ORIGINAL ARTICLE

Epidemiology and Healthcare Costs of Incident *Clostridium difficile* Infections Identified in the Outpatient Healthcare Setting

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OBJECTIVE. To describe the epidemiology and healthcare costs of *Clostridium difficile* infection (CDI) identified in the outpatient setting.

DESIGN. Population-based, retrospective cohort study.

PATIENTS. Kaiser Permanente Colorado and Kaiser Permanente Northwest members between June 1, 2005, and September 30, 2008.

METHODS. We identified persons with incident CDI and classified CDI by whether it was identified in the outpatient or inpatient healthcare setting. We collected information about baseline variables and follow-up healthcare utilization, costs, and outcomes among patients with CDI. We compared characteristics of patients with CDI identified in the outpatient versus inpatient setting.

RESULTS. We identified 3,067 incident CDIs; 56% were identified in the outpatient setting. Few strong, independent predictors of diagnostic setting were identified, although a previous stay in a nonacute healthcare institution (odds ratio [OR], 1.45 [95% confidence interval (CI), 1.13–1.86]) was statistically associated with outpatient-identified CDI, as was age from 50 to 59 years (OR, 1.64 [95% CI, 1.18–2.29]), 60 to 69 years (OR, 1.37 [95% CI, 1.03–1.82]), and 70 to 79 years (OR, 1.36 [95% CI, 1.06–1.74]), when compared with persons aged 80–89 years.

CONCLUSIONS. We found that more than one-half of incident CDIs in this population were identified in the outpatient setting. Patients with outpatient-identified CDI were younger with fewer comorbidities, although they frequently had previous exposure to healthcare. These data suggest that practitioners should be aware of CDI and obtain appropriate diagnostic testing on outpatients with CDI symptoms.

Infect Control Hosp Epidemiol 2012;33(10):1031-1038

Clostridium difficile infection (CDI) is the most common cause of healthcare-associated infectious diarrhea in the United States.[1,2] CDI was once thought to occur almost exclusively among hospitalized patients, an assumption that was partly based on the clustering of the strongest risk factors for CDI (ie, antimicrobial use, advanced age, underlying comorbidity) among hospitalized populations and the surveillance for CDI in the inpatient setting.[2-4] As a result, physicians in ambulatory practice may not consider CDI as a diagnosis among their patients.

Recent research has suggested that CDI is emerging as an important but underdiagnosed infection in the general, nonhospitalized population.[5-11] However, additional evidence is needed to evaluate the potential predictors, outcomes, and healthcare costs associated with CDI identified and managed in the outpatient setting. Furthermore, surveillance for CDI is primarily conducted among inpatients within healthcare facilities and is focused on the setting in which a patient acquired *C. difficile*.[12] Although these surveillance efforts are effective for the identification of CDIs occurring during hospitalization,[12] they do not account fully for infections that occur or are diagnosed in the outpatient setting. Thus, the prevalence of CDI identified in ambulatory populations is unclear, as are any differences between patients presenting with CDI in the outpatient setting versus the inpatient setting.

To address these knowledge gaps, we conducted a retrospective cohort study to (1) describe the epidemiology of CDI identified in the outpatient setting, (2) estimate healthcare costs among patients with CDI, and (3) provide comparisons in the distribution of potential risk factors among patients with outpatient- versus inpatient-identified CDI.

METHODS

We conducted a population-based, retrospective cohort study among Kaiser Permanente Colorado and Kaiser Permanente Northwest members between June 1, 2005, and September 30, 2008. During the study time period, Kaiser Permanente

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Received February 10, 2012; accepted May 4, 2012; electronically published August 23, 2012.

 0899-823X/2012/3310-0010$15.00. DOI: 10.1086/667733

Northwest and Kaiser Permanente Colorado collectively had a membership of approximately 900,000 on any given day. Data on patient membership, pharmacy dispensings, demographics, and clinical measures were collected from regional electronic databases. The study was reviewed and approved by the Institutional Review Boards at both health plans.

Identification and Categorization of *Clostridium difficile* Infections and Follow-Up

In the outpatient setting, we identified CDIs through (1) a diagnosis of *International Classification of Diseases, Ninth Revision* (ICD-9) code 008.45 (intestinal infection due to *C. difficile*) or (2) a positive *C. difficile* toxin test. We further required that positive toxin tests be associated with metronidazole or vancomycin dispensed in the outpatient pharmacy in the 7 days before or after a positive test. All CDIs in the inpatient setting were identified by ICD-9 code 008.45; that code's sensitivity and specificity has been shown to be high for inpatients.[13,14] The index date of CDI was defined as the date on which the first indication of CDI occurred (eg, date of *C. difficile* diagnosis, positive toxin test result, or metronidazole or vancomycin dispensing). Both health plans consistently utilized the Meridian Premier toxin A/B enzyme immunoassay (Meridian Bioscience) during the study time period. For inpatient-identified CDIs, the index date was the admission date for the hospitalization during which the infection was diagnosed. We then categorized CDIs by the setting (inpatient or outpatient) in which they were first identified.

Patients were required to have continuous membership in the health plan and prescription drug coverage for at least 1 year before the CDI index date. Exclusion criteria were a recorded history of a prior CDI in the 180 days before the index date, as evidenced by a *C. difficile* diagnosis, a positive *C. difficile* toxin test, or an outpatient prescription fill for vancomycin. For patients with more than 1 CDI during the study time period, we used the first incident CDI for data collection and analysis.

Measurement of Potential Risk Factors for CDI Identified in the Outpatient Setting

We assessed patient demographic characteristics and comorbidity in the 365 days before the CDI index date. Healthcare utilization and outpatient prescription medication use were gathered for the preceding 180 days to ensure incident events; however, only 60 days of history for these exposures were used in the model to predict the setting of CDI identification.

To measure underlying comorbidity, we determined whether persons with CDI were diagnosed with cardiovascular disease, chronic pulmonary disease, diabetes, inflammatory bowel disease, liver disease, malignancy and metastatic tumors, or rheumatologic disease, as identified by ICD-9 diagnosis codes (codes available on request). We used estimated glomerular filtration rates to evaluate renal function[15] and hemoglobin laboratory values to identify anemia. A history of immunosuppression or chemotherapy was identified through diagnosis and procedure codes or medication utilization. Healthcare utilization was measured at baseline by identifying inpatient and outpatient healthcare encounters or an admission to a nonacute healthcare institution.

We identified prescription medications filled at outpatient pharmacies in the preceding 60 days, specifically, antimicrobials, gastric acid suppressants (including proton pump inhibitors and histamine-2 receptor antagonists), statins, and chronic oral corticosteroids. We did not evaluate exposure to medications during hospital admissions. We examined receipt of selected antimicrobials, number of unique antimicrobials received, and timing of the receipt of antimicrobials in relation to the CDI index date. Antimicrobials were categorized by class, although we also created a category for other antimicrobials that included clindamycin, daptomycin, linezolid, metronidazole, rifampin, telithromycin, synercid, and tigecycline. Use of gastric acid suppressants and statins was categorized as never received or ever received. Chronic corticosteroid use was defined as at least a 90-day supply dispensed in the previous 180 days.

Measurement of Healthcare Utilization and Adverse Events following Outpatient-Identified CDI

We measured the occurrence of outpatient visits, emergency department visits, and hospitalizations listing a diagnosis of ICD-9 code 008.45 in the 180-day time period including and following the index date of CDI. For patients with outpatient-identified CDI who were subsequently hospitalized, we reported time from outpatient diagnosis of CDI to hospital admission. In addition, we collected information about all-cause mortality among patients with CDI. Patients were included in this analysis if they had 180 days of complete follow-up or complete follow-up until death during the 180-day time period after CDI. It should be noted that we did not include a non-CDI comparison group, so these follow-up findings should not be construed to imply attribution to CDI.

Statistical Analyses

We calculated summary statistics for demographic characteristics, healthcare utilization, comorbid conditions, and medication use. We utilized a logistic regression model to determine how strongly baseline characteristics predict outpatient-identified versus inpatient-identified CDIs. Patients were excluded from modeling if they had missing values for covariates. Covariates were not selected on the basis of statistical significance.[16] Instead, we initially included all covariates and excluded only those that measured a concept similar to another variable in the model (eg, number of antimicrobial agents). Thus, our model is a full model, and, as recommended by Harrell,[16] we minimized potential overfitting by allowing at least 20 CDI events per degree of freedom. All

TABLE 1. Baseline Demographic Characteristics and Healthcare Utilization of Patients with *Clostridium difficile* Infections Identified in the Outpatient and Inpatient Settings

	Outpatient setting (n = 1,712)		Inpatient setting (n = 1,355)	
Variable	No.	%	No.	%
Age, mean, years (SD)	62.8 (19.4)		69.9 (16.3)	
Age, years				
0–9[a]	≤5	≤1	≤5	≤1
10–19[a]	≤5	≤1	≤5	≤1
20–29	67	3.9	16	1.2
30–39	108	6.3	38	2.8
40–49	165	9.6	86	6.3
50–59	283	16.5	158	11.7
60–69	309	18.0	250	18.5
70–79	363	21.2	346	25.5
80+	378	22.1	445	32.8
Sex				
Female	1,098	64.1	766	56.5
Male	614	35.9	589	43.5
Body mass index, mean (SD)	27.4 (6.5)		27.3 (7.2)	
History of hospital admission				
In previous 30 days	455	26.6	576	42.5
In previous 60 days	645	37.7	740	54.6
In previous 90 days	720	42.1	796	58.8
In previous 180 days	797	46.6	873	64.4
History of a stay in a nonacute healthcare institution				
In previous 30 days	307	17.9	331	24.3
In previous 60 days	355	20.7	378	27.9
In previous 90 days	366	21.4	398	29.4
In previous 180 days	392	22.9	429	31.7
No. of outpatient physician visits, mean (SD)	8.5 (9.0)		10.5 (12.6)	

[a] Exact data are not reported because cell counts are less than 6.

odds ratios (ORs) were simultaneously adjusted for other characteristics in the logistic regression model.

Calculation of Healthcare Costs Associated with *Clostridium difficile* Infection

We calculated healthcare costs in the 180-day time period including and following the first occurrence of CDI among patients with complete follow-up during that time. We based our costing method on previously developed procedures.[17] For outpatient costs, standard prices were created for office visits by specialty, department, and type of clinician (eg, physician, physician assistant). The number of visits (per department and clinician type) for each patient was then multiplied by the appropriate unit price. Medication costs approximate retail prices within the local community and were based on Kaiser Permanente Northwest only. Hospitalizations were classified into diagnosis-related groups, and the average daily rate per diagnosis-related groups was then multiplied by the length of stay. Laboratory testing costs were derived from the 2009 Centers for Medicare and Medicaid Services Medicare fee schedule. All costs are reported in 2009 US dollars, using year-specific inflation factors from the US Bureau of Labor and Statistics.

RESULTS

Between June 1, 2005, and September 30, 2008, we identified 3,067 CDIs. Of these, 1,712 (56%) were identified in the outpatient setting. Among CDI cases in the outpatient setting, 62% were identified through a positive toxin test, with the remaining 38% being identified through an ICD-9 code alone. All of the CDIs identified in the outpatient setting through a positive toxin test also received treatment for CDI.

The majority of CDIs occurred among persons 65 years and older, although individuals with outpatient-identified CDI were, on average, nearly 7 years younger than those with inpatient-identified CDI (Table 1). Persons with outpatient-identified CDI were less likely to have a history of hospitalization or a stay in a nonacute healthcare institution than those with inpatient-identified CDI (Table 1). Furthermore, the majority of comorbid conditions was less prevalent among patients with outpatient-identified CDI in the 1 year before infection (Table 2).

TABLE 2. Prevalence of Comorbid Conditions in the 1 Year before *Clostridium difficile* Infection Identified in the Outpatient and Inpatient Settings

	Outpatient setting (n = 1,712)		Inpatient setting (n = 1,355)	
Comorbid condition	No.	%	No.	%
Cardiovascular disease	506	29.6	762	56.2
Chronic pulmonary disease	519	30.3	577	42.6
Rheumatologic disease	88	5.1	82	6.1
Liver disease	31	1.8	59	4.4
Diabetes	350	20.4	456	33.7
Malignancy or metastatic solid tumor	215	12.6	355	26.2
Inflammatory bowel disease	39	2.3	72	5.3
Immunosuppression	299	17.5	446	32.9
Chemotherapeutic procedures or therapies	329	19.2	384	28.3
Anemia[a]	404	23.6	529	39
Renal function, eGFR				
≥60	964	56.3	636	46.9
30–59	379	22.1	428	31.6
15–29	54	3.2	105	7.8
<15	20	1.2	80	5.9

NOTE. eGFR, estimated glomerular filtration rate.

[a] Patients are defined as anemic if the blood test performed closest to but before the incidence date had a hemoglobin result of less than 12 mg/dL.

Antimicrobials were dispensed from an outpatient pharmacy to 78% of persons with outpatient-identified CDI in the previous 60 days (Table 3). The percentage of patients with outpatient-identified CDI who received an outpatient antimicrobial dispensing increased to 86% when the exposure time window was increased to 180 days. Patients with CDI had commonly received fluoroquinolones (outpatient-identified CDI, 30%; inpatient-identified CDI, 33.6%) or cephalosporins (outpatient-identified CDI, 20.6%; inpatient-identified CDI, 20.3%; Table 3). Furthermore, persons with outpatient-identified CDI received gastric acid suppression, statins, and chronic oral corticosteroids from an outpatient pharmacy less frequently than persons with inpatient-identified CDI, although these medications were received by a minority of patients (Table 3).

Nearly half (45%) of outpatient-identified CDI cases and about one-fourth (26.9%) of inpatient-identified CDI cases were associated with an additional CDI-related outpatient visit in the 180 days following infection (Table 4). Emergency department visits were far less common, at 5.7% and 2.7% for outpatient-identified and inpatient-identified CDI, respectively. The majority of patients with outpatient-identified CDI received at least 1 and, on average, 3.7 dispensings of CDI-related medication on or following their date of infection (Table 4). Further, of patients with outpatient-identified CDI, 10.5% were hospitalized with a CDI-related diagnosis code during the follow-up period. These hospitalizations occurred, on average, 27 days following outpatient identification of CDI and lasted an average of 10 days (Table 4). Additionally, 9.8% of persons with outpatient-identified CDI and 32.5% of persons with inpatient-identified CDI died from any cause in the 180 days following infection.

Outpatient care costs were higher among persons with CDI identified in the outpatient setting, with pharmacy representing the greatest percentage of these costs in either group. Similarly, patients with inpatient-identified CDI had higher inpatient costs than patients with outpatient-identified CDI ($10,708.40 vs $837.40; Table 5).

The logistic regression model utilized 1,279 outpatient-identified CDIs and 1,131 inpatient-identified CDIs (21% were removed because of missing values). Few individual patient characteristics were significantly associated with identification of CDI in the outpatient setting (Table 6). However, collectively, the 21 characteristics in the model discriminate CDIs identified in the outpatient setting from inpatient-identified CDIs with moderate effectiveness (c-statistic, 0.76). After controlling for all other covariates, a previous stay in a nonacute healthcare institution (OR, 1.45 [95% confidence interval (CI), 1.13–1.86]) was statistically associated with outpatient-identified CDI (Table 6). Age from 50 to 59 years (OR, 1.64 [95% CI, 1.18–2.29]), 60 to 69 years (OR, 1.37 [95% CI, 1.03–1.82]), and 70 to 79 years (OR, 1.36 [95% CI, 1.06–1.74]), when compared with age from 80 to 89 years, was also associated with outpatient-identified CDI.

DISCUSSION

We conducted this study to identify and describe patients with CDI diagnosed in the outpatient setting, as well as to characterize CDI-related healthcare utilization and costs

https://doi.org/10.1086/667733 Published online by Cambridge University Press

TABLE 3. Prevalence and Timing of Outpatient Medication Dispensings among Patients with *Clostridium difficile* Infections in the 180 Days before Identification in the Outpatient and Inpatient Settings

Variable	Outpatient setting (n = 1,712)		Inpatient setting (n = 1,355)	
	No.	%	No.	%
Any outpatient antimicrobial dispensing				
In previous 30 days	1,198	70.0	514	37.9
In previous 60 days	1,341	78.3	681	50.3
In previous 90 days	1,395	81.5	770	56.8
In previous 180 days	1,466	85.6	898	66.3
Antimicrobials dispensed, mean (SD)	1.9 (1.3)		1.3 (1.3)	
Antimicrobial classes				
Aminoglycosides	48	2.8	37	2.7
β-lactams/β-lactamase inhibitors	241	14.1	147	10.9
Cephalosporins	353	20.6	275	20.3
Fluoroquinolones	517	30.2	455	33.6
Macrolides	183	10.7	131	9.7
Penicillins	243	14.2	142	10.5
Sulfonamides	158	9.2	121	8.9
Tetracyclines	125	7.3	84	6.2
Other antimicrobials	1,021	59.6	274	20.2
Other medication use				
Any outpatient gastric acid suppressant dispensing[a]	658	38.4	623	46.0
Any outpatient statin dispensing	496	29.0	508	37.5
Chronic corticosteroid use[b]	82	4.8	109	8.0

[a] Includes proton pump inhibitor and histamine-2 receptor antagonist use.
[b] Defined as at least a 90-day supply dispensed in the 180 days before the incident date.

among these patients. We also compared baseline characteristics of persons with outpatient- and inpatient-identified CDI to help clinicians and researchers better understand how patients with CDI infections identified in the 2 settings may differ. We found that slightly more than one-half of incident CDIs were identified in the outpatient setting. These patients tended to be younger with less comorbidity than patients with CDI identified in the inpatient setting. Collectively, our results emphasize that CDI is being identified and treated among younger, healthier ambulatory populations.

Our study categorized patients by the setting in which infection was first identified rather than the setting where *C. difficile* was likely acquired (ie, community associated, healthcare facility associated). We acknowledge that widely used surveillance approaches that categorize infections by location in which a patient may have been exposed to *C. difficile* are important in identifying outbreaks and designing prevention efforts. However, the setting in which CDI is identified represents the first opportunity for clinicians to diagnose and intervene on infections. As such, our study is important for understanding characteristics of the growing number of patients presenting with CDI in the outpatient setting. In addition, our results suggest that a large number of CDIs are not captured by current efforts focused on CDI among hospitalized patients. This knowledge can inform efforts to improve timely clinical recognition and treatment of infection among outpatients, thus potentially preventing prolonged illness, adverse outcomes, and additional healthcare utilization.

We found few apparent differences between patients with CDI in either setting, with the exception that patients with outpatient-identified CDI were younger and had lower comorbidity load. These observations could be a reflection of the differences in the demographic and clinical characteristics of ambulatory and hospitalized patients rather than a difference in epidemiology between the 2 settings. We also utilized a logistic regression model to compare persons with infections identified in the 2 settings. Almost all of the variables in our model were associated with identification of CDI among hospitalized patients rather than among outpatients. However, we did find that collectively, the 21 patient characteristics in the model adequately discriminated the setting in which CDI was identified (c-statistic, 0.76). This suggests that patients who seek outpatient care for CDI differ from patients with CDI identified in the inpatient setting, although it may be difficult for providers to anticipate the setting in which a patient will present with a CDI because the individual predictors are so subtle. Finally, because our study did not include a population without CDI, these results should not be used to infer any statistical differences between populations with CDI and those without.

A substantial proportion of CDI patients in our population were exposed to antimicrobials before identification of their

TABLE 4. Inpatient and Outpatient Healthcare Utilization for *Clostridium difficile* Infections (CDIs) in the 180-Day Time Period including and following Infection Identified in the Outpatient and Inpatient Settings, for Patients with Complete 180-Day Follow-Up

	Outpatient setting (n = 1,650)		Inpatient setting (n = 1,316)	
Variable	No.	%	No.	%
Subsequent hospitalization[a]	173	10.5	285	21.6
Cumulative days of hospitalization, mean (SD)	10.0 (17.0)		14.9 (20.9)	
Days between index date of CDI in outpatient setting and admission to a hospital, among patients with a hospitalization, mean (SD)	27.2 (33.1)		NA	
Patients with CDI with at least 1 outpatient visit	745	45.2	354	26.9
Outpatient visits among patients with at least 1 outpatient visit, mean (SD)	1.5 (1.1)		1.8 (1.4)	
Patients with at least 1 ED visit	94	5.7	35	2.7
ED visits among patients with at least 1 ED visit, mean (SD)	1.1 (.2)		1.0 (.2)	
Patients with CDI with at least 1 outpatient dispensing of oral metronidazole or oral vancomycin (%)	1,520	92.1	834	63.4
Treatment dispensings among patients with at least 1 outpatient dispensing of oral metronidazole or oral vancomycin, median (range)	3.7 (2.9)		8 (3.0)	

NOTE. Data include only outpatient visits, emergency department (ED) visits, and hospitalizations with *International Classification of Diseases, Ninth Revision* code 008.45 for CDI. NA, not applicable.

[a] Refers to initial hospitalization for patients with outpatient-identified CDI and rehospitalization among patients with inpatient-identified CDI.

infection. Still, 14% of patients with outpatient-identified CDI had not received an antimicrobial in the 180 days before CDI. In addition, although prior research has suggested that the majority of CDI in the outpatient setting may be attributed to inpatient exposures,[18] only 27% of our patients with outpatient-identified CDI had a history of hospitalization in the previous 30 days, the period of time used by the Centers for Disease Control and Prevention to define community-onset, healthcare facility–associated CDI. Taken together, our observations reinforce the fact that CDI is occurring among ambulatory patients who may be considered at low risk. Furthermore, these results suggest that a substantial proportion of these infections not only were identified in the outpatient setting but also were acquired there.

In our population, the impact of CDI on healthcare utilization and cost was most notable in the setting in which the patient's infection had been identified. For example, patients with outpatient-identified CDI were relatively more likely to seek additional outpatient care, while patients with inpatient-identified CDI were more likely to experience additional hospitalization. However, we found that patients with inpatient-identified CDI received a greater number of treatment dispensings from outpatient pharmacies even after their initial hospitalization, suggesting that disease was unresolved during hospitalization and illness was prolonged after hospital discharge.

Our study provides insight into the patterns of care for patients with CDI, although we must clarify that the cost estimates reported here should be viewed as ceiling estimates because they include visits with joint production of care. For example, the entire cost of care for a patient who experiences a CDI during a hospitalization for heart failure is reported, even though the patient will have also received heart failure care unrelated to CDI. Other investigators[19] have shown that about 30% of total hospital care costs for patients with concomitant CDI are attributable to the infection; thus, we might estimate that about one-third of the cost reported by our study is directly attributable to *C. difficile*. On the other hand, any infection control procedures related to CDI (eg, isolation) that may have been implemented in the hospital setting are not represented in our inpatient cost estimates.

Our study has a number of limitations. First, because of data limitations, we collected only information about outpatient prescription dispensings; as a result, we underestimate

TABLE 5. Healthcare Costs (in 2009 US Dollars) per Patient (All Patients) Associated with *Clostridium difficile* Infection (CDI) Episodes Identified in the Outpatient and Inpatient Settings in the 180-Day Time Period including and following the CDI Index Date, for Patients with Complete 180-Day Follow-Up

	Outpatient setting (n = 1,650)		Inpatient setting (n = 1,316)	
Variable	Cost	SD	Cost	SD
Outpatient care costs	859.40	2,049.40	606.30	1,944.50
Laboratory tests[a]	7.90	14.00	14.70	17.70
Pharmacy[b]	424.30	1,480.40	362.70	1,428.10
Telephone encounters	21.80	64.80	8.90	41.40
Outpatient visits	323.20	1,056.40	194.20	943.40
Emergency department	82.20	426.90	25.80	220.00
Inpatient care costs	837.40	4,327.70	10,708.40	32,389.00

NOTE. Data include utilization and costs from encounters with a *C. difficile* diagnosis in any position.

[a] Laboratory tests include *C. difficile* toxin tests only.

[b] Pharmacy costs include only outpatient dispensings of metronidazole or vancomycin.

https://doi.org/10.1086/667733 Published online by Cambridge University Press

TABLE 6. Baseline Patient Characteristics and How Strongly They Predicted Outpatient Identification of *Clostridium difficile* Infection (CDI) versus Inpatient Identification

Variable	Adjusted OR[a]	95% CI
Sex, female	1.18	0.98–1.42
Age, years		
<20	2.72	0.91–8.17
20–29	1.98	0.88–4.47
30–39	1.46	0.82–2.57
40–49	1.21	0.79–1.84
50–59	1.64	1.18–2.29
60–69	1.37	1.03–1.82
70–79	1.36	1.06–1.74
80+	Reference	...
Low socioeconomic status[b]	0.89	0.67–1.19
Body mass index (categorical)[c]	1.19	0.97–1.47
Cardiovascular disease	0.51	0.42–0.63
Chronic pulmonary disease	0.82	0.68–1.0
Rheumatologic disease	1.12	0.77–1.61
Liver disease (mild or moderate/severe)	0.56	0.34–0.94
Diabetes (with and without complications)	0.85	0.69–1.0
Cancer	0.54	0.43–0.68
Inflammatory bowel disease	0.42	0.26–0.67
Anemia[d]	0.84	0.68–1.03
Renal function, eGFR		
≥60	Reference	...
30–59	0.77	0.62–0.94
15–29	0.53	0.36–0.79
<15	0.25	0.14–0.46
Hospitalization in previous 60 days	0.78	0.63–0.96
Stay in a nonacute healthcare institution in previous 60 days	1.45	1.13–1.86
Outpatient physician visits in previous 60 days	1.00	0.98–1.02
Outpatient antimicrobial dispensing in previous 60 days	0.33	0.27–0.40
Outpatient gastric acid suppressant dispensing in previous 60 days[e]	1.17	0.97–1.42
Outpatient steroid dispensing in previous 60 days	1.08	0.75–1.55
Chemotherapy in previous 60 days	0.70	0.56–0.87
Immunosuppression in previous 60 days	0.61	0.45–0.83

NOTE. Patients with missing values (eg, laboratory findings) were excluded, which resulted in the inclusion of 1,131 inpatient CDIs and 1,279 outpatient CDIs. CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

[a] Adjusted for all other covariates in the model.

[b] Low socioeconomic status defined as greater than 25% of census block with less than twelfth grade education or greater than 20% of census block below the federal family poverty level.

[c] Body mass index categorized as 30 or less and greater than 30, with 30 or less as the reference group.

[d] Patients are defined as anemic if the blood test performed closest to but before the incidence date had a hemoglobin result of less than 12 mg/dL.

[e] Includes proton pump inhibitor and histamine-2 receptor antagonist use.

medication exposures among hospitalized patients. In addition, because gastric acid suppressants are available over-the-counter, we could not measure use among patients who did not acquire these medications through prescription. Second, we identified patients with CDI in the inpatient setting through ICD-9 codes only. Although it would have been optimal to obtain results for *C. difficile* toxin testing from this population, the ICD-9 code for CDI has reasonable sensitivity and specificity for detecting cases in inpatient settings.[13,14] It is possible that CDIs identified through ICD-9 codes during a hospitalization may actually represent patients with a history of CDI. However, we believe that we minimized this possibility by requiring that patients have no evidence of CDI in the previous 180 days and by using only initial infections in our analysis. Moreover, we could not determine the date on which symptoms first occurred or CDI was diagnosed during a hospitalization; thus, data collection for these cases is based on the admission date of the hospitalization during which

CDI was diagnosed. In contrast, we used both ICD-9 codes and toxin test results to identify CDI in the outpatient setting and required patients with a positive toxin test result to also have a *C. difficile* diagnosis or evidence of CDI treatment. Thus, we likely identified the majority, if not all, of the cases occurring in the outpatient setting. Finally, although we were able to measure potential risk factors (eg, patterns of antimicrobial use) among the patients in this study, we do not know whether they differ from background rates of exposures and patient characteristics of the general outpatient and inpatient populations.

Our study documented that slightly more than one-half of all CDIs occurring in our population were identified in the outpatient setting; thus, we conclude that CDI demands greater attention in the outpatient setting. Our results suggest that obvious risk factors for CDI in the outpatient setting may be lacking; nevertheless, clinicians should obtain appropriate diagnostic testing on outpatients with potential CDI.

ACKNOWLEDGMENTS

We gratefully acknowledge the analytic efforts and expertise of Karen Glenn in this work.

Financial support. This study was supported by Sanofi Pasteur. A draft of the manuscript was made available to the funding source for review; however, publication was not contingent on their approval of study results or manuscript content.

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

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Presented in part: 17th Annual HMO Research Network Conference; Boston, Massachusetts; March 23–25, 2011.

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