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Major Article

High 30-day readmission rates associated with *Clostridium difficile* infection

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Key Words:
Clostridium difficile
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Risk factors

Background: *Clostridium difficile* infection (CDI) is a leading cause of community-onset and healthcare–associated infection, with high recurrence rates, and associated high morbidity and mortality. We report national rates, leading causes, and predictors of hospital readmission for CDI.
Methods: Retrospective study of data from the 2013 Nationwide Readmissions Database of patients with a primary diagnosis of CDI and re-hospitalization within 30-days. A multivariate regression model was used to identify predictors of readmission.
Results: Of 38,409 patients admitted with a primary diagnosis of CDI, 21% were readmitted within 30-days, and 27% of those patients were readmitted with a primary diagnosis of CDI. Infections accounted for 47% of all readmissions. Female sex, anemia/coagulation defects, renal failure/electrolyte abnormalities and discharge to home (versus facility) were 12%, 13%, 15%, 36%, respectively, more likely to be readmitted with CDI.
Conclusions: We found that 1-in-5 patients hospitalized with CDI were readmitted to the hospital within 30-days. Infection comprised nearly half of these readmissions, with CDI being the most common etiology. Predictors of readmission with CDI include female sex, history of renal failure/electrolyte imbalances, anemia/coagulation defects, and being discharged home. CDI is associated with a high readmission risk, with evidence of several predictive risks for readmission.

Clostridium difficile infection (CDI) has emerged as one of the leading causes of health care–associated infections in the United States. Between 2000 and 2009, there was an almost 200% increase in CDI hospitalizations.[1] In 2011 alone, there were nearly half a million cases, of which approximately 29,000 deaths were associated with CDI within 30 days of diagnosis.[2] This growing incidence and mortality secondary to CDI have placed a financial burden on the health care system. Health care costs related to CDI in acute care facilities alone are estimated to be $4.8 billion annually.[1,3]

C difficile is an anaerobic gram-positive bacterium. Once in the colon, 2 potent toxins inactivate regulatory pathways, leading to colonic inflammation. Infection with the bacterium can cause a spectrum of clinical manifestations, ranging from asymptomatic carriage to diarrhea, abdominal pain, fevers, and fulminant colitis, with toxic megacolon and death.[4] The estimated number of total deaths within 30 days after diagnosis of community-acquired and health care–associated *C difficile* infection is 1.3% and 9.3%, respectively, with approximately 50% mortality directly attributable to *C difficile*.[2] CDI is directly responsible for 14,000 deaths per year in the United States.[2] With an increasing incidence of CDI, high recurrence rates have been reported

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and are a cause of concern, as they lead to subsequent hospitalizations and readmissions.[5] Despite current treatment recommendations, recurrence rates with appropriate therapy range between 20% and 65%.[2,6-8] In an effort to reduce readmission, many facilities have implemented educational models for medical and nonmedical staff as well as patients.[9] In addition, efforts are being made to develop more effective antibiotics to decrease CDI recurrence rates.[10-12]

Prior studies reviewing CDI readmission rates report data from individual medical centers or regional health care systems and lack geographic diversity.[13-18] However, many of the large population studies are nearly a decade old and may not correctly report more recent trends. Scarcity of large studies and lack of geographic diversity have made it difficult to draw meaningful conclusions regarding readmission rates due to CDI across the United States.

With evidence of the growing incidence of CDI and high mortality rates, it becomes necessary to examine the demographics and populations at risk. In addition to the already high financial burden of the disease, new reimbursement models make it prudent for all health care providers to review risk factors for readmission. In this study, we evaluate readmission rates following CDI, the etiology of readmissions, demographics, and predictors of readmission using data from the Nationwide Readmissions Database (NRD), one of the largest publicly available nationwide databases.

METHODS

Data source

Study data were collected from NRD for 2013. NRD is a subset of the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality and one of the largest publicly available all-payer inpatient care databases in the United States, including data on approximately 14 million discharges in 2013, estimating roughly 36 million discharges from 21 states with reliable, verified linkage numbers. NRD represents 49.1% of total US hospitalizations. Readmissions were tracked across the same or different hospitals. If a patient was transferred to a different hospital on the same day, the 2 events were combined as a single stay and the second event not counted as a readmission, in that transfers are not readmissions.[19] Patients were tracked using the variables "NRD_visitlink" and "NRD_DaysToEvent" for time between the 2 admissions. Time to readmission was calculated by subtracting length of stay of primary admission from time between the 2 admissions. National estimates were produced using sampling weights provided by the sponsor. Details regarding NRD data are available online.[19]

Study population

We queried NRD using the ICD-9-CM code for *C difficile* infection (00.845). The deidentified patient database contains a representative census of demographically and geographically diverse inpatients from large and small as well as teaching and nonteaching hospitals. We identified 38,409 patients after excluding patients <18 years old, those readmitted more than 30 days after initial admission, and those with missing data. Patients admitted in the month of December were also excluded, as there were no follow-up data available. Included were patients >18 years old readmitted to the hospital within 30 days in the same calendar year. Baseline patient characteristics included were age, sex, Charlson/Deyo comorbidity index, median household income, and primary expected payer. Hospital characteristics such as location, teaching status, and bed size were also included.[19]

Outcomes measured

The primary study outcome was 30-day readmission rates for patients admitted with a primary diagnosis of CDI. Readmissions were identified according to the methodology outlined by the Healthcare Cost and Utilization Project.[19] Secondary outcomes included patients admitted with any diagnosis within 30 days, with a primary diagnosis of CDI, stratified by age, sex, comorbidities, etiology, primary payer, and discharge disposition. Other secondary outcomes included mortality as well as predictors of CDI, non-CDI, and all-cause readmissions within 30 days.

Statistical analysis

Stata/IC 11.0 (StataCorp, College Station, TX) and SAS 9.4 (SAS Institute, Cary, NC) were utilized for analyses. Differences between categorical variables were tested using the χ^2 test, and differences between continuous variables were tested using the Student t test. Hierarchical 2-level logistic models with hospital identification as random effect were used to evaluate predictors of readmission and short-term mortality. In multivariate models for readmission, patient-level variables included age, sex, Deyo modification of the Charlson comorbidity index, principal admission type (elective vs nonelective), primary payer (private [including health maintenance organization] vs nonprivate), comorbidities (including history of obesity, diabetes, or chronic pulmonary disease; codiagnosis of congestive heart failure, peripheral vascular disease, renal failure, or electrolyte imbalance; and anemia or coagulation defect), disposition during principal admission, and length of stay (<3 as reference, 3-6, 7-10, >10). Multivariate model for readmission was run only on patients who survived principal admission.

RESULTS

Our study analysis included 38,409 patients who were admitted with a primary diagnosis of CDI in 2013 (Table 1). The mean age was 67.6 ± 17.6 years, and 65.0% were women. The majority of patients were over the age of 50 (83.6%), with nearly two-thirds being over the age of 65 (62.6%). Just under half of patients had at least 2 or more comorbidities (44.7%). The most common comorbidities were (1) renal and other electrolyte abnormalities (72.4%), (2) hypertension (63.4%), (3) anemia and other coagulopathies (31.4%), and (4) diabetes mellitus (26.8%). The primary insurance payer for 76.2% of the patients was Medicare or Medicaid. The in-hospital mortality was 2.4% during the principal admission with CDI. In-hospital mortality for all-cause readmission was 6.5%.

Of the 38,409 patients initially admitted for CDI, 8,198 (21.3%) were readmitted to the hospital within 30 days. Of these, 2,206 (26.9%) were readmitted with CDI as the primary diagnosis, which accounted for 5.7% of all patients initially admitted with CDI (Fig 1), and 71.1% were discharged home and 26.0% discharged to facilities or locations other than home (Table 1).

Among all readmitted patients, *C difficile* infection was the leading cause of readmission (26.9%) (Table 2). Infectious etiologies (CDI 26.9%, septicemia 11.6%, urinary tract infection 3.2%, diarrhea 2.5%, and pneumonia 2.1%) accounted for 45.5% of readmissions. Congestive heart failure (3.6%), malignancy (2.4%), acute kidney injury or failure (2.3%), diabetes (1.7%), and pulmonary embolism or deep vein thrombosis (1.6%) were among the other top 10 leading causes of readmission.

Women were 12% more likely to be readmitted with CDI when compared with men (1.12 OR, 1.02-1.24 95% CI, $P = .017$). However, women in the non-CDI and all-cause readmission cohorts were 16% and 9%, respectively, less likely to be readmitted to the hospital within 30 days (0.84 OR, 0.79-0.89 95% CI, $P < .001$ and 0.91 OR,

Table 1
Baseline demographics of study population

	Overall	Readmission without CDI	Readmission with CDI	Never readmitted	*P* value
Total admissions, n (%)	38,409 (100%)	5,992 (15.60%)	2,206 (5.74%)	30,211 (78.66%)	
Patient-level variables					
Age, %					
18-34	6.23	6.51	5.21	6.25	.025
35-49	10.14	10.45	9.25	10.14	
50-64	21.01	20.31	19.72	21.24	
65-79	31.29	31.04	31.64	31.31	
≥80	31.33	31.69	34.18	31.05	
Gender %					
Male	34.98	39.92	31.41	34.26	< .001
Female	65.02	60.08	68.59	65.74	
Charlson/Deyo Co-Morbidity Index* (%)					
0	33.74	22.95	33.27	35.92	< .001
1	21.6	19.56	23.3	21.88	
≥2	44.6	57.49	43.43	42.21	
Median household income category for patient's zip code† (%)					
1. 0-25th percentile	24.83	25.65	25.11	24.65	.046
2. 26th-50th percentile	26.47	26.08	28.65	26.39	
3. 51st-75th percentile	24.6	23.87	24.66	24.74	
4. 76th-100th percentile	22.6	22.8	20.44	22.72	
Primary Payer (%)					
Medicare/Medicaid	76.23	81.43	81.05	74.85	< .001
Private including HMO	18.21	14.24	13.6	19.34	
Self-pay/no charge/other	5.49	4.27	5.26	5.75	
IV antibiotic use (%)					
	2.68	2.75	2.49	2.67	.809
Hospital characteristics					
Hospital bed size‡ (%)					
Small	11.73	11.43	10.65	11.87	.332
Medium	24.47	24.63	23.89	24.48	
Large	63.8	63.94	65.46	63.65	
Hospital teaching status (%)					
Metropolitan non-teaching	46.88	46.38	48.59	46.85	N/A
Metropolitan teaching	43.45	45.89	42.2	43.05	
Non-metropolitan hospital	9.67	7.73	9.2	10.1	
Admission type (%)					
Nonelective	95.64	96.07	96.69	95.64	.027
Elective	4.23	3.93	3.31	4.36	
Admission day (%)					
Weekdays	75.84	76.02	74.98	75.87	.603
Weekend	24.16	23.98	25.02	24.13	
Disposition (%)					
Home	71.07	69.01	77.74	70.99	< .001
Facility/others	26.01	30.39	21.44	25.48	
In-Hospital Mortality (%)	2.38	–	–	–	N/A
Length of Stay (days) (± SD)	6.28 ± 0.03	6.52 ± 0.1	5.67 ± 0.1	6.28 ± 0.1	< .001
Cost of Care (USD) (± SD)	10,617 ± 97	11,413 ± 364	8,990 ± 148	10,578 ± 99	< .001

CDI, Clostridium difficile infection; *HMO*, health maintenance organization; *IV*, intravenous; *N/A*, not applicable; *USD*, United States dollar; *ZIP*, Zone Improvement Plan.
*Charlson/Deyo Comorbidity index (CCI) was calculated as per Deyo classification.
†Represents a quartile classification of the estimated median household income of residents in the patient's ZIP code, derived from ZIP code demographic data. The quartiles are identified by values of 1 to 4, indicating the poorest to wealthiest populations. Because these estimates are updated annually, the value ranges vary by year.
‡The bed size cut-off points divided into small, medium, and large have been done so that approximately one-third of the hospitals in a given region, location, and teaching status combination would fall within each bed size category.

0.86-0.96 95% CI, $P < .001$). Having 2 or more comorbidities did not affect rates of readmission due to CDI. Patients with 2 or more comorbidities were 90% more likely to be readmitted in the non-CDI cohort and 60% more likely to be readmitted in the all-cause cohort (1.90 OR, 1.74-2.07 95% CI, $P < .001$ and 1.60 OR, 1.49-1.73 95% CI, $P < .001$), respectively. Congestive heart failure had no impact on readmission due to CDI but contributed to increased odds of readmission in the non-CDI and all-cause readmission groups (1.20 OR, 1.11-1.30 95% CI, $P < .001$ and 1.14 OR, 1.06-1.22 95% CI, $P = .000$), respectively. Patients with renal failure or electrolyte imbalances were more likely to be readmitted with a CDI, but this had no impact on the non-CDI and all-cause readmission groups (1.15 OR, 1.03-1.27 95% CI, $P = .011$). Patients with anemia or coagulation defects were more likely to be readmitted in all groups—CDI (1.13 OR, 1.03-1.25 95% CI, $P = .012$), non-CDI (1.18 OR, 1.11-1.26 95% CI, $P < .001$), and all-cause (1.17, 1.11-1.24, <0.001). Nonmetropolitan hospitals had decreased readmission rates in the non-CDI (0.80 OR, 0.71-0.89 95% CI, $P = .001$) and all-cause (0.82 OR, 0.74-0.91 95% CI, $P < .001$) groups, but there was no significant impact on the CDI group.

There was no significant impact on readmission based on hospital size (large, medium, or small) in all 3 cohorts. There was no significant impact on readmission based on median household income in all 3 cohorts. There was no significant impact on readmission in metropolitan teaching and nonteaching hospitals in all 3 cohorts. Patients with private insurance or health maintenance organization had decreased rates of CDI, non-CDI, and all-cause readmissions by 23%, 22%, and 22%, respectively, when compared with patients with Medicare or Medicaid (0.67 OR, 0.58-0.78 95% CI, $P < .001$ and 0.68 OR, 0.62-0.74 95% CI, $P < .001$ and 0.68 OR, 0.63-0.73 95% CI, $P < .001$). Patients being discharged to facilities or locations other than home

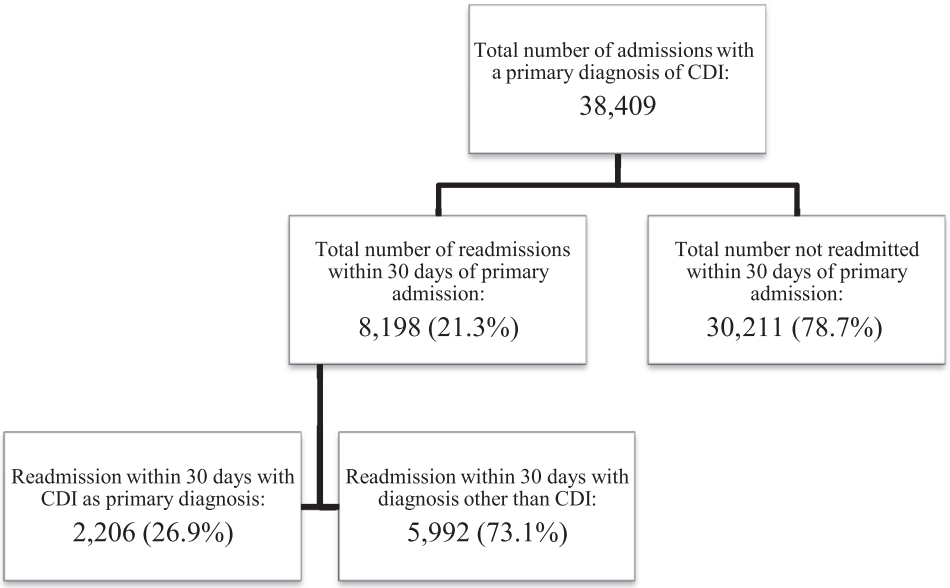

Fig 1. Flow diagram of 30-day readmission with *Clostridium difficile* infection (CDI).

were 36% and 7%, respectively, less likely to be readmitted with CDI or all causes when compared with patients being discharged home (0.64 OR, 0.57-0.71 95% CI, $P < .001$ and 0.93, 0.87-0.99, 0.023). Discharge location did not impact readmission rates in the non-CDI cohort. Patients in all cohorts—all-cause, CDI, and non-CDI—were more likely to have an increased length of stay (4-6 or >7 days) when readmitted. Comorbid history of obesity, diabetes, or chronic pulmonary disease had no significant impact on readmission in any group. Intravenous antibiotic use had no significant impact on readmission in any group. Patients' median household income, hospital bed size, and admission type (elective or nonelective) had no significant impact on readmission in all 3 cohorts.

DISCUSSION

We found that approximately 1 in 5 patients (21.3%) who were hospitalized with a primary diagnosis of CDI were readmitted to the hospital within 30 days. The leading cause of readmission was recurrent CDI (26.9%), which indicates that 5.4% of all patients with primary CDI are readmitted for recurrent disease. As far as we know, this study is unique from other reports in the literature, in that we utilized a national database with a geographically and demographically diverse representative sample, estimating over 36 million discharges. These rates are similar to readmission rates reported by most studies, which range from 23.2% to 30.1%. A study of 2009 national hospital readmissions reported 4.8% CDI readmission rates, indicating readmission rates have increased over the last half decade.[20] Compared with prior studies, all-cause readmission rates have trended down from 29.1% in 2009 to 23.2% in 2011 to our reported 21.3% in 2013.[20,21]

Table 2
Top readmission etiologies within 30 days following a *C difficile* infection

Etiology of readmission	Overall, n (%)
Clostridium difficile infection	2,206 (26.9)
Septicemia NOS (not including *C difficile* septicemia)	951 (11.6)
Congestive heart failure	295 (3.6)
Urinary tract infection (including pyelonephritis)	262 (3.2)
Diarrhea (including bacterial and viral gastroenteritis)	205 (2.5)
Malignancy	197 (2.4)
Acute kidney injury/failure	189 (2.3)
Pneumonia	172 (2.1)
Diabetes	139 (1.7)
Thromboembolism (lower extremity DVT and PE)	131 (1.6)

DVT, deep vein thrombosis; *NOS*, not otherwise specified; *PE*, pulmonary embolism.

The etiology for increased rate of readmission due to *C difficile* infection compared with non-CDI etiology is unclear, and this study was not designed to answer this question. Our findings suggest significant readmission rates for CDI among women, similar to findings by Bouwknegt et al,[2] who report a 26% increased CDI rate among women after initial *C difficile* infection. Our findings suggest significant readmission rates for CDI among women, similar to findings by Lessa et al[22], who report a 26% increased incidence of CDI in women than among men. All populations reviewed were noted to have increased risk of readmission with a prior secondary diagnosis of anemia, which may be due to its relation to chronic illness, although little data are available on the independent risk of anemia on readmission rates.[23]

Notably, there was a 33% decreased risk of readmission in those with private insurance as the primary payer compared with Medicare or Medicaid. These findings are consistent with prior reports that examined readmission trends over a 5-year period by payer type across 20 high-volume conditions.[24] These findings are likely due to several factors, including reimbursement models, fiscal penalties, and baseline patient demographics.[25] Patients with private insurance are more likely to have less comorbidity compared with Medicare or Medicaid patients, who are older and have more chronic conditions and less access to prescription medications.[26,27]

Our results show that patients who are discharged to a facility (ie, location other than home) are 36% *less* likely to be readmitted for CDI. These findings could be a result of regimented care and subsequent testing for recurrent symptoms in facilities, leading to increased compliance with antibiotic course compared with those discharged home, who may stop antibiotics early when they feel subjectively better.[28,29] The current cost of antibiotic treatment options for recurrent *C difficile* infection is high, particularly for medications such as vancomycin and fidaxomicin.[30,31] The direct cost to patients is mitigated when admitted to facilities. Actions to increase medication

compliance, such as "bedside pharmacy" prior to patient discharge, pharmacist medication review, patient counseling, and telephone follow-up, have been shown to reduce readmission and medication treatment failures.[15,32] In one study of patients admitted with asthma, those receiving prescription medications prior to discharge had significantly lower odds of returning to the emergency department or readmission within 30 days.[33]

Our results found no increased risk of CDI readmission in several patient cohorts, including patients with a history of obesity, diabetes, congestive heart failure, chronic pulmonary disease, or peripheral vascular disease and those receiving intravenous antibiotics. Additional factors, including patients' household income, were not associated with an increased or decreased risk of readmission; this is likely offset by the notable finding of readmission rates based on insurance coverage. Hospital bed size and teaching status also had no bearing on readmission rates.

Our study reveals a 2.4% in-hospital mortality risk during the principal CDI admission. Of all those readmitted, the all-cause in-hospital mortality rate increased to 6.5%. Previous reports describing mortality in CDI have varied, ranging from 1.3% to 13.1%.[2,34-36] One study reviewing different geographic sites throughout the United States found a 30-day mortality rate of 1.3% in community-associated CDI and 9.3% in hospital-associated CDI.[2] A smaller study in Pennsylvania found an 11.8% in-hospital mortality in hospital-onset CDI, as compared to 7.3% in propensity matched controls without CDI.[34] Among 2 European-centered studies, 1 single-center study found a 9.9% all-cause 30-day mortality risk among those with CDI, whereas another larger study reported 13.1% all-cause 30-day mortality risk among those with CDI.[35,36] Although previous literature may report different mortality rates, these studies are limited to smaller samples and, typically, smaller geographic locations.[2,34-36] Several studies describe that a range in mortality may be attributable to endemic or epidemic rates of infection and different population locations.[34,36] In addition, our study is limited to all-cause mortality, as the data limit our ability to determine if case fatality is directly related to CDI, as may be reported in other studies.

The current antibiotic treatment models are based on illness severity and infection recurrence. The mainstays of CDI treatment in 2013 were metronidazole and vancomycin. With newer Infectious Diseases Society of America guidelines made available for the treatment of CDI at the start of 2018, it will be critical to evaluate the impact on infection and readmission rates.[37] Therapies that are currently available are effective in the treatment of acute infection, although they have little impact on recurrent disease. New therapies, such as fecal microbiota transplant, are now approved for the treatment of recurrent CDI but were not widely used in 2013. These new treatments have been shown to significantly reduce rates of recurrent CDI and possibly reduce hospital readmission rates.[16-18,26,38]

Our study has several limitations. First, we utilized a retrospective nationwide database analysis using only 1 year of data. The first full (2016) calendar year readmission database was not made available until August 2018. Although the data we present are 5 years old, the significant proportion of patients readmitted for CDI compared with other etiologies has ongoing relevance. As with all database analyses, our study lacks clinical details regarding individual patient specifics (such as comorbid diagnosis and severity of CDI). We cannot separate or distinguish those with hospital-onset CDI from those with community-acquired CDI. Similarly, given that NRD utilizes ICD-9, we may not have identified all CDI cases and may therefore have potentially underestimated our findings. Additionally, lack of both laboratory and pharmacy data does not allow for thorough patient risk stratification. In our analysis, we were unable to track individual patients over time from initial admission to readmission to review etiology and risks of each CDI readmission. Although our findings indicate that certain aspects of patient health have marked impact on readmission (eg, renal failure, electrolyte disturbances, anemia, coagulation defects), we were unable to stratify laboratory values or cutoff values that may further describe these at-risk populations (ie, creatinine, hematocrit, or potassium cutoff levels).

Our data have identified risk factors for readmission. This information may provide a framework for hospitals to develop increased awareness of at-risk populations. Further studies can be aimed at evaluating the role of new therapies on cost and readmission.

CONCLUSIONS

C difficile infection is common. One in 5 patients is readmitted after hospitalization with CDI within 30 days after discharge, with recurrent CDI as the leading diagnosis. We found multiple factors that impacted readmission rates for CDI- and all-cause–related readmission, including female sex, history of renal failure or electrolyte imbalance, anemia or coagulation defects, and discharge home. Identifying at-risk patients and potentially modifiable risk factors should help us focus on high-risk populations and direct interventions appropriately.

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