)	213 (20)	<0.001
HIV/AIDS	47 (2)	27 (3)	0.068
Skin/soft tissue infection	108 (4)	57 (5)	0.039
Pneumonia	364 (13)	185 (17)	<0.001
Urinary tract infection	553 (19)	299 (28)	<0.001
Organ abscess	21 (1)	13 (1)	0.147
Surgical site infection	83 (3)	25 (2)	0.342
Device-associated infection	119 (4)	45 (4)	0.936
Bacteraemia / endocarditis	473 (16)	229 (22)	<0.001
Bone infection	62 (2)	19 (2)	0.523
Clinical sepsis	216 (8)	103 (10)	0.010
Dialysis	158 (6)	115 (11)	<0.001
G-tube placement	144 (5)	99 (9)	<0.001
Low creatinine clearance (<70 mL/min)	1138 (39)	599 (56)	<0.001
Haemoglobin	10.4 (3.1–19.5)	10.0 (3.7–17.1)	<0.001
Albumin	3.1 (1–5.1)	2.8 (1.2–4.7)	<0.001
White blood cell count during index CDI hospitalization			
Normal	1029 (36)	364 (34)	Ref
Low (<3.8 × 10^3 /μL)	423 (15)	170 (16)	0.308
High (>9.8 × 10^3 /μL)	1444 (50)	528 (50)	0.451
Medications during index CDI hospitalization			
Gastric acid suppressor	2298 (79)	906 (85)	<0.001
Antifungal	864 (30)	434 (41)	<0.001
Vasopressor	868 (30)	315 (30)	0.926
Antibiotics during index CDI hospitalization			
IV vancomycin: 0 days	1486 (51)	435 (41)	Ref
IV vancomycin: 1–7 days	890 (31)	390 (37)	<0.001
IV vancomycin: >7 days	520 (18)	237 (22)	<0.001
Fluoroquinolone: 0 days	1746 (60)	603 (57)	Ref
Fluoroquinolone: 1–7 days	877 (30)	321 (30)	0.388
Fluoroquinolone: >7 days	273 (9)	138 (13)	<0.001
First-generation cephalosporin: 0 days	2440 (84)	923 (87)	Ref
First-generation cephalosporin: 1–7 days	388 (13)	125 (12)	0.184
First-generation cephalosporin: >7 days	68 (2)	14 (1)	0.044
Second-generation cephalosporin: 0 days	2755 (95)	1031 (97)	Ref
Second-generation cephalosporin: >0 days	141 (5)	31 (3)	0.007
Third-generation cephalosporin: 0 days	2590 (89)	902 (85)	Ref
Third-generation cephalosporin: 1–7 days	269 (9)	132 (12)	0.002
Third-generation cephalosporin: >7 days	37 (1)	28 (3)	<0.001
Fourth-generation cephalosporin: 0 days	1791 (62)	548 (52)	Ref

Continued

TABLE 1. Continued

Variable	Alive at 180 days (n = 2896) n (%) or median (range)	Died within 180 days (n = 1062) n (%) or median (range)	p
Fourth-generation cephalosporin: 1–7 days	623 (22)	301 (28)	<0.001
Fourth-generation cephalosporin: >7 days	482 (17)	213 (20)	<0.001
Linezolid: 0 days	2739 (95)	972 (92)	Ref
Linezolid: 1–7 days	97 (3)	44 (4)	0.084
Linezolid: >7 days	60 (2)	46 (4)	<0.001
β-lactamase inhibitor: 0 days	2468 (85)	864 (81)	Ref
β-lactamase inhibitor: 1–7 days	321 (11)	134 (13)	0.126
β-lactamase inhibitor: >7 days	107 (4)	64 (6)	0.001
Aminoglycoside: 0 days	2652 (92)	950 (90)	Ref
Aminoglycoside: 1–7 days	196 (7)	93 (9)	0.040
Aminoglycoside: >7 days	48 (2)	19 (2)	0.853
Carbapenem: 0 days	2519 (87)	903 (85)	Ref
Carbapenem: 1–7 days	189 (7)	68 (6)	0.937
Carbapenem: >7 days	188 (7)	91 (9)	0.034
Macrolide: 0 days	2611 (90)	936 (88)	Ref
Macrolide: 1–7 days	219 (8)	94 (9)	0.190
Macrolide: >7 days	66 (2)	32 (3)	0.141

[a]HCFO/HCFA, Healthcare facility onset/healthcare facility associated; CA, Community associated; CO/HCFA, Community onset/healthcare facility associated; non-BJH HCFA, non-Barnes-Jewish Hospital healthcare facility associated.

Functional decline after hospitalization has been demonstrated to be related to mortality [19,20], and delayed mortality after other diarrhoeal illnesses has been reported [21–23]; however, the exact reasons for the delayed effect of CDI and recurrent CDI on mortality are unknown and warrant further investigation.

The results of the multivariable analysis indicate that recurrent CDI is associated with significantly decreased survival independent of patient demographics, comorbidities and medications received during their index CDI hospitalization. Patients with recurrent CDI had 33% higher hazards of death at 180 days compared with patients without recurrent CDI (p=0.001). Two variables, surgical admission and receipt of a second-generation cephalosporin, were associated with decreased likelihood of death within 180 days. Patients with non-emergent surgical admissions are generally healthier than the overall hospital population, and second generation cephalosporins are used almost exclusively as surgical prophylaxis for gynaecological and intestinal procedures at our institution. Hence, these two variables probably capture a population of comparatively healthier CDI patients who are less likely to develop CDI recurrence. Older age, serious comorbidities (e.g. leukaemia or lymphoma), overall poor health (e.g. low albumin), and longer courses of antibiotics (>7 days) during the index CDI hospitalization were associated with increased likelihood of death within 180 days. Pepin found renal failure, measured by peak creatinine level, to be an independent risk factor for complicated CDI, which included death within 30 days [11]. Haemodialysis and low estimated creatinine clearance were significantly associated with 180-day mortality in our study, confirming that renal failure is an important risk factor for death after CDI.

The primary limitation of this study is the use of the hospital microbiology database to identify recurrent CDI cases. To minimize this bias all patient medical charts were reviewed to identify additional recurrent CDI cases diagnosed in the outpatient setting or at other facilities and transferred to BJH for treatment. These cases were classified as having recurrent CDI. However, patients diagnosed and treated for recurrent CDI entirely as outpatients (with toxin testing sent to an outside laboratory) or other facilities would not have been identified as having a recurrence, potentially biasing our results toward moderate-to-severe cases of recurrent CDI.

TABLE 2. Mortality at 30, 60, 90 and 180 days in patients with and without recurrent *Clostridium difficile* infection (CDI)

Time to death	Recurrent CDI Died n (%)	No recurrence Died n (%)	Log-rank p
≤30 days	33 (7.8)	306 (8.7)	0.532
≤60 days	75 (17.8)	506 (14.3)	0.076
≤90 days	102 (24.2)	627 (17.7)	0.002
≤180 days	153 (36.3)	909 (25.7)	<0.001

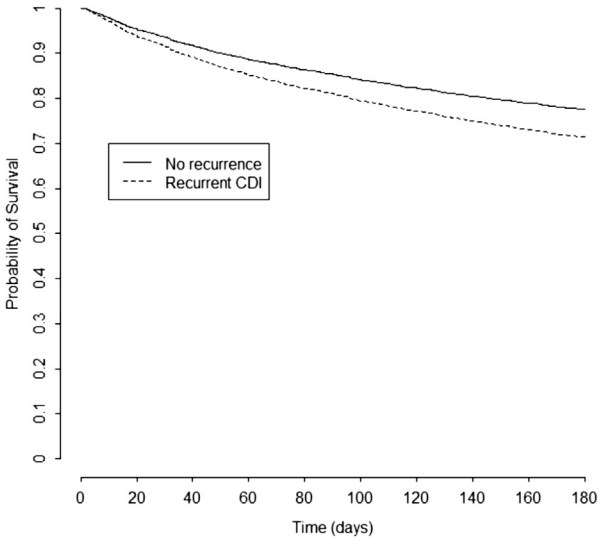

FIG. 1. Kaplan–Meier curve of survival at 180 days by recurrent CDI status.

TABLE 3. Factors associated with mortality within 180 days in Cox proportional hazards model

Variable	HR (95% CI)	p
Recurrent CDI	1.33 (1.12–1.58)	0.001
Age[a]	1.48 (1.32–1.67)	<0.001
Index CDI admission from a healthcare facility[b]	1.17 (1.01–1.34)	0.032
Index CDI discharged to a healthcare facility[b]	1.53 (1.32–1.77)	<0.001
Index CDI surgical admission	0.78 (0.68–0.90)	<0.001
Comorbidities		
Metastatic solid tumour	2.47 (2.01–3.03)	<0.001
Leukaemia or lymphoma	2.36 (1.97–2.83)	<0.001
HIV/AIDS	2.36 (1.58–3.52)	<0.001
Liver disease	1.92 (1.53–2.42)	<0.001
Congestive heart failure	1.48 (1.29–1.71)	<0.001
Rheumatological disease	1.39 (1.05–1.84)	0.021
Cancer	1.33 (1.10–1.60)	0.003
Peptic ulcer disease	1.31 (0.99–1.72)	0.055
Urinary tract infection	1.24 (1.07–1.43)	0.004
Dialysis	1.53 (1.24–1.88)	<0.001
G-tube placement	1.33 (1.07–1.66)	0.011
Low estimated creatinine clearance (<70 mL/min)	1.34 (1.16–1.55)	<0.001
Haemoglobin (mg/dL)	0.96 (0.92–1.00)	0.031
Albumin[c]	0.63 (0.53–0.75)	<0.001
Medications during index CDI hospitalization		
Antifungal	1.25 (1.09–1.44)	0.002
Fluoroquinolone: 0 days	Reference	
Fluoroquinolone: 1–7 days	0.94 (0.82–1.08)	0.392
Fluoroquinolone: >7 days	1.21 (0.99–1.47)	0.057
Second-generation cephalosporin: 0 days	Reference	
Second-generation cephalosporin: >0 days	0.54 (0.37–0.78)	0.001
Third-generation cephalosporin: 0 days	Reference	
Third-generation cephalosporin: 1–7 days	1.10 (0.91–1.33)	0.317
Third-generation cephalosporin: >7 days	1.59 (1.09–2.34)	0.016
β-lactamase inhibitor: 0 days	Reference	
β-lactamase inhibitor: 1–7 days	1.04 (0.86–1.25)	0.712
β-lactamase inhibitor: >7 days	1.41 (1.08–1.84)	0.011

[a]Results presented as 75th percentile vs. 25th percentile.
[b]Long-term care facility, outside hospital, other healthcare facility
[c]Modelled as spline variable. Results presented as 75th percentile versus 25th percentile.

Another limitation was the lack of data on *C. difficile* strain. This is important because the 027/BI/NAP1 strain has been associated with both increased risk of CDI recurrence and mortality [24,25]. Data used in this study were subject to the inherent limitations of retrospective data. Despite adjustment for a variety of demographics, comorbidities and medications, residual confounding may exist.

This study has several strengths. The sample size of our CDI population was large, and a wide variety of demographics, comorbidities, medications and laboratory and microbiological data were included in multivariable models. Death dates used to calculate mortality were collected from multiple sources (hospital data and the Social Security Death Index), and so any ascertainment bias with death should be minimal.

Very few data exist on the outcomes of patients with recurrent CDI. The results of this study suggest that recurrent CDI is associated with significantly increased mortality, with more than a third of recurrent CDI patients dying within 6 months after completion of index CDI treatment. This mortality estimate may decrease with better ascertainment of CDI recurrence, particularly recurrent CDI patients with milder symptoms diagnosed and treated solely as outpatients. In the time since follow up for this study has ended, many studies have been published recently describing promising new treatment strategies for CDI patients [26–29]. Recurrent CDI was not the patient characteristic most strongly associated with increased mortality in multivariable analysis in our study; severe comorbidities (such as leukaemia/lymphoma, metastatic solid tumour or HIV/AIDS) were associated with higher hazards of death. These characteristics are not easily modifiable, and newer treatments for recurrent CDI may not significantly improve survival in these patients. Nevertheless, our results indicate that recurrent CDI is independently associated with excess mortality, after adjustment for comorbidities. These results should be confirmed at other institutions. Our finding of increased mortality associated with recurrent CDI should give further impetus to research on the effect of recurrent CDI on survival in patients whose recurrent infections were treated with these newer therapies.

Transparency declaration

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