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Epidemiology and Outcomes of Community Acquired *Clostridium difficile* Infections in Medicare Beneficiaries

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Abstract

Background—The incidence of community-acquired *Clostridium difficile* (CACD) is increasing in the US. Many CACD infections occur in the elderly who are predisposed to poor outcomes. We aimed to describe the epidemiology and outcomes of CACD in a nationally representative sample of Medicare beneficiaries.

Study Design—We queried a 5% random sample of Medicare beneficiaries (2009–2011 Part A inpatient and Part D prescription drug claims, N=864,604) for any hospital admission with a primary ICD-9 diagnosis code for *C. difficile* (008.45). We examined patient sociodemographic and clinical characteristics, pre-admission exposure to oral antibiotics, prior treatment with oral vancomycin or metronidazole, inpatient outcomes (colectomy, ICU stay, length of stay, mortality), and subsequent admissions for *C. difficile*.

Results—A total of 1566 (0.18%) patients were admitted with CACD. Of these, 889(56.8%) received oral antibiotics within 90 days of admission. Few were being treated with oral metronidazole (N=123, 7.8%) or vancomycin (N=13, 0.8%) at the time of admission. While 223(14%) patients required ICU admission, few (N=15, 1%) underwent colectomy. Hospital mortality was 9%. Median length of stay (LOS) among survivors was 5 days (IQR 3–8). One-fifth of survivors were re-admitted with *C. difficile* with a median follow up time of 393 days (IQR 129–769).

Conclusions—Nearly half of Medicare beneficiaries admitted with CACD have no recent antibiotic exposure. High mortality and re-admission rates suggest that the burden of *C. difficile* on patients and the healthcare system will increase as the US population ages. Additional efforts at primary prevention and eradication may be warranted.

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Introduction

The incidence of *Clostridium difficile* (CD) in patients over 65 years of age has increased 8-fold in the past two decades.¹ Currently, more than 90% of deaths due to CD are in this age group.² Although CD recently replaced methicillin-resistant *Staphylococcus aureus* (MRSA) as the most common hospital-acquired infection in the United States,³ there are also increasing reports of CD in community dwelling adults with no recent history of hospitalization or antibiotic use. Given current trends in CD infections and the rapid aging of the US population, this once largely nosocomial pathogen is poised to become a major burden on the healthcare system in terms of morbidity and mortality as well as healthcare costs.⁴

Recent evidence suggests that CD infections, including community-acquired CD (CADC) are becoming more virulent over time.^{5,6} Lack of knowledge about these “atypical” cases of CD may lead to delay in diagnosis which can contribute to poor outcomes.⁷ While there have been some studies describing epidemiology and outcomes of CADC, none have focused on elderly Americans, despite the high morbidity and mortality in these individuals.^{8–13} Importantly, there is a paucity of national data on CADC. We undertook the present epidemiologic study to examine the characteristics and outcomes of elderly patients hospitalized with CADC using Medicare claims data.

Methods

Data Source and Subject Selection

We queried Medicare inpatient claim files (Medicare Provider and Analysis Review/MEDPAR) and Part D (prescription drug use) event files for a random 5% national sample of Medicare beneficiaries from 2009–2011. Patients were included in the present study if they were age 65 years or older on January 1, 2009 and had 12 months of continuous Part A and B coverage and 12 months of continuous Part D enrollment without health maintenance organization (HMO/Part C) enrollment for either year to assure completeness of data.

Medicare denominator files were used for demographic factors (age, sex, race). MEDPAR was used to obtain variables related to hospitalization (diagnoses [up to fifteen], procedures [up to ten], length of stay [LOS], intensive care unit [ICU] stay, in-hospital mortality) and to calculate each patient’s Elixhauser comorbidity index.¹⁴ Part D files provided data on outpatient medication type, dosage, strength, date of prescription and date the prescription was filled

Case Identification

Cases of CD were defined as any hospital admission with a *primary* diagnosis of CD (ICD-9 code: 008.45) as documented in MEDPAR. To restrict our cohort to those with a new community-acquired infection (CADC), we included only the patient’s first admission with a primary diagnosis of CD. Furthermore, we excluded patients receiving intravenous or intramuscular antibiotics, patients admitted from a skilled nursing facility (SNF), and anyone with an inpatient hospitalization within 90 days prior to the index CD admission.

Previous exposure to outpatient antibiotic treatment was determined using Part D claims. The date of oral antibiotic prescription fill for all drugs was compared to the date of admission for CD, then patients were classified as having received oral antibiotics within 30 days, 31–60 days, and 61–90 days prior to their index CD admission. Part D claims were also used to determine the time from antibiotic prescription to admission and the number of antibiotic days in the period leading up to the index CD admission. Antibiotic usage was further broken down by class (see Appendix 1, online only, for antibiotic classifications). Exposure to gastric acid suppressants (proton pump inhibitors [PPIs] and histamine [H2] blockers) was similarly queried.

Statistical Analysis

We used descriptive statistics to determine the incidence of CACD and to describe patient demographic characteristics (age, gender, and race), co-morbidity profile (Elixhauser Index), pre-admission antibiotic use, outpatient treatment with oral vancomycin and/or oral metronidazole within 7 days of admission, and inpatient outcomes (need for colectomy, ICU length of stay (LOS), overall LOS, in-hospital mortality, and subsequent admissions for a diagnosis of CD).

This study was deemed exempt by the University of Massachusetts Medical School 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, 2013).

Results

Patient Characteristics

Among the 864,604 patients who met our eligibility criteria, 4121 (0.48%) were admitted with a new diagnosis of CD by primary ICD-9 code. Of these, 1566 (38%) had CACD based on our a priori criteria, for an overall CACD incidence of 0.18%. Patients with CACD were predominantly female, white, and in the 8th decade of life (Table 1). Over 70% of CACD patients were 75 years of age and older and approximately 40% were older than 85 years. The average Elixhauser index for CACD patients was 2.5, with over half having no Elixhauser defined co-morbidities. Approximately 1 in 5 patients with CACD had gastroesophageal reflux disease, but few had diverticular disease, peptic ulcer disease, or colon cancer. Approximately two-thirds (65%) of the study population did not have a history of gastrointestinal disorders.

Antibiotic and Gastric Acid Suppressant Use

Approximately 43% of CACD patients had no reported antibiotic use in the 90 days prior to admission. Of those who did have antibiotics within 90 days of admission, a majority (625, 70% of antibiotic users, 40% of all patients) had last filled an antibiotic prescription within 30 days of their CACD admission. Median time elapsed between the last antibiotic fill date and subsequent initial CACD admission was 19 days (IQR 9–37). Rate of pre-admission CD treatment (oral metronidazole or vancomycin) use was low with less than 1% of patients having used PO vancomycin and less than 10% receiving PO metronidazole within one

week prior to admission. Eighteen percent of CACD patients filled a prescription for either vancomycin or metronidazole within 30 days prior to admission and 21% did so within 90 days.

Of patients with pre-admission antibiotic exposure, fluoroquinolones were the most commonly used with 17% of patients filling a prescription within 30 days of their CACD admission and 27% within 90 days (Table 2). Other commonly used antibiotics in the pre-admission period were cephalosporins (8.7% within 30 days, 13% within 90 days) and penicillin (8.6% within 30 days, 14% within 90 days). Patients receiving antibiotics used an average of 1.4 antibiotics with a median of 9 antibiotic days (IQR 6–11) in the 30 days prior to CACD admission and 2 antibiotics with a median of 10 antibiotic days (IQR 7–19) in the 90 days prior to admission. Only 8.8% of patients filled a prescription for a PPI in the month prior to CD admission and 1.3% filled a prescription for an H2 blocker.

Hospital Outcomes

Slightly less than 1 in 10 patients admitted with CACD died during their hospitalization (Table 3). Approximately 14% required ICU admission with a median ICU stay of 4 days (IQR 2–7). The rate of colectomy was low at 1%. Median overall hospital stay was just under 1 week (5 days, IQR 3–8). Approximately 20% of patients who survived their CACD hospitalization were readmitted with a primary diagnosis of CD within the study period with a median follow up time of 393 days (IQR 129–769 days). Median time from CACD discharge to readmission was 21 days (IQR 8–43). The median number of re-admissions during our follow-up period was 2 (IQR 2–4) with a range of 1–7.

Discussion

In this representative national sample of elderly Americans, we found that more than one third of all cases of CD were community acquired. While the majority of CACD patients did have recent exposure to oral antibiotics, nearly half of patients were not exposed to what historically has been considered the greatest risk factor for developing CD. CACD largely affected patients in the 8th decade of life and conferred a high mortality with nearly one in ten dying of their disease. Meanwhile, CD recurred at least once in two out of ten survivors after their initial CACD hospitalization.

We found that around 4 in 10 of our CD admissions were community-acquired infections which is at the higher end of previous reports that have estimated that CACD accounts for 20–40% of all CD cases.^{9,10,12} Importantly, these studies included patients of all ages whereas over 70% of our population was older than 75 and advanced age has been linked to a higher incidence of CD in both the hospital and in the community.^{1,2,15} Despite their advanced age, however, the majority of our cohort had few co-morbidities and a low incidence of gastrointestinal disorders such as inflammatory bowel disease, diverticulitis, or peptic ulcer disease. This indicates that CACD often affects relatively healthy, community dwelling elderly Americans who may not appear at risk for CD infection. Recent studies have shown that between 50 and 75% of CACD cases occur in patients over the age of 65, emphasizing the need for a high degree of clinical suspicion for CD in this age group.^{16–18}

Historically CD infections have been nearly universally associated with antibiotic use.^{19–21} However, most studies linking CD with antibiotic exposure were conducted in a hospital setting. Recent studies on CD in the community have reported lower rates of antibiotic exposure (47–78%).^{9,10,12,13,22} However, many of these studies have used locoregional data across multiple age groups that may not be generalizable nationally to older Americans. In our nationally representative sample of Medicare beneficiaries, approximately half of CACD patients had no antibiotic use within the 90 days prior to hospital admission. While antibiotic exposure may play a role in the acquisition of CACD, physicians should be aware that patients without recent antibiotic use may still be at risk for CD infection.

Among the patients who did use antibiotics prior to CACD admission, fluoroquinolones were the most commonly used antibiotic class in our cohort. Penicillins and cephalosporins were also used with some frequency. Fluoroquinolones have been cited as a more virulent cause of CD in several studies;^{21,23,24} however, there is no consensus regarding the antibiotic class most associated with CD infection. Two recent meta-analyses investigating the relationship between antibiotics and CACD stated that clindamycin and fluoroquinolones seem to pose the greatest risk of CD, but each acknowledged a wide amount of variation in the reported association of CD with various antibiotic classes.^{25,26} For CACD patients with pre-admission antibiotic exposure, the majority had received antibiotics within 30 days prior to admission. These findings are consistent with the previous literature that has suggested that the risk of antibiotic associated CD is greatest in the 4–6 weeks after use as this is when the colonic flora is the most disrupted.^{21,27} These data suggest that physicians should be most vigilant for antibiotic-related CACD in the immediate post-antibiotic period.

Only about 8% of patients in our cohort filled a prescription for vancomycin or metronidazole in the week prior to CD admission indicating that few were undergoing CD treatment at the time of their hospitalization. However, nearly 20% of patients received either vancomycin or metronidazole within the 30 days prior to their CD admission. This could represent a failure of treatment in patients receiving vancomycin and/or metronidazole. Recent studies have shown that CD infections have become more resistant to treatment with failure rates as high as 14–28%.^{28,29} Alternatively, vancomycin/metronidazole may have been prescribed for another indication (such as diverticulitis) in which case their use would not reflect an attempt at CD treatment. More than three quarters of the individuals in our study had no record of a prescription for vancomycin or metronidazole for any indication in the 90 days prior to their CD hospitalization. These data suggest that CD may be being under diagnosed and undertreated in the community setting.

Our patient population had very low rates of both PPI (8.8%) and H2 blocker (1.3%) use. Since many gastric acid suppressants are now available over the counter and so would not have been captured by Part D records it likely that our study underestimated exposure to these agents. Although some studies have shown that gastric acid suppressants in general, and PPIs in particular, may increase patients' risk of CD infection^{22,30,31} other studies have found no increased risk with either PPIs or H2 blockers.^{9,16,32} The mechanisms by which gastric acid suppression may increase patients' risk of CD is not well understood and warrants further investigation. Given the low frequency of PPI and H2 blocker use in our

sample we are unable to comment on any possible association between CACD and gastric acid suppressants.

We found a significant mortality risk of nearly 1 in 10 for patients admitted with CACD. This is nearly three-times higher than the mortality rates previously reported for CACD (2–4%).^{9,12,13} The rate of colectomy for our cohort (1%) was also higher than reported in other studies (0.3–0.8%).^{6,13,33} This may reflect a higher rate of severe/complicated cases of CD in our elderly cohort as advanced age has been shown to be an independent predictor of severe CD infection and poor outcomes.^{34,35} However, one study examining colectomy rates for CD patients in an intensive care unit reported a two-fold higher rate of colectomy in CACD patients compared with hospital acquired CD patients, indicating that CACD itself may be a predictor for severe disease.³³

One in every five patients with CACD in our study were re-admitted with CD during our study period, consistent with recurrence rates reported in other studies.^{9,12,36} On average, patients readmitted with CD returned to the hospital within a month of their initial CD hospitalization, indicating that CD infections may not have been fully eradicated during the index admission. Furthermore, the fact that so many patients had multiple re-admissions (as many as seven in our data period) suggests that there may be a chronic component to CD. Because rates of CD recurrence increases with each subsequent infection,^{35,37} more aggressive efforts to completely eradicate CD prior to discharge may be warranted in order to both break the cycle of CD relapse and to prevent infected patients from transmitting CD to others in the community. Additionally, the criteria for adequate CD treatment may need to be redefined.

This retrospective study of claims data does have several limitations. First, we do not have detailed clinical data that physicians may consider in their approach to elderly patients suspected of having CACD. Importantly, we lack laboratory or radiologic information that would allow us to comment more specifically on disease severity. 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.³⁸ In addition, prescription drug information is limited to medications that are paid for by Medicare. Over the counter medications or medications paid for out of pocket (e.g. low cost generic antibiotics) are not captured in our dataset even though they may play a role in the pathogenesis of CACD. Finally although we do not have detailed information about patients' living situations so it is possible that although patients admitted from nursing facilities were excluded, individuals in non-community settings such as group homes may be included in our cohort.

Nevertheless, to our knowledge, this national study is the first to utilize prescription drug data as a measure of antibiotic exposure. Prior studies have primarily relied on chart review or electronic medical record reports and have not been derived from national samples.^{10–13,16,32} This allowed us to capture when patients were filling prescriptions and better quantify relationships between CD and outpatient medications. Furthermore, given emerging data on the burden of CD on the elderly our use Medicare data allows us to

comment specifically on this group of patients who are underrepresented in the current literature.

The results of this study suggest that CACD is a significant source of mortality for elderly Americans, even those without significant comorbidities or risk factors for CD such as antibiotic use or gastrointestinal disease. Furthermore, many patients requiring admission for CD did not receive treatment in the outpatient setting indicating that physicians should be alert to the presence of CACD in order to diagnose and treat it early in the clinical course. Finally, a significant proportion of CACD patients who survive index hospitalization require readmission for CD after their index hospitalization, raising the concern that these infections are not being adequately eradicated in the hospital.

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Appendix 1. Antibiotic Classifications

Cephalosporins
Cefdinir/Omnicef
Cefpodoxime/Vantin
Cefaclor/Ceclor
Cefuroxime/Ceftin
Cephalexin/Keflex
Cephadroxil/cefadroxil
Cefprozil
Cefditoren/Pivoxil
Cefixime/Suprax
Ceftibuten/Cedax
Fluoroquinolones
Ciprofloxacin/Cipro
Gatifloxacin
Levofloxacin/Levaquin
Moxifloxacin/Avelox
Gemifloxacin/Factive
Norfloxacin/Noroxin
Ofloxacin/floxin
Lomefloxacin/Maxaquin
Penicillins
Amoxicillin/Amoxil
Oxacillin
Penicillin V/V-cillin K
Augmentin/Amoxicillin-clavulanic acid
Ampicillin
Dicloxicillin/dynapen
Carbenicillin/Geocillin
Macrolide
Azithromycin/Zithromax
Clarithromycin/Biaxin
Erythromycin/Erythrocin
Clindamycin
Clindamycin/Cleocin
Tetracyclines
Doxycycline/Vibratabs
Tetracycline
Minocycline

<u>Lymecycline</u>
<u>TB Drugs</u>
<u>Rifampin/Rifadin</u>
<u>Bactrim</u>
<u>Bactrim/Trimeth-Sulfa/Septra</u>
<u>Other Antibiotics</u>
Lorabid/loracarbef
Linezolid(zyvox)
Fosfomycin/Monurol
Telithromycin/Ketek
Nitrofurantoin

Precis

Community-acquired *Clostridium difficile* often affects healthy elderly patients, nearly half of whom had no exposure to antibiotics prior to their diagnosis. More than 10% of affected patients died during their *C difficile* hospitalization and 20% were hospitalized for a recurrence.

Table 1

Demographic and Clinical Characteristics of Medicare Beneficiaries with Community-Acquired *Clostridium difficile* Infection Requiring Hospital admission During 2009–2011 (n=1,566)

Characteristic	
Demographics	
Average age, y (SD)	80.3 (8.2)
Age group, y, n (%)	
65–74	446 (28.5)
75–84	532 (34)
85–94	536 (34.2)
95	52 (3.3)
Female, n (%)	1194 (76.3)
Race/ethnicity, n (%)	
Non-Hispanic white	1344 (85.8)
Non-Hispanic black	83 (5.3)
Hispanic	106 (6.8)
Other	33 (2.1)
Clinical characteristics	
Elixhauser score, n (%)	
0	855 (54.6)
1	72 (4.6)
2	107 (6.8)
3	131 (8.4)
4	401 (25.6)
Average Elixhauser score (SD)	2.5 (1.7)
Specific gastrointestinal comorbidities	
GERD	285 (18.2)
Diverticular disease	158 (10.1)
Inflammatory bowel disease	2.5 (1.7)
Colon cancer	23 (1.5)
Peptic ulcer disease	24 (1.5)
Antibiotic use within 90 d of admission	889 (56.8)
Treatment for <i>C. difficile</i> in the 7 days prior to CACD admission	
Oral metronidazole	123 (7.8)
Oral vancomycin	13 (0.8)

CACD, community-acquired *Clostridium difficile*.

Table 2

Antibiotic* Use by Class in Medicare Beneficiaries with Community-Acquired *Clostridium difficile* Requiring Hospital Admission (n = 1,566)

	Total used within 90 d prior to admission, n (%)	Used within 30 d prior to admission, n (%)	Used 31–60 d prior to admission, n (%)	Used 61–90 d prior to admission, n (%)
Any antibiotic	889 (56.8)	625 (40)	362 (23.1)	267 (17)
Fluoroquinolone	422 (26.9)	264 (16.9)	126 (8)	104 (6.6)
Cephalosporin	205 (13.1)	136 (8.7)	53 (3.4)	38 (2.4)
Penicillin	218 (13.9)	134 (8.6)	69 (4.4)	43 (2.7)
Clindamycin	135 (8.6)	56 (3.6)	61 (3.9)	26 (1.7)
Bactrim	136 (8.7)	73 (4.7)	53 (3.4)	35 (2.2)
Macrolides	114 (7.3)	57 (3.6)	38 (2.4)	34 (2.2)
Tetracycline	40 (2.6)	16 (1)	15 (1)	11 (0.7)
Tuberculosis drugs	4 (0.3)	1	3	2
Other antibiotics	136 (8.7)	39 (2.5)	27 (1.7)	26 (1.7)

* Excludes oral vancomycin and metronidazole, which are typically used to treat *C difficile*.

Table 3

Hospital Outcomes for Medicare Beneficiaries Admitted with Community-Acquired Clostridium difficile (n=1,566)

Clinical outcomes	
Mortality, n (%)	141 (9)
Colectomy, n (%)	15 (1)
ICU admission, n (%) [*]	223 (14.2)
ICU median length of stay, d (IQR)	4 (2–7)
Hospital median length of stay, d (IQR)	5 (3–8)
Subsequent admission for <i>C difficile</i> , n (%) [†]	306 (19.5)

^{*} No. of patients requiring ICU admission.

[†] No. of patients surviving index CACD hospitalization.