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Major Article

Shift to community-onset *Clostridium difficile* infection in the national Veterans Health Administration, 2003-2014

Kelly R. Reveles PharmD, PhD [a,b,c,*], Mary Jo V. Pugh PhD, RN [c,d], Kenneth A. Lawson PhD [a], Eric M. Mortensen MD, MSc [e,f], Jim M. Koeller MS [a,b], Jacqueline R. Argamany PharmD [a,b], Christopher R. Frei PharmD, MSc [a,b,c]

[a] College of Pharmacy, The University of Texas at Austin, Austin, TX
[b] Pharmacotherapy Education and Research Center, UT Health San Antonio, San Antonio, TX
[c] South Texas Veterans Health Care System, San Antonio, TX
[d] Department of Epidemiology and Biostatistics, UT Health San Antonio, San Antonio, TX
[e] Department of Internal Medicine and Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, TX
[f] Department of General Internal Medicine, VA North Texas Health Care System, Dallas, TX

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Background: *Clostridium difficile* infection (CDI) occurs frequently in inpatient settings; however, community-onset cases have been reported more frequently in recent years. This study evaluated hospital-onset and community-onset CDI in the national Veterans Health Administration (VHA) population over a 12-year period.

Methods: This was a retrospective cohort study of all adult VHA beneficiaries with CDI between October 1, 2002, and September 30, 2014. Data were obtained from the Veterans Affairs Informatics and Computing Infrastructure. CDI was categorized into community-associated CDI (CA-CDI); community-onset, health care facility-associated CDI; and health care facility-onset CDI (HCFO-CDI). Each type was described longitudinally and was assessed as an independent risk factor for health outcomes using multivariable logistic regression.

Results: Overall, 30,326 patients with a first CDI episode were included. HCFO-CDI was the predominant type (60.2%), followed by CO-HCFA-CDI (20.6%) and CA-CDI (19.2%). The proportion of patients with HCFO-CDI decreased from 73.5% during fiscal year 2003 to 53.2% during fiscal year 2014, whereas CA-CDI increased from 8.3% to 26.7%. HCFO-CDI was a positive predictor of severe CDI (odds ratio [OR], 1.71; 95% confidence interval [CI], 1.59-1.84) and 30-day mortality (OR, 1.46; 95% CI, 1.32-1.61), but a negative predictor of 60-day recurrence (OR, 0.41; 95% CI, 0.37-0.46).

Conclusions: HCFO-CDI was the predominant CDI type. The proportion of patients with CA-CDI increased and HCFO-CDI decreased in recent years. Patients with HCFO-CDI experienced higher rates of severe CDI and mortality.

* Address correspondence to Kelly R. Reveles, PharmD, PhD, Pharmacotherapy Education and Research Center, UT Health San Antonio, 7703 Floyd Curl Dr, MSC-6220, San Antonio, TX 78229-3900.
E-mail address: kdaniels46@utexas.edu (K.R. Reveles).

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Clostridium difficile infection (CDI) occurs frequently in inpatient settings due to exposure to antibiotic agents, comorbid illness, and environment factors that facilitate organism transmission; however, community-onset cases have been reported more frequently in the literature during recent years. The Centers for Disease Control and Prevention (CDC) estimate that 52% of CDI cases originate in the outpatient setting, predominately in patients with recent contact with a health care system.[1] Similarly, a national prevalence study by Lessa et al[2] found that 66% of CDI cases were health care-associated, but only 24% of those patients had onset during hospitalization. Of particular concern in community-onset cases, approximately 10%-20% of patients have no prior exposure to a health care system.[1,3,4]

The majority of CDI epidemiologic data are acquired from hospital administrative data; therefore, few studies have described characteristics of patients with community-onset CDI. Even fewer studies have evaluated health outcomes in these distinct patient populations. Therefore, the primary objective of this study was to describe the incidence of hospital-onset and community-onset CDI in the national Veterans Health Administration (VHA) patient population over a 12-year period. This study also compared CDI health outcomes among these subgroups.

METHODS

This was a retrospective cohort study of patients receiving care at any inpatient or outpatient VHA facility in the United States. Data for this study were obtained from the Veterans Affairs Informatics and Computing Infrastructure. Specifically, Veterans Affairs Informatics and Computing Infrastructure includes administrative, clinical, laboratory, and pharmacy data repositories that are linked using unique patient identifiers. This study was approved by the South Texas Veterans Health Care System Research and Development Committee and the Institutional Review Board at University of Texas Health San Antonio.

Patients were included in the study if they were aged 18-89 years and had any inpatient or outpatient ICD-9-CM code for CDI (008.45) plus any positive CDI stool test (eg, glutamate dehydrogenase, enzyme immunoassay, and polymerase chain reaction) during or within 7 days of the visit from October 1, 2002, through September 30, 2014. To limit our cohort to first-episode CDI patients only, we excluded patients with an ICD-9-CM code for CDI (008.45) during the year before study inclusion.

Patient demographic characteristics included age, sex, race, and ethnicity. CDI was categorized as either a principal (ICD-9-CM code in the first position) or secondary diagnosis (ICD-9-CM code in any position except first). CDI type was categorized based on the typical surveillance definitions constructed by the CDC.[5] Administrative codes do not contain the date of CDI diagnosis; therefore, we used CDI therapy receipt as a surrogate for the first date of CDI diagnosis. Community-onset, health care facility-associated CDI (CO-HCFA-CDI) was defined based on the presence of a prescription for a CDI therapy (eg, metronidazole, oral vancomycin, fidaxomicin, nitazoxanide, rifaximin, or probiotics) as an outpatient or on day 1 or 2 of hospitalization, plus 1 or more prior hospitalizations occurring within 90 days preceding CDI diagnosis. Community-associated CDI (CA-CDI) was defined similarly, except that patients did not have a prior hospitalization. Lastly, health care facility-onset CDI (HCFO-CDI) was defined as CDI therapy on or after day 3 of hospitalization.

Charlson comorbidities and other relevant diagnoses, as defined by ICD-9-CM codes, were identified for the year before the first CDI episode. We also calculated the Charlson comorbidity score.[6] In addition, we collected other infections that occurred during a CDI episode (between CDI outpatient visit date or hospital admission date and CDI therapy end date), including bacteremia, pneumonia, skin infection, intra-abdominal infection, urinary tract infection, device-related infection, endocarditis, and acute respiratory infection. Severe CDI was defined as the presence of any of the following severity markers at any time during the episode: intensive care unit admission, sepsis/septicemia, shock, acute renal failure, megacolon, prolonged ileus, perforated intestine, colectomy, white blood cell count, C-reactive protein, serum creatinine, and albumin.

Medication use during the 90 days before the episode (prior use) and during or up to 60 days after the episode (concomitant use) were collected for non-CDI antibiotics (excludes oral vancomycin, metronidazole, fidaxomicin, rifaximin, and nitazoxanide), non-CDI high-risk antibiotics (third- and fourth-generation cephalosporins, fluoroquinolones, and clindamycin), gastric acid-suppressing drugs (antacids, histamine 2 blockers, and proton pump inhibitors), antidiarrhea medications, narcotics, and bowel prep medications.

Severe CDI was defined as any of the following: intensive care unit admission, sepsis, shock, acute renal failure, megacolon, prolonged ileus, perforated intestine, white blood cell count ≥15,000 cells/μL, C-reactive protein ≥160 mg/L, albumin <2.5 g/dL, serum creatinine >1.5 mg/dL, or colectomy. Mortality was defined as death from any cause within the 30, 60, or 90 days following CDI treatment discontinuation. CDI recurrence was defined as a CDI inpatient or outpatient episode identified with a second CDI ICD-9-CM code within the 30, 60, or 90 days following the initial episode and with a minimum 3-day gap between initial therapy discontinuation and new therapy initiation. Hospital length of stay was defined as date of discharge minus date of admission plus 1 day.

Data extraction and variable creation were conducted using SAS version 9.2 (SAS Institute Inc, Cary, NC). All other data and statistical analyses were conducted using JMP version 13.0 (SAS Institute Inc).

All independent and dependent variables were first presented descriptively. For baseline characteristics (eg, sex, race, and ethnicity), we included a missing category. Other variables that were absent from the medical chart (eg, comorbidities) were assumed to have not occurred.[7,8] Baseline characteristics were compared among patients with each surveillance definition using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. Because of the large sample size, a P value < .0001 was considered statistically significant.

We described the epidemiology of CDI first episodes from fiscal year (FY) 2003 to FY 2014. We first presented CDI type descriptively as the proportion of patients with each surveillance definition. We then described trends longitudinally, with FY as the independent variable, and the surveillance definition as the dependent variable. Finally, we assessed CDI onset type as an independent risk factor for specific outcomes using a series of logistic regression models. CDI outcomes (severe CDI; 30-, 60-, and 90-day mortality; and hospital length of stay ≥14 days) served as the dependent variables and CDI onset-type as the independent variable. For recurrence analyses, we excluded those patients who died before the recurrence. CA-CDI was assigned as the reference category. Control variables included all independent variables listed in Table 1 that were statistically significant between groups at P value < .0001 and occurred in at least 5% of the population. For severe CDI, the model excluded individual severity indicators as covariates. The results were presented as odds ratios (ORs) and 95% confidence intervals (CIs).

RESULTS

Baseline characteristics

Overall 30,326 patients met study inclusion criteria. Table 1 describes the patients' baseline characteristics by CDI type. Patients

Table 1
Baseline characteristics

Characteristic	CA-CDI (n = 5,830)	CO-HCFA-CDI (n = 6,236)	HCFO-CDI (n = 18,260)	*P* value
Age, y	66 (78-59)	68 (61-79)	68 (60-78)	< .0001
Male sex	92.8	96.4	96.7	< .0001
Race & ethnicity				< .0001
Non-Hispanic white	68.3	68.1	65.0	
Non-Hispanic black	19.4	20.7	21.7	
Hispanic	5.4	5.3	5.4	
Other	3.7	3.6	4.8	
Missing	3.2	2.3	3.1	
Principal CDI diagnosis	43.1	48.2	16.5	< .0001
Comorbidities				
Hypertension	71.4	82.9	77.8	< .0001
Dyslipidemia	53.5	60.3	53.0	< .0001
Obesity	16.4	17.9	16.0	.0022
Myocardial infarction	6.3	13.7	12.1	< .0001
Congestive heart failure	17.9	31.3	27.7	< .0001
Peripheral vascular disease	13.4	22.4	20.3	< .0001
Cerebrovascular disease	14.7	21.3	20.4	< .0001
Dementia	2.4	3.9	4.1	< .0001
COPD	31.6	43.5	38.0	< .0001
Rheumatologic disease	2.4	3.1	2.8	.0337
Peptic ulcer disease	2.9	5.1	5.1	< .0001
Liver disease	6.1	7.9	7.3	.0007
Diabetes	35.8	43.7	41.9	< .0001
Hemiplegia or paraplegia	2.7	4.1	4.6	< .0001
Renal disease	21.7	33.7	28.6	< .0001
Cancer	21.7	30.8	30.6	< .0001
HIV/AIDS	1.9	1.9	1.9	.9300
GERD	27.2	31.3	25.5	< .0001
Transplant	2.0	2.5	1.8	.0083
Inflammatory bowel disease	4.3	2.8	1.7	< .0001
Irritable bowel syndrome	1.7	1.2	0.9	< .0001
Charlson score	2 (1-5)	4 (2-6)	4 (2-6)	< .0001
Concomitant infections				
Bacteremia	4.0	6.0	8.3	< .0001
Pneumonia	13.6	17.7	27.9	< .0001
Skin infection	6.8	9.3	12.8	< .0001
Intra-abdominal infection	7.2	6.0	5.6	< .0001
Device-related infection	1.8	2.3	4.0	< .0001
Acute respiratory infection	3.4	3.2	3.5	.4068
Endocarditis	0.5	3.2	1.3	< .0001
Urinary tract infection	1.4	1.3	2.1	< .0001
CDI severity indicators				
Intensive care unit admission	2.2	2.8	3.8	< .0001
Sepsis/septicemia	11.9	17.6	19.6	< .0001
Shock	3.4	5.2	5.7	< .0001
Acute renal failure	24.1	30.2	33.1	< .0001
Megacolon	0.3	0.4	0.3	.6089
Prolonged ileus	2.7	2.9	4.9	< .0001
Perforated intestine	0.2	0.5	0.6	.0004
WBC ≥15,000 cells/μL	30.1	37.1	42.8	< .0001
CRP ≥160 mg/L	1.2	1.1	2.0	< .0001
Albumin <2.5 g/dL	21.9	27.3	38.2	< .0001
SCr >1.5 mg/dL	20.0	27.0	24.8	< .0001
Colectomy	0.1	0.2	0.1	.0129
Medications				
Prior antibiotics	38.3	86.4	52.5	< .0001
Prior high-risk antibiotics	20.6	67.1	34.4	< .0001
Prior GAS drugs	39.2	78.4	55.4	< .0001
Prior narcotics	25.3	53.1	38.4	< .0001
Prior antidiarrheals	8.3	12.6	5.8	< .0001
Prior bowel prep	7.4	23.1	15.8	< .0001
Concomitant antibiotics	42.4	68.3	84.8	< .0001
Concomitant high-risk antibiotics	35.0	45.9	60.3	< .0001
Concomitant GAS drugs	65.0	77.6	84.4	< .0001
Concomitant narcotics	36.7	45.9	57.6	< .0001
Concomitant antidiarrheals	9.9	12.7	11.3	< .0001
Concomitant bowel prep	11.4	12.5	24.4	< .0001

NOTE. Values are presented as median (interquartile range) or %.
CA-CDI, community-associated CDI; *CDI*, *Clostridium difficile* infection; *COPD*, chronic obstructive pulmonary disease; *CO-HCFA-CDI*, community-onset, health care facility-associated CDI; *CRP*, C-reactive protein; *GAS*, gastric acid-suppressing; *GERD*, gastroesophageal reflux disease; *HCFO-CDI*, health care facility-onset CDI; *Scr*, serum creatinine; *WBC*, white blood cells.

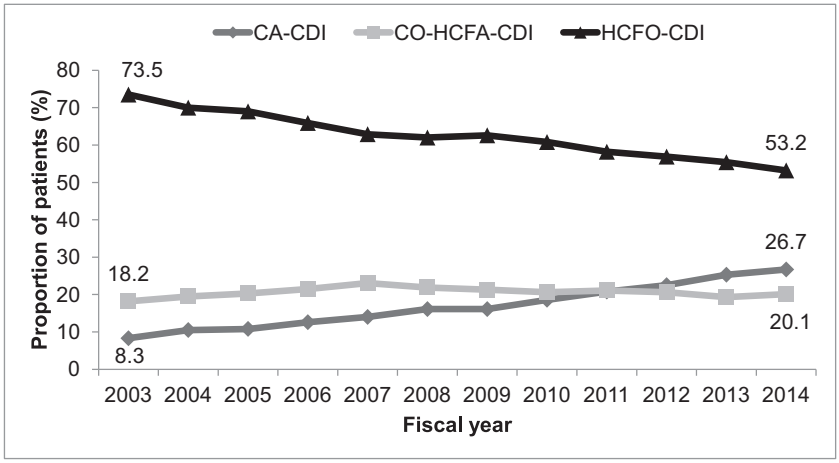

Fig 1. Proportion of patients with each *Clostridium difficile* infection (CDI) type from fiscal year 2003 to fiscal year 2014 (N = 30,326). *CA-CDI*, community-associated CDI; *CO-HCFA-CDI*, community-onset, health care facility-associated CDI; *HCFO-CDI*, health care facility-onset CDI.

with HCFO-CDI, CO-HCFA-CDI, and CA-CDI differed with respect to demographic characteristics, comorbidities, and medications received. Overall, patients with HCFO-CDI tended to have more comorbid conditions, more severe CDI indicators, and a higher proportion of prior or concomitant high-risk medication use.

CDI type and outcomes

A total of 18,260 (60.2%) patients were classified as HCFO-CDI. Among community-onset patients, 20.6% were classified as CO-HCFA-CDI and 19.2% were classified as CA-CDI.

There was a shift from HCFO-CDI to CA-CDI over the study period (Figure 1). The proportion of patients with HCFO-CDI decreased from 73.5% during FY 2003 to 53.2% during FY 2014, whereas CA-CDI increased from 8.3% during FY 2003 to 26.7% during FY 2014. The proportion of patients with CO-HCFA-CDI remained relatively stable over the study period.

Overall, patients with HCFO-CDI had the highest rates of severe CDI (70.2%); 30-day (24.5%), 60-day (29.4%), and 90-day (32.6%) mortality; and hospital length of stay ≥14 days (62.5%) compared with patients with CA-CDI or CO-HCFA-CDI (Table 2). Alternatively, patients with HCFO-CDI had the lowest rates of 30-day (7.2%), 60-day (9.5%), and 90-day (10.6%) recurrence. Patients with CO-HCFA-CDI had higher rates of severe CDI, mortality, and length of stay ≥14 days, but similar recurrence rates compared with CA-CDI. In multivariable models, HCFO-CDI was a positive independent predictor of severe CDI (OR, 1.71; 95% CI, 1.59-1.84), 30-day mortality (OR, 1.46; 95% CI, 1.32-1.61), 60-day mortality (OR, 1.48; 95% CI, 1.35-1.62), 90-day mortality (OR, 1.54, 95% CI, 1.41-1.68), and hospital length of stay ≥14 days (OR, 3.56; 95% CI 3.26-3.89). HCFO-CDI was a negative predictor of 30-day recurrence (OR, 0.41; 95% CI, 0.37-0.46), 60-day recurrence (OR, 0.40; 95% CI, 0.37-0.45), and 90-day recurrence (OR, 0.41; 95% CI, 0.37-0.46).

DISCUSSION

This study documents the burden of CDI by onset type among all adult VHA enrollees over a 12-year period. We found that HCFO-CDI remains the predominant CDI type, but community-onset cases are on the rise. Furthermore, we found that HCFO-CDI patients often

Table 2
Clostridium difficile infection (CDI health outcomes by CDI type, N = 30,326)

Outcome	CA-CDI (n = 5,830)	CO-HCFA-CDI (n = 6,236)	HCFO-CDI (n = 18,260)
Severe CDI*	50.0	61.1	70.2
	1.00 (reference)	**1.34 (1.23-1.46)**	**1.71 (1.59-1.84)**
30-d mortality†	12.4	18.5	24.5
	1.00 (reference)	**1.22 (1.09-1.37)**	**1.46 (1.32-1.61)**
60-d mortality†	14.8	23.7	29.4
	1.00 (reference)	**1.36 (1.22-1.51)**	**1.48 (1.35-1.62)**
90-d mortality†	16.2	26.7	32.6
	1.00 (reference)	**1.40 (1.26-1.56)**	**1.54 (1.41-1.68)**
30-d recurrence†	19.0	20.6	7.2
	1.00 (reference)	1.02 (0.91-1.14)	**0.41 (0.37-0.46)**
60-d recurrence†	23.3	26.3	9.5
	1.00 (reference)	1.03 (0.93-1.14)	**0.40 (0.37-0.45)**
90-d recurrence†	24.8	28.1	10.6
	1.00 (reference)	1.02 (0.91-1.15)	**0.41 (0.37-0.46)**
Hospital length of stay ≥14 d†	21.3	28.2	62.5
	1.00 (reference)	**1.43 (1.28-1.59)**	**3.56 (3.26-3.89)**

NOTE. Boldface type indicates statistical significance compared with CA-CDI. Values are presented as % and odds ratio (95% confidence interval).
*Multivariable logistic regression covariates included age, sex, race, principal CDI diagnosis, hypertension, dyslipidemia, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, diabetes, renal disease, cancer, GERD, bacteremia, pneumonia, skin infection, prior and concomitant gastric acid-suppressing drugs, prior and concomitant antibiotics, prior and concomitant narcotics, prior and concomitant antidiarrheals, and prior and concomitant bowel prep.
†Multivariable logistic regression covariates included those listed above, plus sepsis, acute renal failure, white blood cell count ≥15,000 cells/μL and albumin <2.5 g/dL.

have higher rates of severe CDI and mortality and longer hospital stays, but fewer CDI recurrences compared with CA-CDI and CO-HCFA-CDI. Our study is the first to describe health outcomes among patients according to all 3 CDI surveillance definitions. Our study is strengthened by the large national sample and comprehensive data collection.

Similar to prior studies, we found that the majority of patients developed CDI in the hospital.[1,3,9-11] In addition, those patients who developed CDI in the community often had recent health care exposure. We found a shift from HCFO-CDI to CA-CDI over the study period. This could be due to several reasons. First, there has been an increase in the use of high-risk antibiotics, such as fluoroquinolones, in the community.[12] This more frequent use could result in a greater number of community-dwelling patients developing CDI. Furthermore, there has also been a significant increase in other high-risk medications, such as proton pump inhibitors, in the community, which could also contribute to higher CDI rates.[13] Finally, there has been an increase in the number of elderly patients admitted to long-term care facilities. These facilities serve as reservoirs for *C difficile* and have been previously identified as a risk factor for the development of CDI.[14] In line with our findings, a prior study by Jen et al[15] found an increase in the proportion of probable community-acquired CDI of 6% over a 12-year study period (from 7% during 1998 to 13% during 2010) using data from English Hospital Episode Statistics.

Importantly, patients with HCFO-CDI had significantly worse outcomes compared with community-onset CDI. Garg et al[9] found that patients with HCFO-CDI have significantly higher intensive care unit admission (26% vs 3.5%), median hospital length of stay (10 vs 4 days), and median number of comorbidities (2 vs 1). Patients presenting from the community are also traditionally younger, placing them at lower risk for poor health outcomes. Khanna et al[16] found that patients with CA-CDI were younger (median, 50 years vs 72 years), had lower comorbidity scores, were less likely to have severe infection (20% vs 31%), and were less likely to have been exposed to antibiotics (78% vs 94%). In addition, patients with CA-CDI often do not present with traditional risk factors for CDI. In a study of 984 patients with CA-CDI, 36% had not received antibiotics during the prior 12 weeks, 18% had no recent health care exposure, and 40% had low-level outpatient exposure.[4] Further research is needed to more accurately predict CDI risk among community-dwelling patients.

We found that patients with HCFO-CDI have lower rates of recurrence compared with CA-CDI. This reason for this association is unclear. We hypothesize that these patients may receive more aggressive therapy in the inpatient setting, thus decreasing their likelihood for recurrence. Additionally, known risk factors for recurrence may be more easily minimized in controlled hospital environments. However, this association may also represent the use of outdated CDI surveillance definitions. These definitions date back to a CDC working group in 2007, and no longer fully describe the settings in which CDI exposure occurs in the evolving landscape of our health care system.[4,5,17] For example, to be considered CO-HCFA-CDI a patient must have a history of hospitalization with a minimum inpatient stay of 48 hours. This narrow definition fails to include a growing population of patients with outpatient or inpatient day procedures occurring at dialysis centers, transplant centers, or chemotherapy clinics that may serve as community reservoirs of spores. These patients are at high risk of recurrence due to repeated exposures or immunosuppression but are currently defined as CA-CDI.

The need for hospitalization has tremendous impact on health care costs and patient outcomes. Hospitalization inadvertently exposes patients to other risks, avoidable complications, and other nosocomial infections. Therefore, patients with CA-CDI who are older or who have higher comorbidity burden, should be monitored closely and managed more aggressively in the community to prevent poor outcomes.

There are potential limitations to this study. First, our use of a retrospective cohort study design might be subject to misclassification bias and confounding, particularly due to the use of electronic medical data that is not collected for primary research purposes. Our study attempted to minimize misclassification of CDI by defining CDI cases as ICD-9-CM codes and positive microbiologic data. We limited confounding using multivariable modeling with covariates likely to affect study outcomes; however, we cannot determine whether outcomes were specifically attributable to CDI rather than other unmeasured variables. Next, the large study sample size increases the likelihood of detecting statistically significant differences between groups; therefore, absolute group differences should be considered along with *P* values. Finally, the veteran population, which is predominately male, might limit the generalizability of our findings to other settings.

CONCLUSIONS

HCFO-CDI was the predominant CDI onset type among a national cohort of adult veterans. The proportion of patients with CA-CDI and CO-HCFA-CDI increased in recent years, whereas HCFO-CDI decreased. Patients with HCFO-CDI experienced higher rates of severe CDI and mortality and longer hospital stays, but fewer CDI recurrences.

References

1. Centers for Disease Control and Prevention. Vital signs: preventing *Clostridium difficile* infections. MMWR Morb Mortal Wkly Rep 2012;61:157-62.
2. Lessa FC, Winston LG, McDonald LC. Emerging infections program CdST. Burden of *Clostridium difficile* infection in the United States. N Engl J Med 2015;372:2369-70.
3. Kutty PK, Woods CW, Sena AC, Benoit SR, Naggie S, Frederick J, et al. Risk factors for and estimated incidence of community-associated *Clostridium difficile* infection, North Carolina, USA. Emerg Infect Dis 2010;16:197-204.
4. Chitnis AS, Holzbauer SM, Belflower RM, Winston LG, Bamberg WM, Lyons C, et al. Epidemiology of community-associated *Clostridium difficile* infection, 2009 through 2011. JAMA Intern Med 2013;173:1359-67.
5. McDonald LC, Coignard B, Dubberke E, Song X, Horan T, Kutty PK. Recommendations for surveillance of *Clostridium difficile*-associated disease. Infect Control Hosp Epidemiol 2007;28:140-5.
6. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-9.
7. Shapiro NI, Wolfe RE, Moore RB, Smith E, Burdick E, Bates DW. Mortality in Emergency Department Sepsis (MEDS) score: a prospectively derived and validated clinical prediction rule. Crit Care Med 2003;31:670-5.
8. Huang CC, Kuo SC, Chien TW, Lin HJ, Guo HR, Chen WL, et al. Predicting the hyperglycemic crisis death (PHD) score: a new decision rule for emergency and critical care. Am J Emerg Med 2013;31:830-4.
9. Garg S, Mirza YR, Girotra M, Kumar V, Yoselevitz S, Segon A, et al. Epidemiology of *Clostridium difficile*-associated disease (CDAD): a shift from hospital-acquired infection to long-term care facility-based infection. Dig Dis Sci 2013;58:3407-12.
10. Dubberke ER, Butler AM, Yokoe DS, Mayer J, Hota B, Mangino JE, et al. Multicenter study of surveillance for hospital-onset *Clostridium difficile* infection by the use of ICD-9-CM diagnosis codes. Infect Control Hosp Epidemiol 2010;31:262-8.
11. Price MF, Dao-Tran T, Garey KW, Graham G, Gentry LO, Dhungana L, et al. Epidemiology and incidence of *Clostridium difficile*-associated diarrhoea diagnosed upon admission to a university hospital. J Hosp Infect 2007;65:42-6.
12. Linder JA, Huang ES, Steinman MA, Gonzales R, Stafford RS. Fluoroquinolone prescribing in the United States: 1995 to 2002. Am J Med 2005;118:259-68.
13. Rotman SR, Bishop TF. Proton pump inhibitor use in the U.S. ambulatory setting, 2002-2009. PLoS ONE 2013;8:e56060.
14. McFarland LV, Mulligan ME, Kwok RY, Stamm WE. Nosocomial acquisition of *Clostridium difficile* infection. N Engl J Med 1989;320:204-10.
15. Jen MH, Saxena S, Bottle A, Pollok R, Holmes A, Aylin P. Assessment of administrative data for evaluating the shifting acquisition of *Clostridium difficile* infection in England. J Hosp Infect 2012;80:229-37.
16. Khanna S, Keddis MT, Noheria A, Baddour LM, Pardi DS. Acute kidney injury is an independent marker of severity in *Clostridium difficile* infection: a nationwide survey. J Clin Gastroenterol 2013;47:481-4.
17. Bloomfield LE, Riley TV. Epidemiology and risk factors for community-associated *Clostridium difficile* infection: a narrative review. Infect Dis Ther 2016;5:231-51.