CLOSTRIDIUM DIFFICILE IN AN URBAN, UNIVERSITY-AFFILIATED LONG-TERM ACUTE CARE HOSPITAL

A Thesis
Submitted to
the Temple University Graduate Board

In Partial Fulfillment
of the Requirements for the Degree
MASTER OF SCIENCE

---

by
Jerry Jacob, MD
May 2016

Thesis Approvals:

Deborah B. Nelson, PhD, Thesis Advisor, Dept of Epidemiology and Biostatistics
Jingwei Wu, PhD, Dept of Epidemiology and Biostatistics
Jennifer Han, MD, MSCE, University of Pennsylvania

ABSTRACT

Background: *Clostridium difficile* is the most common cause of healthcare-associated infections in the United States, and has been associated with adverse outcomes in the acute care setting. However, little is known regarding the burden or impact of *C. difficile* infection (CDI) in long-term acute care hospitals (LTACHs).

Methods: A retrospective matched cohort study was performed among patients at an urban, university-affiliated LTACH between July 2008 and October 2015. The incidence rate of LTACH-onset CDI was assessed and patient characteristics associated with adverse outcomes examined. Patients with CDI were matched to concurrently hospitalized LTACH patients without a diagnosis of CDI. A multivariable model using logistic regression was developed to determine characteristics associated with a composite primary outcome of either 30-day readmission to an acute care hospital or mortality. Subgroup analyses were performed for patients with a diagnosis of severe CDI.

Results: The overall incidence of CDI was 21.4 cases per 10,000 patient-days. Patients with CDI had a mean age (±SD) of 70 ±14 years and a mean admission Charlson Comorbidity Index (CCI) of 4 ±2. Median (IQR) time between admission and diagnosis of CDI was 16 days (range: 9-23 days). In the final multivariable model, CDI was not a significant risk factor for the primary outcome (OR, 1.06 [95% confidence interval {CI}, 0.53-2.10]). Congestive heart failure (OR, 2.27 [95% CI, 1.15-4.57]), albumin level (OR, 0.44 [95% CI, 0.22-0.79]), and immunosuppression (OR, 2.94 [95% CI, 1.06-8.39]) were independent risk factors for the primary outcome. On subgroup analysis, severe CDI and CCI were significant risk factors for the primary outcome in bivariable analysis (OR,

2.91 [95% CI 1.03-8.20] and OR, 1.36 [95% CI 1.06-1.80], respectively). Only CCI remained significant in the multivariable model (OR, 1.32 [95% CI 1.02-1.75]).

Conclusions: LTACH-onset CDI was found to have a relatively high incidence in an urban, university affiliated LTACH. CDI was not a significant risk factor for the composite outcome of 30-day readmission or mortality. Future research should focus on infection prevention and antibiotic stewardship measures to decrease CDI specifically in the LTACH setting.

TABLE OF CONTENTS

Page

ABSTRACT……ii

LIST OF TABLES……...v

LIST OF FIGURES……...….vi

CHAPTER

1. INTRODUCTION……...1

2. BACKGROUND…….3

Clostridium difficile Infection……..……3

Long-term Acute Care Hospitals……..……...……4

CDI in LTACHs……...7

3. METHODS……..9

Study Design……9

Study Population…….9

Data Collection……..10

Statistical Analysis……11

4. RESULTS……..13

5. DISCUSSION……22

REFERENCES CITED……..27

LIST OF TABLES

Table Page

1. Characteristics of Patients with LTACH-onset CDI.....15

2. Characteristics of Unmatched Patients.....16

3. Characteristics of Matched CDI and non-CDI Patients.....17

4. Bivariable Logistic Regression Results…….18

5. Multivariable Logistic Regression Results……18

6. Characteristics of Severe CDI and Matched non-CDI Patients……19

7. Severe CDI Bivariable Logistic Regression Results…….20

8. Severe CDI Multivariable Logistic Regression Results……21

LIST OF FIGURES

Figure Page

1. Flowchart: Selection of CDI Hospitalizations…..…….....13

2. CDI Incidence by Year of Hospitalization ……..…….....14

3. Days to CDI Onset ……...……15

CHAPTER 1

INTRODUCTION

Clostridium difficile infection (CDI) is the most common healthcare-associated infection in the United States. It is associated with increased cost of hospitalization, prolonged length of stay, as well as substantial infection-related morbidity and mortality[1]. Significant quality improvement efforts and research funding have been invested into understanding the epidemiology, prevention, and control of CDI in healthcare settings. The majority of this work has been performed in the context of acute care hospitals. Only a few studies have been conducted in post-acute care settings, particularly skilled nursing facilities[2,3,4].

Long-term acute care hospitals (LTACHs) provide post-acute care to a complex patient population which is particularly susceptible to CDI due to prolonged healthcare contact, frequent antimicrobial use, and the presence of multiple comorbidities. Given the mortality and morbidity associated with CDI, the impact of these infections in LTACHs may be considerable. However, there have only been three studies to date describing the epidemiology and impact of CDI in the LTACH setting[5,6,3]. An improved understanding of CDI within LTACHs is becoming increasingly important as the baby boomer generation ages and more patients are cared for in these facilities. Knowledge of the burden of disease will help guide the allocation of resources between CDI prevention and other patient safety initiatives. Such knowledge will also be necessary to guide future interventional studies on infection prevention and antibiotic stewardship strategies tailored to this setting. Acute care hospitals will correspondingly benefit from this line of

research since there are frequent patient transfers between the two settings. Interventions to reduce CDI rates in LTACHs may, in turn, reduce CDI rates in acute care hospitals.

The Centers for Medicare and Medicaid Services (CMS) have included CDI rates as part of the LTACH Quality Reporting Program (QRP) from fiscal year 2016 onwards. The results of LTACH QRP metrics are made available to the public and may eventually affect payments for inpatient stays, similar to the current Hospital Value Based Purchasing program for acute care hospitals. Additional relevant outcomes for LTACHs include mortality rates and acute care hospital readmission rates. The latter outcome has been included in CMS LTACH QRP for fiscal year 2018.

Given this context, the overall objective of this retrospective cohort study was to provide a better understanding of the incidence and impact of CDI in an urban, university-affiliated LTACH. The primary aim of this study was to evaluate the association between LTACH-onset CDI and risk of 30-day readmission to an acute care hospital or death after onset of CDI. Secondary aims were: 1) To determine the impact of severe CDI on risk of 30 day readmission to an acute care hospital or death after onset of CDI; 2) To describe the incidence and severity of CDI in an LTACH; and 3) To describe the patient characteristics associated with LTACH-onset CDI.

CHAPTER 2

BACKGROUND

Clostridium difficile Infection

Clostridium difficile is a toxin-producing bacteria that infects the colon and produces a diarrheal illness among humans. It was first recognized as the cause of antibiotic-associated colitis in 1978, and has since developed a worldwide distribution. After a dramatic increase in incidence over the past few decades, *C. difficile* infection (CDI) is now the most commonly reported healthcare-associated infection in the United States.

The organism is transmitted from person to person in the form of spores which are resistant to heat, acid, and antibiotics. These spores are ubiquitous in healthcare facilities, and found in low levels in the environment and the food supply, allowing for both healthcare and community transmission. Patients colonized with *C. difficile* may have a spectrum of disease ranging from asymptomatic to potentially fatal as a result of colonic perforation. After CDI recovery, the risk of recurrence is 20% and as high as 60% after multiple recurrences. *C. difficile* infection-related mortality is 5%.[1] Major risk factors for CDI include antibiotic use, advanced age, chemotherapy, and gastric acid suppression. Antibiotics alter the normal ecology of the colonic microbiome, and thereby predispose to colonization and infection with *C. difficile.* As a result, antibiotic stewardship is an important focus in CDI prevention efforts[7].

Between 2001 and 2010, there was a significant increase in the incidence of CDI, in part due to the emergence of the virulent NAP1/027 strain which was responsible for CDI epidemics in the US and Canada. The second half of the decade saw a 47% increase

in cases of CDI compared to the first half.[8] A study in 2011 identified 453,000 *C. difficile* infections and 29,000 associated deaths in the US.[9] The current CDI incidence rate is almost 15 cases per 1000 hospital discharges[10], and 20 cases per 100,000 person years in the community[11]. Nosocomial infection with CDI quadruples the cost of hospitalization[1], and costs the US 1.5 billion dollars in expenditures every year.[12] Prior studies examining attributable length of stay due to CDI have demonstrated a range of results using various methodologies and designs. Most recently, a study of Veterans Affairs (VA) facilities using multistate modeling found an attributable length of stay of 4.11 days for cases of severe CDI, and 2.27 days for CDI cases overall.[13] For all of these reasons, *C. difficile* was designated as an "urgent threat" by the Centers for Disease Control and Prevention (CDC) in 2013.

Long-Term Acute Care Hospitals

Studies describing the epidemiology of *C. difficile* and other multi-drug resistant organisms have typically been performed in the context of the acute care hospital setting, and less commonly in the community setting. However, there is a third setting that plays an increasingly important role in acquisition of these pathogens, namely post-acute care. Post-acute care facilities, including long-term acute care hospitals (LTACHs), skilled nursing homes, subacute care, and inpatient rehabilitation facilities, are increasingly important healthcare settings that provide care for patients who have significant medical needs after an acute care hospitalization and are unable to be discharged to home.

LTACHs, in particular, were designed to help transition medically complex patients following acute care hospitalizations and decrease lengths of stay and Medicare spending in acute-care hospitals. LTACHs were first created in the 1980s and quadrupled in number between 1990 and 2004 as a result of incentives created by federal legislation. There are currently over 500 LTACHs in the US. LTACHs can be divided by for-profit or nonprofit lines, or, more commonly, according to their hospital affiliation: free–standing or ward-based (e.g., leasing a portion of preexisting acute care hospitals but remaining a separate entity)

LTACHs are required by CMS to care for patients who have "medically complex" circumstances, and a mean length of stay ≥ 25 days. They were originally geared towards patients in need of prolonged weaning from a mechanical ventilator, but current admission diagnoses include a wide range of diseases. Ventilator dependent respiratory failure remains the most common admission diagnosis. Other comorbidities include recent surgeries, malnutrition, chronic infections, receipt of total parenteral (i.e., intravenous) nutrition, and pressure ulcers[14]. These patients also have high rates of indwelling urinary catheter use, central venous catheter use, and percutaneous feeding tubes. Not surprisingly, the average severity of illness tends to be greater for LTACH patients than inpatients of acute care hospitals.

The majority of LTACH patients have had extended stays in acute care hospitals and particularly in intensive care units (ICUs). These healthcare exposures confer increased risk of hospital-based acquisition of *Clostridium difficile* and other multi-drug resistant organisms (MDROs). Prior studies in LTACHs have shown prevalence rates of

colonization with MDROs between 55% and 64%.[15,16] Multiple outbreaks with carbapenemase-producing organisms, referred to in the media as "superbugs", have been documented at LTACHs[17,18]. In circumstances where several regional facilities have experienced an MDRO outbreak, the spread among hospitals appears to follow the flow of colonized patients between acute care hospitals, LTACHs, and nursing homes.

Broad-spectrum antibiotic usage is high in LTACHs. The rates of carbapenem and vancomycin use in LTACHs are higher than the 50th percentile of hospital medical ICU use as reported by the National Nosocomial Infections Surveillance System. Furthermore, fluoroquinolones (a class of antibiotics strongly associated with development of CDI) were administered at a rate comparable to the 90th percentile for use in ICUs.[15] It is not known whether this level of antibiotic use is appropriate given the underlying disease states of the LTACH population. It is clear, however, that there is an urgent need for effective antibiotic stewardship programs in LTACHs.

As others have noted, all of these characteristics make LTACHs the "perfect storm" for antibiotic resistance and CDI infection.[15] LTACHs concentrate patients with medically complex situations, multiple comorbidities, colonization with multi-drug resistant organisms, and high rates of indwelling device and antibiotic use in one facility for extended periods of time. As a result, it would be expected that these facilities would also have high rates of infection, particularly with a healthcare-associated pathogen such as *C. difficile.* Despite the high prevalence of MDROs in this setting, very few studies have evaluated the epidemiology of MDROs in LTACHs.

CDI in LTACHs

While several investigators have studied CDI in the context of other long-term care facilities, very few studies have examined the epidemiology and impact of CDI specifically within LTACHs. In one of the earliest studies[3], investigators conducted point prevalence surveys among patients receiving antibiotics and developing diarrhea at a skilled nursing facility and a "chronic-care" hospital in Toronto from 1989 to 1990. The prevalence of CDI ranged from 7.1% to 14.1% in three point prevalence surveys over the course of a year at this "chronic-care" hospital. Most of the CDIs were associated with endogenous carriage of the organism, and little evidence was found for transmission.

Another study, published by Goldstein et al. in 2009, examined the incidence and prevalence of CDI in an 88 bed LTACH in the west Los Angeles area. Over a one month period, all new patient admissions to the LTACH without a prior diagnosis of CDI were screened using a *C. difficile* stool test. Patients were subsequently followed for development of diarrhea. Of those who had stool samples collected on admission, 4 of 31(12.9%) were found to be colonized with *C. difficile.* During the follow-up period, an additional 5 of 36 (13.8%) patients developed CDI. The incidence of CDI was 31.2 per 10,000 patient-days, and the average time from screening to the onset of diarrhea was 38.4 days.[6]

In 2013, Brakovich et al. examined the impact of a comprehensive infection control program on the incidence of CDI in an LTACH in the southeastern US. The program included components of environmental disinfection, surveillance, and antibiotic stewardship. Prior to implementation of the program, the quarterly incidence of CDI in

the facility was 56.52 infections per 10,000 patient-days. Over a two year period, the rate dropped by 44% to 31.51 infections per 10,000 patient days.[5] A search of the PubMed database found no other published studies examining the epidemiology of *C. difficile* specifically within the context of LTACHs.

It is important to note that all of the current literature on CDI in LTACHs focuses on the prevalence or incidence of CDI. There has been no published analysis of the clinical outcomes associated with CDI in LTACHs. Furthermore, none of the prior studies provide an accurate assessment of the baseline incidence and patient characteristics currently associated with CDI in LTACHs.

CHAPTER 3

METHODS

Study Design

We performed a retrospective matched cohort study examining the association between LTACH-onset CDI and a composite outcome of 30-day readmission to an acute care hospital or death. The study was performed at the Good Shepherd Penn Partners (GSPP) Specialty Hospital, a 38 bed long-term acute care hospital located in Philadelphia, Pennsylvania and affiliated with both the University of Pennsylvania Health System (UPHS) and the Good Shepherd Rehabilitation Network. The GSPP Specialty Hospital uses stool testing based on a combination of enzyme immunoassay and polymerase chain reaction for laboratory diagnosis of *C. difficile*. LTACH-onset CDI was defined as a hospitalization with a positive *C. difficile* stool test on day 4 or later at the GSPP Specialty Hospital between July 1, 2008 and October 1, 2015. This definition is based on criteria defined by the CDC for healthcare facility-onset CDI.

Study population

Theradoc clinical surveillance software was used to obtain a list of hospitalizations with a positive *C. difficile* stool test within the specified time period, along with the date of LTACH admission and the date of the positive test. Hospitalizations with multiple positive *C. difficile* tests were included only once, using the date of the initial positive stool toxin as the date of diagnosis. Severe CDI was diagnosed according to a recently derived and validated clinical prediction tool using three variables: age $\geq$ 65 years, peak serum creatinine $\geq$ 2 mg/dL and peak peripheral leukocyte count of $\geq$ 20,000 cells/μL.[19]

One point was assigned for each variable. Patients with scores of 2 or higher were classified as having severe CDI.

LTACH-onset CDI cases were matched to non-CDI hospitalizations based on length of stay prior to CDI diagnosis. Specifically, patients without CDI were matched to those with CDI based on concurrent hospitalization at the time of CDI diagnosis, and LTACH admission dates within 3 days of each other. The primary outcome was a composite measure of readmission to an acute care hospital or death within 30 days of the CDI diagnosis.

Data Collection

The list of selected CDI and matched non-CDI hospitalizations was submitted to the Penn Data Store, a clinical data warehouse consolidating information from multiple clinical systems within UPHS. Penn data store provided data for patient characteristics, dates of subsequent admissions to an acute care hospital, date of LTACH discharge, antibiotic administration between LTACH admission and CDI diagnosis, ventilator status, selected laboratory results and death. Laboratory values were retrieved from the time period between 5 days before to 2 days after collection of the stool sample. In rare cases where Penn Data Store was unable to distinguish between discharge from the LTACH to a non-UPHS acute care hospital or a lower level of care, LTACH patient records were reviewed directly by the study investigators to determine readmission status. Admission ICD-9 codes were obtained directly from the GSPP admissions department.

ICD-9 codes were used to determine baseline comorbidities and presence of immunosuppression as defined by transplant status, AIDS, or chronic steroid use.

The Charlson Comorbidity Index (CCI) is a score used to classify comorbid conditions and validated to predict mortality.[20] The CCI at admission to the LTACH was calculated for each patient using comorbidities identified on ICD-9 codes, and used as a marker for complexity of underlying illness.

Statistical Analysis

Descriptive statistics were calculated for baseline characteristics comparing CDI and non-CDI patients. Mean/median or standard deviation (SD)/interquartile range (IQR) were summarized for continuous variables and frequencies for categorical variables. Logistic regression was performed using a binary measure for the composite primary outcome as the dependent variable, and CDI exposure as the primary independent variable. Bivariable analyses were performed to assess for risk factors for the primary outcome. Subgroup analyses were performed to assess the risk of the primary outcome among those patients with severe CDI compared to their matched non-CDI patient.

Multivariable logistic regression was used to identify independent factors associated with risk of readmission or death within 30 days. Variables with $P<0.10$ on bivariable analysis and those considered clinically important were included the final multivariable model. Statistical analysis was performed using JMP, Version 12.1.0 (SAS Institute Inc., Cary, NC)

The study protocol was approved by the Temple University IRB, the University of Pennsylvania IRB, and the Research Committee at Good Shepherd Penn Partners.

CHAPTER 4

RESULTS

A total of 150 hospitalizations with a positive *C. difficile* toxin were identified between July 1, 2008 and October 1, 2015. One-hundred and thirty hospitalizations met criteria for LTACH-onset CDI. Of these, 107 CDI hospitalizations were able to be matched to a non-CDI hospitalization (Figure 1), and together, these 214 hospitalizations comprised the study population analyzed for the primary outcome.

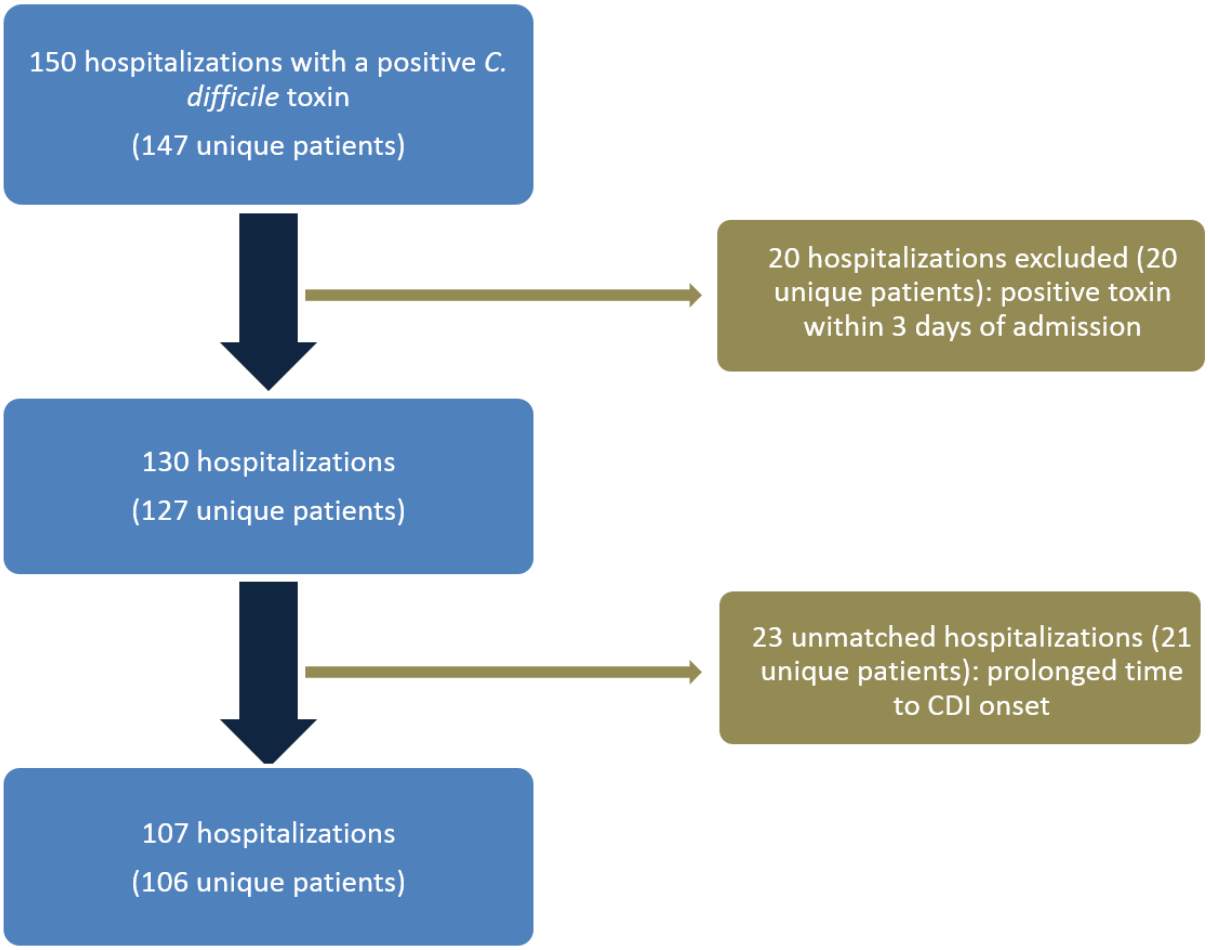

Figure 1. Flowchart: Selection of CDI Hospitalizations

The overall incidence rate of CDI was 21.4 per 10,000 patient-days. CDI incidence was relatively similar during each year of the study, with the exception of 2009 and 2010, when the incidence was 46.7 per 10,000 patient-days and 42.9 per 10,000 patient-days, respectively (Figure 2). Excluding years 2009 and 2010, the CDI incidence was 14.4 per 10,000 patient-days. The incidence of severe CDI was 5.6 per 10,000 patient-days.

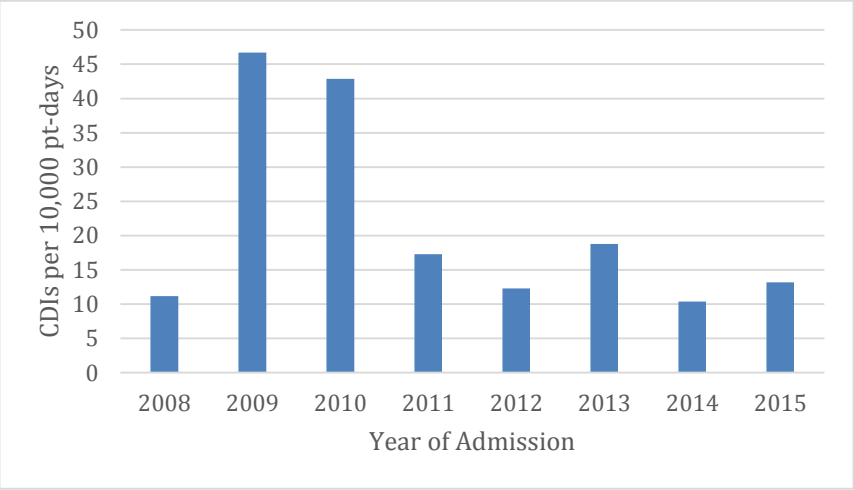

Figure 2. CDI Incidence by Year of Admission

Table 1 shows the characteristics of patients with LTACH-onset CDI. Patients with LTACH-onset CDI had a mean ±SD age of 70 ±14 years, and a mean ±SD CCI of 4±2. Twenty-seven percent of patients were classified as having severe CDI. Seventy-four percent of patients had respiratory failure, and one-half were noted to have a pressure ulcer on admission. The most common antibiotic class administered preceding CDI diagnosis was cephalosporin.

Table 1

Characteristics of Patients with LTACH-onset CDI

Characteristic[a]	N=130
Age in years, mean (±SD)	70 (±14)
Female	64 (49)
Length of stay in days, mean (±SD)	39 (±30)
CDI severity score, mean (±SD)	1 (±1)
Albumin (g/dL), mean (±SD)	2.3 (±0.6)
Severe CDI	34 (27)
Prior antibiotic use[b]	103 (79)
Prior fluoroquinolone use[b]	16 (12)
Prior cephalosporin use[b]	57 (44)
Respiratory failure	96 (74)
Pressure ulcer	65 (50)
Chronic kidney disease	54 (42)
Charlson Comorbidity Index, mean (±SD)	4 (±2)

[a]Reported as n (%), unless otherwise noted
[b]Administered between admission and CDI diagnosis

The median (IQR) time to onset of CDI was 16 (9-23) days (Figure 3). Several outliers were present, including one infection diagnosed on hospital day 140.

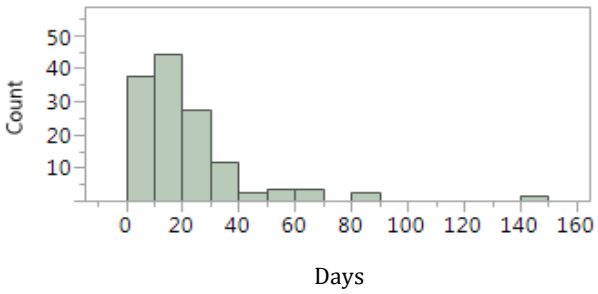

Figure 3. Days to CDI onset

Twenty-three hospitalizations with LTACH-onset CDI could not be matched to non-CDI hospitalizations. The unmatched CDI hospitalizations were noted to have longer times between admission and CDI onset (median [IQR], 34 [23-50] days). Characteristics of unmatched CDI hospitalizations are shown in Table 2.

Table 2

Characteristics of Unmatched CDI Patients

Characteristic[a]	(N=23)
Age in years, mean (±SD)	67 (±14)
Female	11 (48)
CDI severity score, mean (±SD)	1 (±1)
Severe CDI	6 (26)
Prior antibiotic use	22 (96)
Respiratory failure	15 (65)
Chronic kidney disease	14 (61)
Albumin (g/dL), mean (±SD)	2.4 (±0.5)
Pressure ulcer	12 (52)
CHF	11 (48)
CCI, mean (±SD)	4 (±2)
Time to CDI onset in days, median (IQR)	34 (23-50)
Length of stay in days, mean (±SD)	64 (±52)

[a]Reported as n (%), unless otherwise noted

Characteristics for matched CDI and non-CDI patients are shown in Table 3. Patients with CDI were significantly older than non-CDI patients (71 ± 14 vs 67 ± 14; P=0.049) with a higher peripheral leukocyte count (16.1±10.5 vs 10.6±4.9; P<0.01). A larger proportion of non-CDI patients were immunosuppressed (17% vs 7%; P=0.02)

Table 3

Characteristics of Matched CDI and non-CDI Patients

Characteristic[a]	CDI (N=107)	Non-CDI (N=107)	P value
Age, mean (±SD)	**71 (±14)**	**67 (±14)**	**0.049**
Female	54 (50)	59 (45)	0.49
Albumin (g/dL), mean (±SD)	2.3 (±0.6)	2.5 (±0.7)	0.15
Creatinine (mg/dL), mean (±SD)	1.6 (±1.5)	1.4 (±1.4)	0.43
WBC[b], mean (±SD)	**16.1 (±10.5)**	**10.6 (±4.9)**	**<0.01**
Respiratory failure	81 (76)	77 (72)	0.53
Chronic kidney disease	40 (37)	29 (27)	0.10
Liver Disease	11 (10)	8 (7)	0.47
Congestive heart failure	48 (45)	42 (39)	0.41
Immunosuppression	**7 (7)**	**18 (17)**	**0.02**
Pressure ulcer	53 (50)	44 (41)	0.22
Charlson Comorbidity index, mean (±SD)	3 (±2)	4 (±3)	0.15
Length of stay in days, mean (±SD)	34 (±19)	32 (±19)	0.32
Prior antibiotic use[c]	81 (76)	82 (77)	0.87
Prior fluoroquinolone use[c]	9 (8)	8 (8)	0.80
Readmission to acute care hospital within 30 days	36 (34)	34 (32)	0.88
Death within 30 days	13 (12)	11 (10)	0.83
Primary Outcome	41 (38)	39 (36)	0.89

[a]Reported as n (%), unless otherwise noted
[b]Peripheral leukocyte count in thousands/µL
[c]Administered between admission and index date (date of CDI diagnosis)

Results of bivariable logistic regression for the primary outcome of 30 day readmission to acute care hospital or death are shown in Table 4. Risk factors which met criteria for inclusion in the multivariable model and were related to the composite outcome included congestive heart failure (OR, 1.68 [95% CI 0.96-2.94]; P=0.07), albumin (OR, 0.50 [95% CI 0.28-0.86]; P=0.02) and immunosuppression (OR, 2.37 [95% CI 1.02-5.52]; P=0.045).

Table 4

Bivariable Logistic Regression Results

Risk Factor	OR (95% CI)	P value
CDI	1.08(0.62-1.88)	0.78
Congestive heart failure	**1.68(0.96-2.94)**	**0.07**
Respiratory failure	0.81(0.43-1.51)	0.51
Pressure ulcer	1.06(0.61-1.85)	0.83
Chronic kidney disease	1.02(0.56-1.84)	0.95
Female	0.74(0.42-1.29)	0.29
Liver disease	1.24(0.48-3.23)	0.66
Immunosuppression	**2.37(1.02-5.52)**	**0.045**
Age	1.01(0.99-1.03)	0.37
Albumin	**0.50(0.28-0.86)**	**0.02**
Charlson Comorbidity Index	1.08(0.96-1.22)	0.22

Multivariable logistic regression results are shown in Table 5. On multivariable analysis, congestive heart failure (OR, 2.27 [95% CI, 1.15-4.57]; P=0.02) and immunosuppression (OR, 2.94 [95% CI, 1.06-8.39]; P=0.04) were associated with a greater risk of the primary outcome. Higher albumin was also inversely related to 30 day readmission or death, with an adjusted OR of 0.44 (95% CI, 0.22-0.79; P=0.01). CDI remained nonsignificant (OR, 1.06 [95% CI, 0.53-2.10]; P=0.87).

Table 5

Multivariable Logistic Regression Results

Risk Factor	OR (95% CI)	P value
CDI	1.06 (0.53-2.10)	0.87
Congestive heart failure	**2.27 (1.15-4.57)**	**0.02**
Albumin	**0.44 (0.22-0.79)**	**0.01**
Immunosuppression	**2.94 (1.06-8.39)**	**0.04**

Note: Generalized R^2, 0.12; P<0.01

A subgroup analysis was performed among those patients with severe CDI and their matched non-CDI patient. Characteristics of these patients are shown in Table 6. As expected, the patients with severe CDI were older (74±7 vs 65±13; P<0.01) with a higher peripheral leukocyte count (23.6±16.1 vs 11.7±6.1; P<0.01) and a higher creatinine (2.69±1.84 vs 1.20±0.81; P<0.01). These patients also had a lower albumin level (2.1±0.5 vs 2.5±0.7; P=0.04), a higher prevalence of congestive heart failure (69% vs 39%; P=0.02), and a higher prevalence of chronic kidney disease (61% vs 26%; P<0.01).

Table 6

Characteristics of Severe CDI and Matched non-CDI Patients

Characteristic[a]	Severe CDI (N=31)	Non-CDI (N=31)	P value
Age, mean (±SD)	**74 (±7)**	**65 (±13)**	**<0.01**
Female	9 (29)	16 (52)	0.07
Albumin (g/dL), mean (±SD)	**2.1 (±0.5)**	**2.5 (±0.7)**	**0.04**
Creatinine (md/dL), mean (±SD)	**2.69 (±1.84)**	**1.20 (±0.81)**	**<0.01**
WBC[b], mean (±SD)	**23.6 (±16.1)**	**11.7 (±6.1)**	**<0.01**
Respiratory failure	23 (74)	25 (81)	0.54
Chronic kidney disease	**19 (61)**	**8 (26)**	**<0.01**
Liver disease	4 (13)	1 (3)	0.35
Congestive heart failure	**21 (68)**	**12 (39)**	**0.02**
Immunosuppression	2 (6)	6 (19)	0.12
Pressure ulcer	15 (48)	12 (39)	0.44
Charlson Comorbidity Index, mean (±SD)	4 (±2)	4 (±3)	0.11
Length of stay in days, mean (±SD)	32 (±23)	31 (±19)	0.94
Prior antibiotic use[c]	24 (77)	26 (84)	0.52
Prior fluoroquinolone use[c]	3 (10)	2 (6)	0.64
Primary Outcome	18 (58)	10 (32)	0.07

[a]Reported as n(%), unless otherwise noted
[b]Peripheral leukocyte count in thousands per µL
[c]Administered between admission and index date (date of CDI diagnosis)

Results of bivariable logistic regression for the primary outcome of 30-day readmission to acute care hospital or death are shown in Table 7. Patients with severe CDI were significantly more likely to meet the primary outcome compared to their matched cohort (OR, 2.91 [95% CI, 1.03-8.20]; P=0.04). The only other significant risk factor was CCI (OR, 1.36 [95% CI, 1.06-1.80]; P=0.02)

Table 7

Severe CDI Bivariable Logistic Regression Results

Risk Factor	OR (95%CI)	P value
Severe CDI	**2.91 (1.03-8.20)**	**0.04**
Congestive heart failure	2.28(0.82-6.37)	0.11
Respiratory failure	0.78(0.24-2.56)	0.68
Pressure ulcer	0.55(0.20-1.55)	0.26
Chronic kidney disease	2.12(0.76-5.88)	0.15
Female	0.92(0.33-2.57)	0.88
Liver disease	5.5 (0.58-52.34)	0.10
Immunosuppression	1.25(0.28-5.53)	0.77
Age	1.02(0.98-1.07)	0.41
Albumin	0.47(0.17-1.19)	0.13
Charlson Comorbidity Index	**1.36(1.06-1.80)**	**0.02**

Multivariable logistic regression results are shown in Table 8. On multivariable analysis, only CCI was a significant risk factor for the primary outcome, with an OR of 1.32 (95% CI, 1.02-1.75; P=0.04). Severe CDI was no longer significant when including the CCI in the model (OR, 2.48 [95% CI, 0.84-7.48]; P=0.10].

Table 8

Severe CDI Multivariable Logistic Regression Results

	OR (95%CI)	P value
Severe CDI	2.48 (0.84-7.48)	0.10
Charlson Comorbidity index	**1.32 (1.02-1.75)**	**0.04**

Note: Generalized R^2, 0.18; P=0.03

CHAPTER 5

DISCUSSION

Our study at an urban, university-affiliated LTACH revealed that the incidence of *Clostridium difficile* infection was 21.4 per 10,000 patient-days over the course of 7.25 years. More than one-quarter of all infections were classified as severe. Patients with CDI also had a prolonged length of stay (39 ± 30 days) compared to the average LTACH length of stay of 25 days (as determined by CMS requirements). The median time between admission and diagnosis of CDI was 16 (9-23 days), with a clustering of infections within the first 2-3 weeks. Even without accounting for antibiotic use during preceding acute care hospitalizations, the rate of prior antibiotic use in this cohort approached 80%. LTACH-onset CDI was not found to be an independent risk factor for the composite primary outcome of 30 day readmission or mortality. Congestive heart failure, immunosuppression and a decreased albumin were each associated with a greater than 2 fold increase in the odds of 30 day readmission or mortality.

The results of our study demonstrate a baseline rate of CDI incidence that is significantly higher than reported rates for acute care hospitals. The CDC's Emerging Infections Program found a median incidence of hospital-onset CDI in acute care hospitals of 5.4 per 10,000 patient days in 2010.[21] Even after removing two years of data from a potential CDI outbreak, the LTACH incidence rate reported here is more than 2.5 times higher than the CDC's reported rate for acute care hospitals. These findings are concerning and highlight a significant LTACH burden of disease which has received little attention in the literature to date. Compared to LTACH incidence rates reported by

Brakovich et al and Goldstein et al, the rate reported here is lower.[5,6] However, those prior reports are limited by shorter time periods and may not reflect more current CDI practices.

These findings confirm our expectations that LTACH patients are at particularly high risk for CDI given their prolonged hospitalizations, frequent antibiotic use, and severe underlying comorbidities. Current CDI prevention efforts in acute care hospitals include antimicrobial stewardship programs, appropriate use of contact isolation precautions, hand hygiene, ideally with soap and water, and effective environmental disinfection. Such efforts may need to be intensified and standardized for the LTACH population. Compared to acute care hospitals, significantly less resources and personnel are currently available for infection prevention efforts in long-term acute care, similar to the circumstances in nursing homes. A "call to action" for antimicrobial stewardship in long-term care facilities, particularly LTACHs, was recently issued in the literature.[22] The results of our study reinforce the need for such action.

Similar to previous studies[23,24], we found that CDI was associated with older age, higher peripheral leukocyte count, and lower albumin. However, immunosuppression has generally been considered a risk factor for CDI based on obvious biological reasons as well as some prior published literature which is contrary to the results here.[25,26] There are a few possible explanations for these findings. The numbers of immunosuppressed patients in each cohort were relatively small, and, therefore, may not have accurately captured the risk for CDI among this group. The use of ICD-9 codes, rather than

medications, to determine immunosuppression status also suggests the possibility of misclassification or inadequate capture of all cases of immunosuppression.

We found no significant association between CDI and the primary composite outcome of 30-day readmission or mortality. Instead, the risk for these adverse outcomes was driven by underlying comorbidities. Congestive heart failure, albumin, and immunosuppression are each markers of biological or physiological reserve. Congestive heart failure reflects the ability of the body to augment cardiac output; albumin is a marker of nutritional status; and immunosuppression affects the body's major defense mechanisms. Each of these factors affects the capacity of a patient to respond to any number of insults, including infections such as *C. difficile*.

These findings suggest that the primary determinant for adverse outcomes in the LTACH population is the extent of their underlying comorbidities and severity of illness, as reflected by albumin. These comorbidities often play a role earlier in the patient's course leading to the prolonged nature of their hospitalizations and the need for LTACH admission. Our results reinforce the notion that LTACH patients require a strong focus on nutrition, rehabilitation, and optimization of underlying medical problems, in addition to standard efforts at prevention and treatment of hospital-acquired infections.

The potential impact of severe CDI on the primary outcome should also be noted. Severe CDI demonstrated an increased risk of 30-day readmission to an acute care hospital or death on bivariate analysis, and trended towards an increased risk on multivariable analysis. This classification system for severe CDI was previously validated to predict adverse outcomes, including ICU admission or death, among

inpatients with CDI at three acute care hospitals.[19] Given that more than a quarter of patients in our study with LTACH-onset CDI were found to have severe disease, the potential association with readmissions and/or death in LTACH patients with severe CDI should be evaluated in larger studies.

Our study has several limitations. First, approximately 18% of hospitalizations with LTACH-onset CDI could not be matched to a non-CDI hospitalization. The unmatched CDI patients appeared to have more extensive comorbidities, as demonstrated by a high rate of chronic kidney disease, a high Charlson Comorbidity Index, and a prolonged length of stay. However, only 30% of these unmatched patients met the primary outcome, compared to 38% among the matched CDI patients. Therefore, it seems unlikely our conclusions would have changed if all LTACH-onset CDI cases had been matched and included. Second, we made no distinction between incident CDI and recurrent CDI. The latter may occur in patients who are older and have refractory disease, which may predispose to more adverse outcomes. Third, we did not capture patients who were discharged to a lower level of care (e.g., home, skilled nursing facility), and then readmitted within 30 days to a non-UPHS hospital. It is important to note that the majority of admissions to the LTACH come through UPHS and more than 85% of acute transfers from the LTACH are sent to UPHS hospitals. Furthermore, there is no clear reason to expect differential admission rates for CDI and non-CDI patients to non-UPHS hospitals. In addition, the high rates of readmission/mortality already noted in our study suggest that no substantial changes would have occurred in our results if these patients had been identified. Fourth, the accuracy of ICD-9 coding is dependent on the medical

coders responsible for chart review during each admission. It is possible that use of ICD-9 coding may have led to misclassification or lack of capture for certain comorbidities, particularly immunosuppression.

The findings here outline the importance of future studies focusing on interventions, such as antimicrobial stewardship programs, to reduce the high incidence of CDI among LTACH populations. In particular, increased use of non-cephalosporin classes of antibiotics may be helpful, as cephalosporins were the most commonly administered antibiotic preceding CDI in our cohort. Studies are also required to determine the source of acquisition for LTACH-onset CDI cases. It is possible that detailed epidemiological or molecular studies may reveal that CDI cases occurring in LTACHs, even on day 4 or later, are acquired in the acute care setting prior to LTACH arrival, in which case efforts may need to be redirected to acute settings.

In summary, our findings indicate that there is a significant burden of *C. difficile* in LTACHs, especially those within an urban and tertiary-care associated setting. LTACH patients have a high baseline risk for a variety of adverse outcomes, indicating that they require specialized attention and care. Given our increasingly aging population and the increasing role of post-acute care in our health systems, there has never been a more urgent time to develop targeted and effective prevention efforts for this fragile group of patients.

REFERENCES CITED

1. Lofgren ET, Cole SR, Weber DJ, Anderson DJ, Moehring RW. Hospital-acquired Clostridium difficile infections: estimating all-cause mortality and length of stay. Epidemiol Camb Mass, **2014**; 25:570–575.

2. Guerrero DM, Nerandzic MM, Jury LA, Chang S, Jump RL, Donskey CJ. Clostridium difficile infection in a Department of Veterans Affairs long-term care facility. Infect Control Hosp Epidemiol, **2011**; 32:513–515.

3. Simor AE, Yake SL, Tsimidis K. Infection Due to Clostridium difficile Among Elderly Residents of a Long-Term-Care Facility. Clin Infect Dis, **1993**;17:672–678.

4. Ziakas PD, Zacharioudakis IM, Zervou FN, Grigoras C, Pliakos EE, Mylonakis E. Asymptomatic carriers of toxigenic C. difficile in long-term care facilities: a meta-analysis of prevalence and risk factors. PloS One, **2015**;10:e0117195.

5. Brakovich B, Bonham E, VanBrackle L. War on the spore: Clostridium difficile disease among patients in a long-term acute care hospital. J Healthc Qual, **2013**; 35:15–21.

6. Goldstein EJC, Polonsky J, Touzani M, Citron DM. C. difficile infection (CDI) in a long-term acute care facility (LTAC). Anaerobe, **2009**;15:241–243.

7. Leffler DA, Lamont JT. Clostridium difficile infection. N Engl J Med, **2015**; 372:1539–1548.

8. Halabi WJ, Nguyen VQ, Carmichael JC, Pigazzi A, Stamos MJ, Mills S. Clostridium Difficile Colitis in the United States: A Decade of Trends, Outcomes, Risk Factors for Colectomy, and Mortality after Colectomy. J Am Coll Surg, **2013**; 217:802–812.

9. Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of Clostridium difficile infection in the United States. N Engl J Med, **2015**;372:825–834.

10. Steiner C, Barret M, Weiss A. HCUP projections: Clostridium difficile hospitalizations 2001 to 2013. HCUP Projections Report #2014-01. Rockville, MD: Agency for Healthcare Research and Quality, **2014**. Available from: http://hcup-us.ahrq.gov/reports/projections/2014-03.pdf

11. Chitnis AS, Holzbauer SM, Belflower RM, et al. Epidemiology of community-associated Clostridium difficile infection, 2009 through 2011. JAMA Intern Med, **2013**;173:1359–1367.

12. Zimlichman E, Henderson D, Tamir O, et al. Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. JAMA Intern Med, **2013**; 173:2039–2046.

13. Stevens VW, Khader K, Nelson RE, et al. Excess Length of Stay Attributable to Clostridium difficile Infection (CDI) in the Acute Care Setting: A Multistate Model. Infect Control Hosp Epidemiol, **2015**; 36:1024–1030.

14. Munoz-Price LS. Long-term acute care hospitals. Clin Infect Dis, **2009**; 49:438–443.

15. Gould CV, Rothenberg R, Steinberg JP. Antibiotic resistance in long-term acute care hospitals: the perfect storm. Infect Control Hosp Epidemiol, **2006**; 27:920–925.

16. Munoz-Price LS, Stemer A. Results of four years of admission multidrug-resistant screening cultures at a long-term acute care hospital (LTACH) [abstract 183]. In: Program and abstracts of the 19th Annual Scientific Meeting of the Society for Healthcare Epidemiology of America (San Diego). Arlington, VA: Society for Healthcare Epidemiology of America, **2009**.

17. Endimiani A, Perez F, Hujer AM, et al. Emergence of blaKPC-containing Klebsiella pneumoniae isolates in a long-term acute care facility (LTACF) in south Florida [abstract C2–3732]. In: Program and abstracts of the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/46th Infectious Diseases Society of America (IDSA) Annual Meeting (Washington, DC). American Society of Microbiology and Infectious Diseases Society of America, **2008**.

18. Lolans K, Rice TW, Munoz-Price LS, Quinn JP. Multicity outbreak of carbapenem-resistant Acinetobacter baumannii isolates producing the carbapenemase OXA-40. Antimicrob Agents Chemother, **2006**; 50:2941–2945.

19. Na X, Martin AJ, Sethi S, et al. A Multi-Center Prospective Derivation and Validation of a Clinical Prediction Tool for Severe Clostridium difficile Infection. PloS One, **2015**;10:e0123405.

20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis, **1987**;40:373–383.

21. Mcdonald LC, Lessa F, Sievert D, et al.Vital Signs: Preventing Clostridium difficile Infections. MMWR Morb Mortal Wkly Rep, **2012**: 61: 157-162.

22. Chopra T, Goldstein EJC. Clostridium difficile Infection in Long-term Care Facilities: A Call to Action for Antimicrobial Stewardship. Clin Infect Dis, **2015**; 60 Suppl 2:S72–6.

23. Tabak YP, Johannes RS, Sun X, Nunez CM, McDonald LC. Predicting the risk for hospital-onset Clostridium difficile infection (HO-CDI) at the time of inpatient admission: HO-CDI risk score. Infect Control Hosp Epidemiol, **2015**;36:695–701.

24. Bulusu M, Narayan S, Shetler K, Triadafilopoulos G. Leukocytosis as a harbinger and surrogate marker of Clostridium difficile infection in hospitalized patients with diarrhea. Am J Gastroenterol, **2000**; 95:3137–3141.

25. Kamthan AG, Bruckner HW, Hirschman SZ, Agus SG. Clostridium difficile diarrhea induced by cancer chemotherapy. Arch Intern Med, **1992**;152:1715–1717.

26. Zacharioudakis IM, Ziakas PD, Mylonakis E. Clostridium difficile infection in the hematopoietic unit: a meta-analysis of published studies. Biol Blood Marrow Transplant, **2014;** 20:1650–1654.