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Predictors and Outcomes of Readmission for *Clostridium difficile* in a National Sample of Medicare Beneficiaries

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Abstract
Background Rates of *Clostridium difficile* (CD) infections are increasing. Elderly patients may be at particular risk of recurrent CD infection. Little is known about the risk for CD readmission specifically in this age group.
Methods A 5 % random sample of Medicare data (2009–2011) was queried for patients surviving a hospitalization for CD by ICD-9 code. Demographic (age, sex, gender), clinical (Elixhauser index, gastrointestinal comorbidities), and hospitalization (length of stay, ICU admission) characteristics as well as exposure to antibiotics and interim non-CD hospitalization were compared for those with and without a readmission for CD. A multivariable survival analysis was used to determine predictors of readmission.
Results Of 7,564 patients surviving a CD hospitalization, 8.5 % were readmitted with CD in a median of 25 days (interquartile range (IQR) 14–57). In multivariable survival analyses, interim non-CD hospital exposure was the strongest predictor of CD readmission (hazard ration (HR) 3.75 95 %, confidence interval (CI) 3.2–4.42). Oral and intravenous/intramuscular (IV/IM) antibiotic use, Elixhauser index, and CD as the primary diagnosis also increased the risk of CD readmission. Discharge to hospice, long-term care or a skilled nursing facility decreased the odds of CD readmission.
Conclusion Hospital exposure and antibiotic use put elderly patients at risk of CD readmission. Exposure to these factors should be minimized in the immediate post discharge period.

Keywords Elderly · *Clostridium difficile* · Readmission · Medicare

Introduction

Rates of *Clostridium difficile* (CD) infection have risen dramatically in the past two decades, particularly in the elderly population who have experienced an eightfold increase in some areas.[1,2] CD relapse and reinfections are also increasing, with some studies reporting recurrence rates as high as 65 %.[3,4] Older age has been consistently shown to be a risk factor for CD recurrence.[4,5] Furthermore, the elderly are at increased risk for severe CD infections and morbidity and mortality related to CD.[6–8] Recurrent infections are concerning due to the risk of both adverse outcomes among individual patients with each subsequent occurrence and spread of CD to others due to incompletely eradicated infections.[9]

Studies examining CD recurrence across all age groups have identified older age, severe CD infection, use of non-CD-related antibiotics, use of antacid medications, and hospital exposure as risk factors for CD recurrence.[4,10,11] Since elderly patients are at increased baseline risk for CD infections along with more medical comorbidities and higher overall fragility, they may have different risk factors for CD readmission than younger patients. To date, no study has examined risk factors for CD recurrence among the US elderly population.

In this study, we used Medicare claims data to identify elderly Americans who were hospitalized for CD or developed CD during hospitalization for another reason. We then identified patients who did and did not require readmission for

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CD to identify risk factors for readmission including demographic and clinical factors, index hospitalization characteristics, and exposure to antibiotics. We hypothesized that older patients with more comorbidities and longer initial hospital stays would be more at risk for CD readmission.

Methods

Data Source

We queried a 5 % random sample of Medicare data for the years 2009–2011 including inpatient/limited outpatient (Medicare Provider and Analysis Review (MedPAR)) and Medicare Part D (prescription drug use) event files. Patients were included in the study if they were 65 years of age or older on January 1, 2009 and had at least 1 year of Medicare Part A and B coverage as well as 12 months of continuous Part D enrollment without Part C (health maintenance organization/managed care) participation for completeness of claims (N= 864,604).

MedPAR was used to obtain variables related to hospitalization including diagnoses (up to 10), procedures (up to 10), need for ICU care, hospital length of stay (LOS), and ICU-LOS for both the index CD hospitalization and CD readmission. MedPAR was also used to calculate each patients' Elixhauser comorbidity index.[12] Part D event files were used to obtain information regarding patients' outpatient antibiotic use including the name, strength and date of prescription as well as the date the prescription was filled. Demographic variables (age, race, gender) were obtained from Medicare denominator files.

Case Identification

Patients were selected if they had been admitted to a short-stay (acute care) hospital with either a primary or secondary diagnosis of *C. difficile* by ICD-9 code (008.45). Admissions to long-term care hospitals (LTH) or skilled nursing facilities (SNF) were not included. Patients were further categorized into community-acquired CD (CACD) and healthcare-acquired CD (HACD) as these have been felt to be different disease pathologies with potentially different clinical courses. CACD was defined as anyone hospitalized with a primary diagnosis of CD with no exposure to intravenous or intramuscular antibiotics and no admission to a hospital/SNF/LTH within 90 days of CD admission. Anyone not meeting the criteria for community-acquired infection (i.e., those with exposure to intravenous/intramuscular (IV/IM) antibiotics or a hospital/SNF/LTH within 90 days of admission) or those with a secondary diagnosis of CD acquired during hospitalization for another reason was determined to have HACD.

CD Readmission

Patients surviving their index CD hospitalization were considered at risk for readmission. Patients who underwent a colectomy during their index admission were not considered at risk for readmission, as any subsequent hospitalization is unlikely to have resulted from CD infection after the removal of the colon. CD readmission was defined as any subsequent admission to a short-stay hospital with CD as the primary diagnosis (by ICD-9 code). Admissions to SNFs and LTH with primary diagnoses of CD were also not included.

Hospital Outcomes

Information regarding length of stay, need for ICU care, ICU-LOS, in-hospital mortality, and need for colectomy (subtotal or total abdominal colectomy) during the index CD hospitalization and CD readmission (where applicable) was identified. Any total or subtotal colectomy identified by ICD-9 procedure code (45.7 and 45.8x) for patients with a primary diagnosis of CD was counted as CD-related colectomies regardless of procedure date. For patients with a secondary diagnosis of CD, only colectomies on dates other than the day of admission were counted as CD-related colectomies, as surgeries performed on the day of admission for non-CD primary admissions could represent elective abdominal operations.

Antibiotic Exposure

Part D claims were used to characterize patients' exposure to oral antibiotics after index CD hospitalization. Patients were considered exposed if they filled a prescription for an oral antibiotic as indicated by Part D claims. Patients' use of CD treatment antibiotics (oral vancomycin/metronidazole) and non-CD treatment antibiotics (all other oral antibiotics) was analyzed separately. The use of intramuscular and intravenous antibiotics was also analyzed separately. Oral vancomycin and metronidazole use was described but not included in the model, as it is unclear which patients received a full course of treatment in the hospital and which patients did not. Furthermore, some patients who were not readmitted may never have had a recurrence and therefore would have no indication for metronidazole/vancomycin.

Statistical Analysis

Demographic (age, race gender), clinical (Elixhauser score, presence of general medical comorbidities and gastrointestinal comorbidities), and index hospital characteristics (LOS, need for ICU care, ICU-LOS, colectomy); exposure to oral antibiotics; and non-CD hospitalization for patients who did and did not require readmission for CD infection were compared using univariate tests of association. Chi-squared tests of

association were used to compare categorical variables, *t* tests for normally distributed continuous variables, and Wilcoxon rank sum tests for non-normally distributed continuous variables. Characteristics of CD readmissions (in-hospital mortality, ICU stay, LOS, ICU-LOS, colectomy) were analyzed using descriptive statistics. The mean and median numbers of readmissions for CD (primary diagnosis only) were also determined for patients with more than one readmission of CD.

A multiple Cox proportional hazards regression model was used to identify independent risk factors for CD readmission. Only the first readmission was considered for this analysis. Patients who died during the study period were censored. A sensitivity analysis was performed where only patients surviving until readmission or surviving the study period without readmission were included (i.e., those who died without readmission were excluded). The results were not significantly different from the original analysis. The initial model included demographic (age, race, sex), clinical (Elixhauser index, presence of individual GI comorbidities), and index hospitalization characteristics (ICU stay, LOS category); exposure to antibiotics (oral and IV/IM); colectomy during index hospitalization; interim non-CD hospitalization; and primary diagnosis at index hospitalization (community-acquired CD, healthcare-acquired CD, other primary diagnosis). Factors not meeting the significance criteria (p value<0.1) were removed until only significant variables remained. This final model included age, gender, Elixhauser score, LOS category, hospitalization prior to CD readmission, antibiotic exposure, and primary diagnosis category. Three risk factors whose status was subject to change during the period after discharge and whose post discharge dates were known were analyzed as time-varying covariates (TVCs): interim hospitalization, antibiotic exposure, and IV/IM exposure. All non-TVCs in the final model passed the test of proportional hazards (PH) assumption for the Cox model (p>0.05).

This study was deemed exempt by the University of Massachusetts Institutional Review Board and was approved by the Center for Medicare and Medicaid Services (CMS) via ResDAC. All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

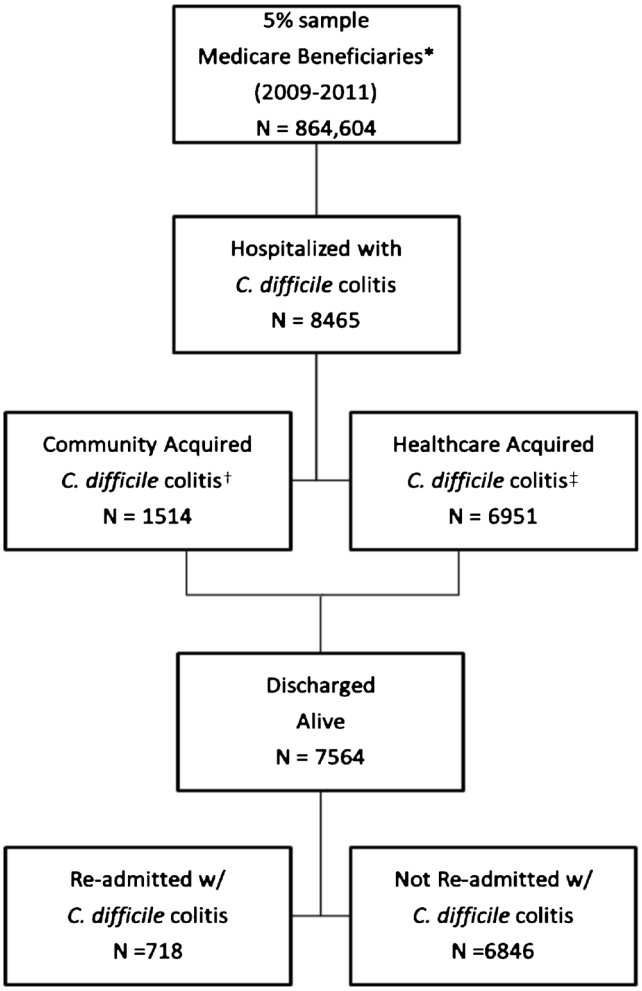

Fig. 1 Patient selection: *asterisk* indicates patients with 1 year Medicare Part A, B eligibility with 1 year of Part D enrollment. *Dagger* indicates patients admitted with *Clostridium difficile* as a primary diagnosis with no exposure to IV antibiotics within 90 days and no admission to hospital or skilled nursing facility within 90 days. *Double dagger* indicates patients admitted with CD as a primary diagnosis with exposure to IV antibiotics or hospital/SNF admission within 90 days or CD as a secondary diagnosis

Results

Of the 3,032,546 records included in the sample, 864,904 (28.5 %) met our eligibility criteria in terms of 1 year of Medicare coverage and Part D enrollment (Fig. 1). Of these, we identified 8,465 (1.0 %) patients who were hospitalized with CD; 1,514 (18 %) patients were originally hospitalized for CACD and 6,951 (82 %) patients had hospitalized for HACD. Of all 8,465 patients, 7,564 (89 %) survived their index hospitalization and did not have a colectomy and were therefore considered at risk for readmission. Of the patients at risk, 718 (8.5 %) were readmitted with CD within the study period. The median time to readmission was 25 days (interquartile range (IQR) 14–57), with 29 % readmitted within 2 weeks and 56 % readmitted within 30 days. The mean number of readmissions for CD during our study period was 2.3 (SD 0.7). The median number of readmissions is 2 (IQR 2–2). Figure 2 shows the probability of readmission as a survival function for all patients in the study; 50 % were readmitted by 25 days after discharge, 80 % were readmitted by 73 days from discharge, and 100 % were readmitted by 1,073 days after discharge.

Just over half (53 %) of the patients readmitted for CD had an interim hospitalization in between their index hospitalization and their CD readmission. Only about a third (34 %)

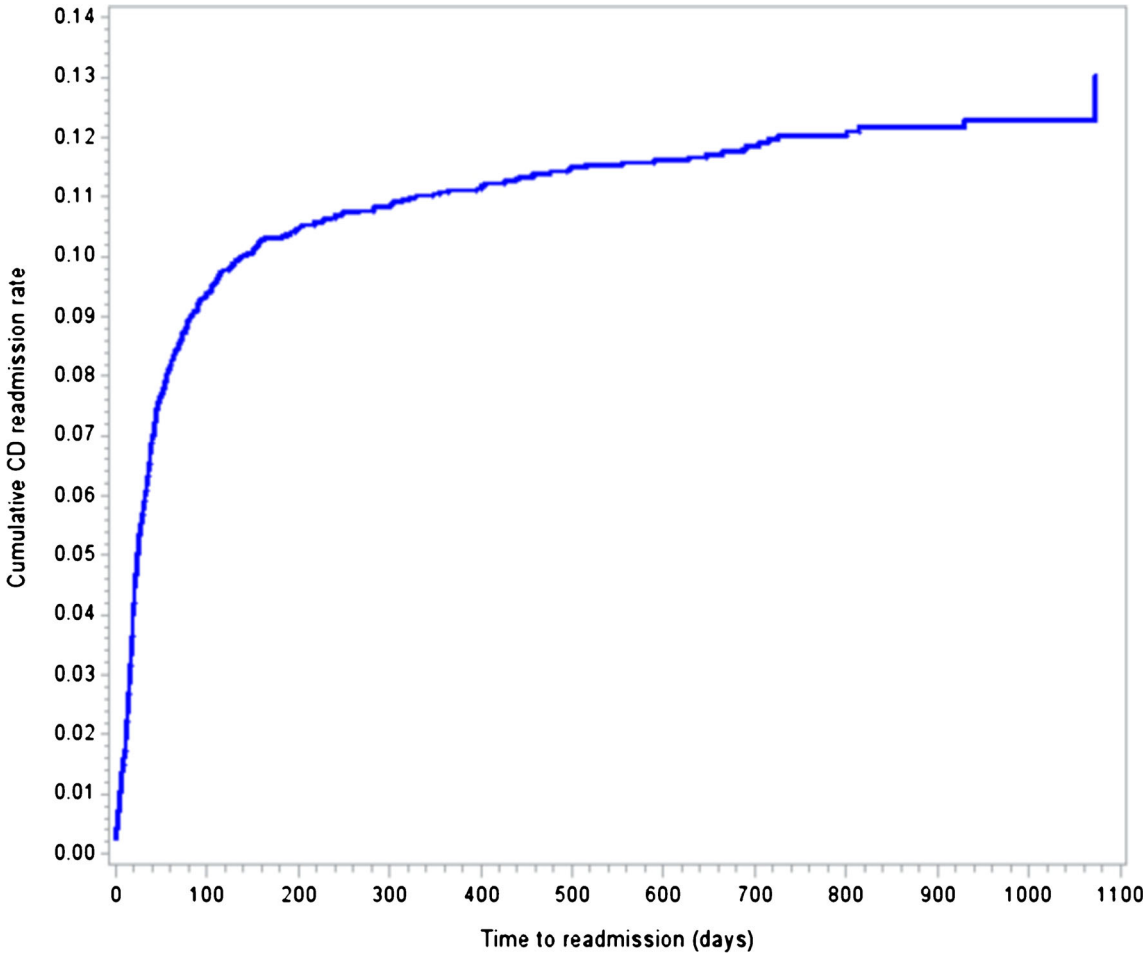

Fig. 2 Cumulative *Clostridium difficile* readmission rates of patients surviving an index hospitalization for *Clostridium difficile* for Medicare beneficiaries 2009–2011 (*N*=7,564)

received CD treatment (oral vancomycin and/or metronidazole) in the outpatient setting between CD admissions, 11 % within a week of their index hospitalization and 17 % within 1 week of readmission. Over one quarter (27 %) received oral antibiotics to treat something other than CD (i.e., antibiotics other than vancomycin/metronidazole) between index hospitalization and readmission. Just under 10 % (9.6 %) were exposed to IV or IM antibiotics between CD admissions.

On univariate analysis, readmitted patients were less likely to be in the youngest age group or to have an Elixhauser score of 0 compared to non-readmitted patients (Table 1). Gender, race, and non-GI comorbidities (except congestive heart failure (CHF)) were similar between those with and without a CD readmission. Readmitted patients were more likely to have gastroesophageal reflux disease and diverticular disease than those not readmitted, but other gastrointestinal conditions were evenly distributed between the groups.

In terms of index hospitalization characteristics, readmitted patients were more likely to have had HACD or CACD as their primary diagnosis while non-readmitted patients were more likely to have had a non-CD primary diagnosis (Table 2). Readmitted patients had shorter index LOS and were less were likely to require ICU care than those not readmitted. Readmitted patients were more likely to have been discharged home (with or without services) while non-readmitted patients were more likely to be discharged to rehab, SNF, or other inpatient facilities.

In multivariable survival analysis, repeat hospitalization was found to be the most significant predictor of CD readmission with HR of 3.75 (95 % CI 3.20–4.42, Table 3). Figure 3 shows the rate of readmission for those with and without interim hospitalization. Other significant predictors of readmission were CD as a primary diagnosis (community- and healthcare-acquired), higher Elixhauser category, antibiotic use (oral and IV/IM), and discharge to an inpatient facility. Discharge to rehabilitation facility or a skilled nursing facility reduced the risk of readmission. Increasing age, gender, and length of stay category had no significant effect on the risk of readmission.

Given the strong effect of interim hospitalizations, we undertook a subgroup analysis looking at patients who were not hospitalized between their index and recurrent CD

Table 1 Comparison of demographic and baseline clinical characteristics of Medicare patients hospitalized with primary or secondary diagnosis of *C. difficile* colitis by readmission status (*N*=7,564)

	Readmitted *N*=718	Not readmitted *N*=6,846	*p* value[a]
Demographics			
Female sex (%)	537 (74.8)	4,956 (72.2)	0.17
Age, median (IQR)	80 (74–85)	81 (74–87)	0.05
Age group (%)			0.01
65–74	191 (26.6)	1,855 (27.0)	
75–84	275 (38.3)	2,307 (33.6)	
85–94	237 (33.0)	2,411 (35.1)	
≥95	15 (2.1)	273 (4.0)	
Race (%)			0.5
White, non-Hispanic	587 (81.8)	5,591 (81.5)	
Black, non-Hispanic	60 (8.4)	622 (9.1)	
Hispanic	53 (7.4)	425 (6.2)	
Other	18 (2.5)	208 (3.0)	
Clinical characteristics			
Elixhauser category (%)			<0.01
0	162 (22.6)	1,803 (26.3)	
1	47 (6.5)	330 (4.8)	
2	86 (12.0)	615 (9.0)	
3	79 (11.0)	824 (12.0)	
>3	344 (47.9)	3,274 (47.7)	
GI comorbidities (%)			<0.01
Diverticular disease	36 (5.0)	226 (3.3)	0.02
IBD	9 (1.3)	59 (0.9)	0.3
GERD	90 (12.5)	686 (10)	0.04
Peptic ulcer disease	12 (1.7)	121 (1.8)	1.0
Colon cancer	4 (0.6)	43 (0.6)	1.0
Other comorbidities (%)			0.16
Diabetes	220 (30.6)	2,176 (31.7)	0.2
Hypertension	441 (61.4)	3,985 (58.1)	0.9
Obesity	43 (6.0)	423 (6.2)	0.7
COPD	197 (27.4)	1,687 (24.6)	0.4
Renal failure	120 (16.7)	1,232 (17.9)	0.1
CHF	151 (21.0)	1,605 (23.4)	0.02

Medicare patients were aged ≥65 on January 1, 2009 and had at least 1 year of continuous Part A and B coverage as well as 12 months of continuous Part D enrollment without health maintenance organization (HMO/Part C) for any year. Analysis of primary or secondary diagnosis of *C. difficile* colitis includes only those patients who survived the index admission. Readmission status defined as readmitted during our study period (Jan. 1, 2009–Dec. 31, 2011) with a primary diagnosis *C. difficile* colitis, median follow-up=9.8 months (IQR 2.4, 21.8); mean follow-up=12.9 months (SD=11.4)

[a] Chi-squared tests (or Fisher exact tests) for categorical variables, Student's *T* test for normally distributed continuous variables, and Wilcoxon rank-sum test for non-parametric comparisons of non-normally distributed variables

Table 2 Characteristics and outcomes of index hospitalization of Medicare patients with *C. difficile* colitis by readmission status (*N*=7,564)

	Readmitted *N*=718	Not readmitted *N*=6,846	*p* value[a]
Primary diagnoses[‡]			<0.01
Community *C. difficile* colitis (%)[b]	194 (27.0)	1,268 (18.5)	
Healthcare *C. difficile* colitis (%)[c]	161 (22.4)	1,015 (14.8)	
Non-CD primary diagnosis	363 (50.6)	4,563 (66.5)	
Outcomes			
Required ICU care (%)	191 (26.6)	2,185 (31.8)	<0.01
ICU LOS, median (IQR)	4 (2–8)	5 (3–9)	0.07
Length of stay, median (IQR)	6 (4–11)	8 (5–13)	<0.01
Length of stay (days)			<0.01
≤2	53 (7.4)	477 (6.9)	0.6
3–7	379 (52.8)	2,939 (42.8)	<0.01
8–14	190 (26.5)	2,114 (30.8)	0.01
15–21	60 (8.4)	786 (11.5)	0.01
>21	36 (5.0)	530 (7.7)	<0.01
Discharge disposition[d]			<0.01
Skilled nursing facility (%)	274 (38.2)	3,015 (43.9)	
Home (%)	216 (30.1)	1,576 (23)	
Home with services (%)	149 (20.8)	1,064 (15.5)	
Other inpatient facility (%)	30 (4.2)	177 (2.6)	
Rehabilitation facility (%)	37 (5.2)	365 (5.3)	
Hospice (%)	4 (0.6)	421 (6.1)	
Long-term acute care (%)	8 (1.1)	228 (3.3)	

C. difficile colitis by readmission status analysis includes only those patients who survived the index admission

[a] Chi-squared tests (or Fisher exact tests) for categorical variables, Student's *T* test for normally distributed continuous variables, and Wilcoxon rank-sum test for non-parametric comparisons of non-normally distributed variables

[‡] Mutually exclusive primary diagnosis codes for the index admission. See Appendix x for details of each category

[b] Anyone hospitalized with a primary diagnosis of *C. difficile* colitis who had no inpatient admission or skilled nursing stay for any reason in 90 days prior to admission and was not treated with IV or IM antibiotics in 90 days prior to admission

[c] Anyone hospitalized with a primary diagnosis of *C. difficile* colitis that was hospitalized in an acute care hospital, receiving care in a skilled nursing facility or being treated with IV/IM antibiotics within 90 days of the index admission

[d] Mutually exclusive discharge disposition categories

hospitalizations to see what, if any, factors would predict CD recurrence. The modeling described above was used, and the final model included age, gender, Elixhauser score, LOS category, oral antibiotic exposure, IV/IM antibiotic exposure, and primary diagnosis category. In the sub-analysis, antibiotic use was the strongest predictor of readmission with an HR of 2.01 (95 % CI 1.51–2.66, Table 4). IV/IM also conferred a significant risk of readmission (HR 1.6 95 %, CI 1.06–2.40). Figure 4 shows readmission rates for those who were not hospitalized for another reason prior to readmission for CD

Table 3 Predictors of CD readmission for Medicare beneficiaries surviving an initial hospitalization for *Clostridium difficile* 2009–2011 (*N*=7,564)

	Unadjusted HR		Adjusted HR	
	HR	95 % CI	HR	95 % CI
Age increase in 10 years	0.98	(0.9, 1.07)	1.01	(0.92, 1.11)
Female gender	1.09	(0.92, 1.30)	1.08	(0.9, 1.27)
Primary diagnosis index hospitalization				
Non-CD primary	Reference	Reference	Reference	Reference
Community-acquired CD[a]	1.64	(1.38, 1.95)	1.87	(1.55, 2.27)
Healthcare-acquired CD[b]	1.85	(1.53, 2.22)	1.86	(1.52, 2.27)
Elixhauser index				
0	Reference	Reference	Reference	Reference
1	1.64	(1.18, 2.27)	1.57	(1.11, 2.19)
2	1.65	(1.27, 2.14)	1.68	(1.28, 2.21)
3	1.16	(0.88, 1.52)	1.17	(0.9, 1.55)
>3	1.35	(1.12, 1.63)	1.29	(1.05, 1.58)
Interim hospitalization	3.32	(2.84, 3.88)	3.75	(3.2, 4.42)
Oral antibiotic exposure[c]	1.76	(1.46, 2.13)	1.53	(1.26, 1.86)
IV/IM antibiotic exposure	2.03	(1.6, 2.61)	1.82	(1.42, 2.35)
Discharge disposition index hospitalization[d]				
Home	Reference	Reference	Reference	Reference
Home with services	1.03	(0.84, 1.27)	1.05	(0.85, 1.31)
Hospice	0.26	(0.1, 0.69)	0.35	(0.13, 0.95)
Long-term acute care	0.35	(0.17, 0.71)	0.42	(0.2, 0.87)
Skilled nursing facility	0.76	(0.64, 0.91)	0.74	(0.61, 0.91)
Other inpatient facility	1.66	(1.13, 2.45)	1.44	(0.77, 2.14)
Rehabilitation facility	0.84	(0.59, 1.19)	0.9	(0.63, 1.28)
Other	0.86	(0.12, 6.12)	1.16	(0.16, 8.30)
Index hospitalization length of stay (days)				
≤2	Reference	Reference	Reference	Reference
3–7	1.13	(0.85, 1.5)	1.17	(0.87, 1.56)
8–14	0.85	(0.63, 1.15)	0.99	(0.72, 1.36)
15–21	0.74	(0.51, 1.06)	0.93	(0.63, 1.37)
>21	0.68	(0.44, 1.04)	0.88	(0.56, 1.37)

[a] Anyone hospitalized with a primary diagnosis of *C. difficile* colitis who had no inpatient admission or skill nursing stay for any reason in 90 days prior to admission and was not treated with IV or IM antibiotics in 90 days prior to admission

[b] Anyone hospitalized with a primary diagnosis of *C. difficile* colitis who was hospitalized in an acute care hospital, receiving care in a skilled nursing facility, or being treated with IV/IM antibiotics within 90 days of the index admission

[c] Excluding oral vancomycin/metronidazole

[d] Mutually exclusive discharge disposition categories

by outpatient oral (Fig. 4a) and IV/IM antibiotic exposure after discharge (Fig. 4b). CD as a primary diagnosis, Elixhauser category, and discharge to an inpatient facility were significant predictors of readmission. Gender, increasing age, and LOS category were not significant predictors of readmission in this group. Discharge to skilled nursing facilities, hospice, rehabilitation, and long-term acute care facilities reduced the risk of readmission.

Of the readmitted patients, 3.7 % died during their readmission. Surviving patients stayed a median of 5 days (IQR 4–8). Just under one in five (19.9 %) required ICU care with a median ICU-LOS of 5 days (IQR 3–7). Colectomy rate was low (0.97 %); 18 % of readmitted patients were admitted an additional time with CD infection during the data period.

Discussion

We found that approximately 1 in 10 elderly patients hospitalized for CD infection are readmitted for CD, usually within the month after discharge. Like others who found an association between comorbid illness and CD recurrence, we found that the presence of comorbid illness confers an increased risk of CD readmission,[3,4] although the risk of readmission did not rise consistently with each increase in Elixhauser score. Interim hospitalization for a reason other than CD after the index CD admission was the strongest predictor for readmission, while antibiotic use was the strongest predictor for those who were not hospitalized prior to their CD readmission. CD as a primary reason for admission, whether healthcare-acquired or community-acquired, was also a significant predictor of CD

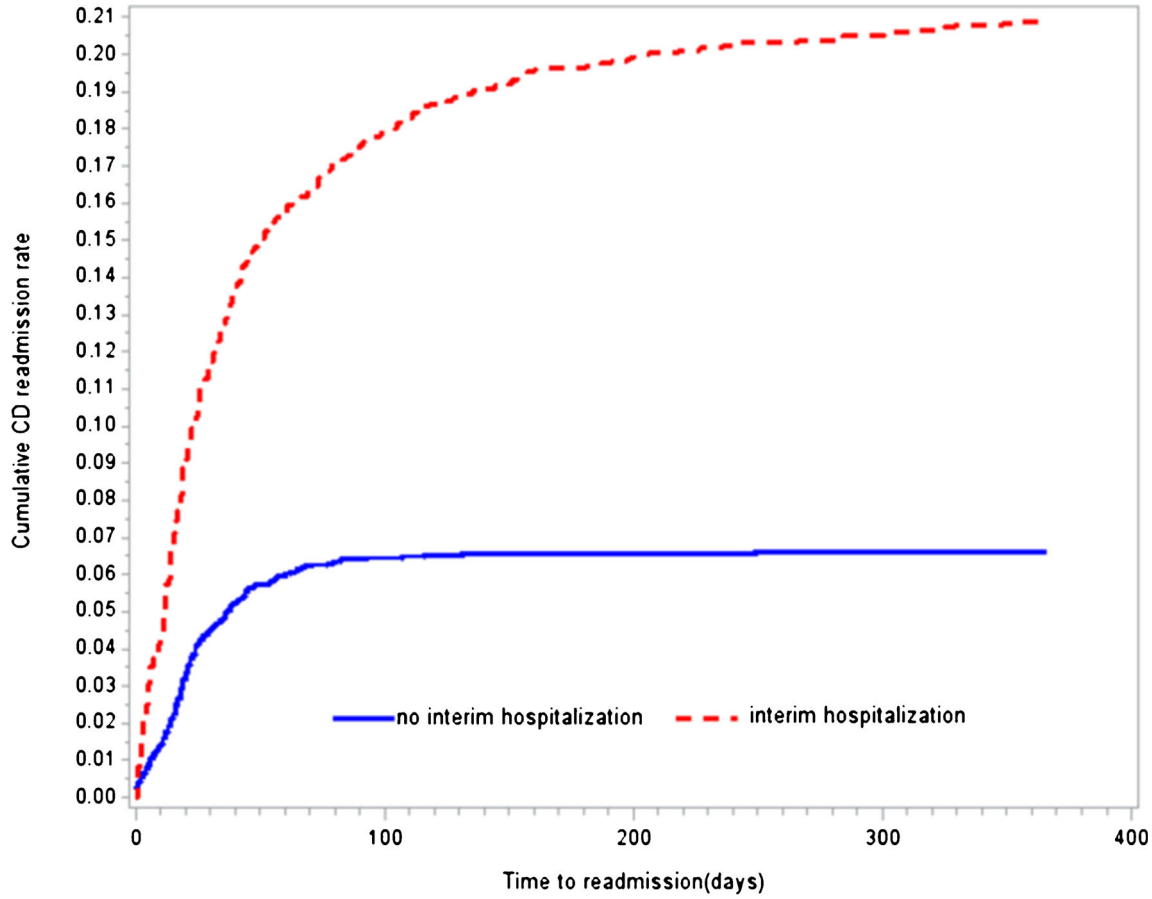

Fig. 3 Cumulative *Clostridium difficile* readmission rates for Medicare beneficiaries by interim hospitalization exposure (N=7,564) of patients surviving index hospitalization for *C. difficile*. Interim hospitalization is taken as time varying covariate in the model

readmission with slightly higher risk for those with healthcare-acquired infection.

The Healthcare Cost and Utilization Project estimated a readmission rate for CD (defined CD as a primary diagnosis) at around 7.8 % for patients over 65, slightly lower than our overall readmission rate of 8.5 %.[13] Importantly, this is more than twice the rate of CD readmission reported in adults 18–44 (3.3 %).[13] This may represent a true elevated baseline risk of CD recurrence, as has been reported in other studies.[3,10,14] It could also represent a lower threshold to admit elderly patients with CD or symptoms concerning for CD due to age, comorbidities, and/or overall frailty. Elderly patients are known to be at increased risk of adverse outcomes after CD infection, which supports the idea that elderly patients should be admitted if there is any doubt as to their diagnosis or their ability to recover safely in the outpatient setting.[15]

Patients readmitted for CD had relatively low mortality rates, but more than one in five required ICU care during their readmission. Furthermore, although less than 10 % of patients with an initial CD infection were readmitted with CD, nearly 20 % of patients readmitted for CD were readmitted an additional time. The rate of CD recurrence has been shown to dramatically increase with each subsequent episode.[16,17] This further demonstrates that breaking the cycle of CD relapse and recurrence should be a priority as each subsequent episode places these elderly patients at risks of adverse outcomes.

We did not find a significant risk of CD readmission with increasing age in this elderly population. Studies have consistently cited age (usually over 65) as a risk factor for CD recurrence.[4,18,19] Our results suggest that although elderly patients may in general be at risk for readmission compared to patients under age 65, increasing age after 65 does not predict CD recurrence. It is possible that the physiologic factors that place elderly patients at risk for CD are already present by age 65 and are not significantly worsened with time. We did find that comorbidity burden predicted an increased risk of CD recurrence, suggesting that overall health status may be more important than physical age when it comes to the risk of CD recurrence in the elderly. However, the increasing comorbidity burden and fragility conferred by increasing age may place the "oldest old" at risk of adverse outcomes after CD infection, including mortality due to CD which has been shown to be the highest among those over 75 years of age.[20] This suggests that, although the oldest old may not be at increased risk of CD recurrence compared to their "younger" old counterparts, they should be monitored

Table 4 Predictors of readmission for patient surviving index CD hospitalization without an interim non-CD hospitalization (N=3,195)

	Unadjusted HR		Adjusted HR	
	HR	95 % CI	HR	95 % CI
Age increase in 10 years	0.81	(0.71, 0.92)	1.01	(0.88, 1.17)
Female gender	0.95	(0.75, 1.2)	0.9	(0.7, 1.17)
Primary diagnosis index hospitalization				
Non-CD primary	Reference	Reference	Reference	Reference
Community-acquired CD[a]	2.43	(1.88, 3.14)	1.94	(1.46, 2.6)
Healthcare-acquired CD[b]	2.64	(2.02, 3.45)	2.01	(1.51, 2.7)
Elixhauser index				
0	Reference	Reference	Reference	Reference
1	1.67	(1.1, 2.52)	1.76	(1.14, 2.70)
2	1.41	(0.99, 2.00)	1.57	(1.02, 2.14)
3	0.97	(0.65, 1.44)	1.13	(0.74, 1.71)
>3	1.11	(0.85, 1.45)	1.33	(0.99, 1.79)
Oral antibiotic exposure[c]	2.29	(1.73, 3.04)	2.01	(1.51, 2.66)
IV/IM antibiotic exposure	1.9	(1.26, 2.81)	1.6	(1.06, 2.40)
Discharge disposition index hospitalization[d]				
Home	Reference	Reference	Reference	Reference
Home with services	1.23	(0.97, 1.58)	1.3	(1, 1.7)
Hospice	0.11	(0.03, 0.33)	0.13	(0.04, 0.42)
Long-term acute care	0.15	(0.04, 0.60)	0.23	(0.05, 0.94)
Skilled nursing facility	0.17	(0.11, 0.24)	0.2	(0.14, 0.31)
Other inpatient facility	2.9	(1.81, 4.60)	3.45	(2.14, 5.56)
Rehabilitation facility	0.38	(0.19, 0.74)	0.45	(0.23, 0.89)
Other	1.18	(0.17, 8.41)	1.36	(0.19, 9.80)
Index hospitalization length of stay (days)				
≤2	Reference	Reference	Reference	Reference
3–7	1.03	(0.73, 1.47)	1.24	(0.87, 1.78)
8–14	0.65	(0.44, 0.96)	1.17	(0.77, 1.76)
15–21	0.46	(0.26, 0.84)	1.02	(0.56, 1.88)
>21	0.38	(0.18, 0.83)	1.02	(0.46, 2.26)

[a] Anyone hospitalized with a primary diagnosis of *C. difficile* colitis who had no inpatient admission or skill nursing stay for any reason in 90 days prior to admission and was not treated with IV or IM antibiotics in 90 days prior to admission

[b] Anyone hospitalized with a primary diagnosis of *C. difficile* colitis who was hospitalized in an acute care hospital, receiving care in a skilled nursing facility, or being treated with IV/IM antibiotics within 90 days of the index admission

[c] Excluding oral vancomycin and metronidazole

[d] Mutually exclusive discharge disposition categories

closely as they may be at particular risk of adverse outcomes with each CD infection.

Readmitted patients tended to return to the hospital within a relatively short period of time, generally within the month after discharge from their index hospitalization. This short time course suggests that the initial CD infection may not have been fully eradicated prior to discharge or that the post discharge treatment regimen has failed. Failure rates for vancomycin and metronidazole have been estimated at around 5–20 % according to a review,[21] and increasing age has been shown to increase the risk of treatment failure even further.[22] Furthermore, the colonic microflora is the most disrupted in the 30 days after CD treatment is completed, making this the most likely time period for a CD relapse or reinfection.[19] Ironically, metronidazole and vancomycin also alter colonic microflora and may contribute to the loss of resistance to CD in the post treatment period.[23] The lack of immune function in elderly patients elevates their risk even further.[8,24] Elderly patients should be closely monitored for signs of CD in the immediate post discharge period, as prompt diagnosis and treatment in the outpatient setting could prevent some of these costly readmissions. Because we did not have information regarding symptom recurrence, we are unable to comment on whether or not oral vancomycin/metronidazole treatment for symptomatic patients protected against readmission specifically for those with a CD recurrence. However, we found that only one third of readmitted patients received vancomycin or metronidazole in the outpatient setting, indicating that recurrences of CD may be being under diagnosed in the outpatient setting or are being diagnosed too late for outpatient treatment to be sufficient.

The most influential risk factor for CD readmission was hospitalization for another reason after initial CD discharge. Elderly patients are more likely to receive broad-spectrum antibiotics when hospitalized.[24,25] While we did not know what, if any, antibiotics were received by our patients during

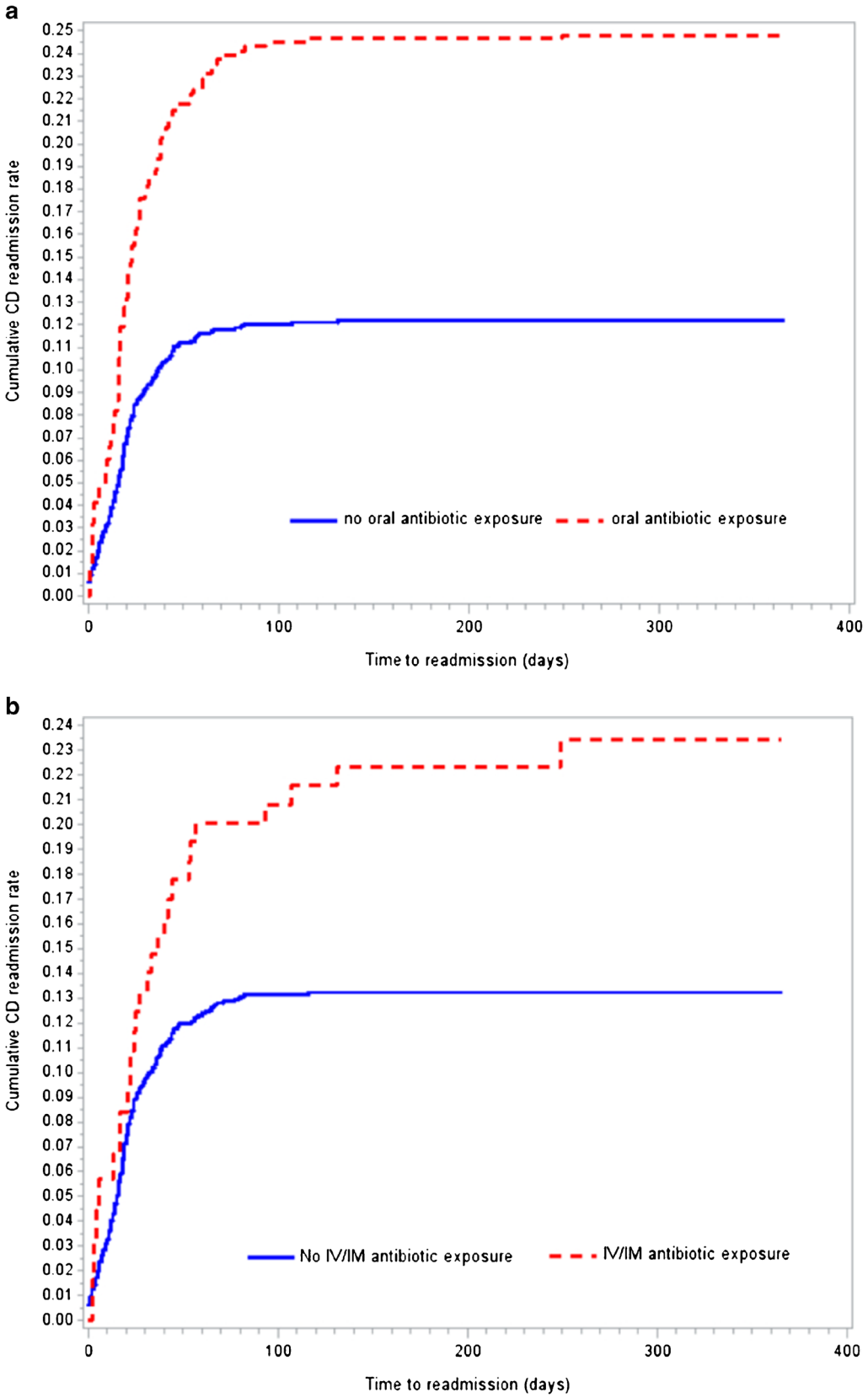

Fig. 4 Cumulative of *Clostridium difficile* readmission rates for Medicare beneficiaries without interim hospital exposure by oral antibiotic exposure (**a**) and IV/IM antibiotics (**b**). *N*=3,195 patients who survived an index hospitalization for *Clostridium difficile* and were not hospitalized prior to CD readmission. Antibiotic use included as a time varying covariate

these interim admissions for non-CD reasons, antibiotic exposure during hospitalization may explain the effect of interim hospitalization on CD recurrence. However, while only ~1 % of US hospitalizations involve documented CD,[26] as many as 20–30 % of hospitalized patients may be asymptomatic carriers capable of infecting others.[27] Therefore, patients such as ours who are recovering from a recent CD infection and may not have reestablished their native colonic flora may be at increased risk of reinfection in an environment where CD infections are common whether or not they are also exposed to antibiotics.[19] Our results indicate that patients who have a history of CD should be carefully monitored for signs of CD relapse and/or reinfection at all subsequent hospitalizations. Furthermore, exposure to other patients with CD and the use of broad-spectrum antibiotics should be minimized where possible in this vulnerable population.

Outpatient antibiotic use was another strong predictor of CD readmission and was the most important readmission predictor for patients without an interim hospitalization. Antibiotic use is a commonly cited risk factor for CD infection.[10] Elderly patients frequently require antibiotics for things such as pneumonias, UTIs, and upper respiratory infections.[28] This increased antibiotic use combined with their decreased immune function and recently disrupted colonic flora places them at particular risk for CD recurrence. Practitioners should be cautious when prescribing antibiotics to elderly patients with recent diagnoses of CD. Patients who do require antibiotics in the post CD period should be carefully monitored for signs of recurrent or relapsing CD infection, and antibiotics known to particularly increase the risk of CD infection (such as clindamycin and fluoroquinolones) should be avoided where possible.[29]

We found that patients with shorter lengths of stays were at increased risk of readmission on univariate analysis. Although this relationship did not remain significant in multivariable analyses, we did not find that longer hospital stays increased the risk of CD readmission as has been reported by other studies.[11,30] One study found that extended hospital stays (over 30 days) decreased the risk of CD recurrence, but still found increased risks for hospital stays 1–16 and 16–29 days.[3] While an extended stay in the hospital does expose patients to risk of CD infection due to the threat of infection from other patients and exposure to risk factors such as antibiotics, early discharge may place patients at risk of treatment failure in their home environment. Our results suggest that there is no protective effect of discharging patients earlier in this population.

We found that in general, patients to an inpatient setting such as skilled nursing facilities or long-term acute care centers were less likely to be readmitted for CD. This again seems contrary to other studies that have reported elevated risk of CD infection in these settings.[8] Patients at rehabilitation facilities or at skilled nursing facilities may be able to be treated at the facility and will not require readmission to a hospital. They may also have symptoms diagnosed earlier in the clinical course as they are being monitored daily by healthcare professionals. This may allow their infection to be treated in a non-acute setting, for example, with oral antibiotics. Additionally, many skilled nursing facilities and long-term rehabilitation centers may have access to IV metronidazole which would allow even more severe cases of CD to be treated in the facility without transfer back to an acute care center. Finally, patients in inpatient settings are monitored for compliance with all antibiotic regimens, something that has been shown to be poor in the outpatient setting.[31] It is possible that the combination of monitoring by healthcare professionals and likely higher rates of medication compliance is contributing the reduced rate of CD readmissions in this group. Elderly patients discharged to home may have difficulty completing the necessary antibiotic course and may also suffer a recurrence of symptoms that is not recognized as CD until it requires rehospitalization. CD treatment (oral metronidazole and/or vancomycin) compliance and prompt outpatient follow-up should be emphasized so that any recurrence can be caught early in the course, potentially avoiding rehospitalization.

Our study does have some important limitations. First, since we used administrative data, we do not have access to clinical information such as laboratory values, inpatient medication administration, or radiology findings that may help us better characterize the severity of CD infection or treatment rendered, something that has been shown to be an important component of recurrence.[4,19] Second, because our results rely on ICD-9 codes, it is subject to errors in coding, particularly with whether CD is a primary or secondary diagnosis. It is possible that we have missed readmissions that truly were due to CD since a primary diagnosis code for CD was requisite in our algorithm to identify recurrence. Similarly, as with all claims databases, we are somewhat limited in characterizing patients' medical problems, as we are only able to report comorbidities that were reported to Medicare via ICD-9 codes during the study period. Third, because we have no clinical information, we are unable to say which patients suffered a symptomatic recurrence after their index discharge, which limits our ability to comment on the role of outpatient treatment for recurrent disease. This also means that we cannot comment on the overall rate of CD recurrence, as we are only able to report how many patients had a CD-related readmission. Patients with CD infection not requiring rehospitalization are not captured in our readmission group. Finally, since we limited our study to patients for whom Part D claims were available, our data may not be representative of all elderly Americans, since female, non-white patients from lower socioeconomic groups have been shown to disproportionately participate in Part D benefits.[32]

However, the strength of this study lies in its use of national data from a large number of older Americans followed over time. This group has not been specifically studied in the past. Furthermore, to our knowledge, no other study has examined specific risk factors for CD readmission among older Americans despite ample evidence that they are at increased risk of recurrent CD infection and poor outcomes. Furthermore, our use of Part D records allows us to track patients' prescription drug use in between hospitalizations in order to analyze outpatient treatment patterns as well as exposure to non-CD treatment antibiotics in the outpatient setting.

Conclusion

In summary, in our national study on risk factors for CD readmission among older Americans, we found that CD as the primary reason for index hospitalization, hospitalization for another reason after recent CD hospitalization, oral antibiotic use after recent CD hospitalization increasing comorbidities, and discharge home all increased the risk of CD readmission for elderly patients surviving an initial hospitalization. Elderly patients should be monitored closely during the immediate post discharge period for signs and symptoms of relapse. Furthermore, contact with known CD risk factors should be avoided during this time.

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Discussant

Dr. Jennifer Holder-Murray (Pittsburgh, PA):

Thank you to the authors for highlighting the importance of CD infections in the elderly population, which have been demonstrated to have an increased risk of CD infection based on their age. Here, you attempted to tease out additional risk factors for readmission in this unique population when using the Medicare administrative database. Though this database has some significant limitations, the information obtained yields some interesting results. I have three questions for the authors.

1. How do you rationalize that discharge to rehab or a skilled nursing facility decreases the readmission rates for CD and that discharge to home increases risk?

2. Readmission rates may actually be much higher than calculated, as this study was limited to patients only with a primary readmission diagnosis of CD. If CD as a secondary diagnosis code was included, was there any difference in the findings?

3. Some patients were defined as having recurrent CD even though recurrence was years later. How do you rationalize this as recurrence versus a new primary infection?

Closing Discussant

1. We were also surprised to see that patients discharged to nursing facilities and rehabilitation facilities generally had lower rates of CD-related readmission, as the rate of CD infection in these settings is reported to be quite high. There are several potential explanations for this. First, patients in healthcare facility are monitored daily by medical personnel who may see the signs of CD infection at early enough stages that they can be treated without readmission to an acute care hospital, for example, with oral antibiotics. Secondly, many non-acute care healthcare facilities may be equipped to adequately treat CD with IV metronidazole and therefore avoid transfer back to the acute care setting even with more severe CD infections. Finally, being in a healthcare setting may help to ensure compliance with medication, particularly of CD treatment medications. Patients discharged with a diagnosis of CD are often given oral antibiotics to take in the outpatient setting. However, compliance with medications in general and antibiotic regimens in particular remains a challenge for all patients but may be an especially problematic issue for certain elderly patients, for example, those with multiple daily medications or those with cognitive issues. Admission to a post acute healthcare facility of any type may improve adherence to post discharge CD treatment due to close monitoring by healthcare personnel and thus may prevent some instances of treatment failure.

2. We defined CD readmission as a hospitalization with CD as the primary diagnosis because we were concerned that CD as a secondary diagnosis could represent a second acquisition of CD after hospitalization for another primary reason, such as heart failure or pneumonia. We wished to capture only readmissions that we were reasonably certain were due to CD infection, hence our exclusion of readmissions primarily due to another pathology. Had we included CD as a secondary diagnosis, we would have had 1,615 readmitted patients for an overall readmission rate of 21 % (compared to our reported readmission rate of 8.5 %). However, looking for predictors of all cause readmissions for patients with CD was not our primary aim so we chose to only analyze patients whose reason for readmission was CD infection.

3. Finally, we did not place a time limit on our readmission data as it has been shown to be difficult, if not impossible, to differentiate a CD relapse from a reinfection no matter what time cutoff is used. Although many studies use 4–6 weeks as the general point at which repeat CD infections are termed "new" infections, studies that have analyzed the specific strains of CD have shown that many "relapses" (i.e., those that occur within 4–6 weeks) are actually new infections and vice versa. Therefore, we attempted to focus on CD readmission without specifying whether the readmission is due to a relapse of the initial infection or a new acquisition of CD. Patients recovering from CD are in fact at risk for both relapse and reinfection due to the presence of CD spores and also due to changes in the colonic microflora that leaves them more susceptible to new infections. We wished to capture both of these types of readmissions so we did not place a time limit on the readmission window. Additionally, because no one had specifically examined readmission in this age group, we were not sure what temporal patterns we would see in regard to readmissions so we wished to capture all the additional hospitalizations for CD that we could. Importantly, the vast majority of readmissions in our sample happened within the first 2 months; therefore, it is unlikely that eliminating the few readmissions after this point would significantly alter the results.