ORIGINAL ARTICLE

Clostridium difficile in an Urban, University-Affiliated Long-Term Acute-Care Hospital

Jerry Jacob, MD, MS;[1] Jingwei Wu, PhD;[2] Jennifer Han, MD, MSCE;[1,a] Deborah B. Nelson, PhD[2,a]

OBJECTIVES. To describe the characteristics and impact of *Clostridium difficile* infection (CDI) in a long-term acute-care hospital (LTACH).

DESIGN. Retrospective matched cohort study.

SETTING. A 38-bed, urban, university-affiliated LTACH.

METHODS. The characteristics of LTACH-onset CDI were assessed among patients hospitalized between July 2008 and October 2015. Patients with CDI were matched to concurrently hospitalized patients without a diagnosis of CDI. Severe CDI was defined as CDI with 2 or more of the following criteria: age ≥65 years, serum creatinine ≥2 mg/dL, or peripheral leukocyte count ≥20,000 cells/μL. A conditional Poisson regression model was developed to determine characteristics associated with a composite primary outcome of 30-day readmission to an acute-care hospital, or mortality.

RESULTS. The overall incidence of CDI was 21.4 cases per 10,000 patient days, with 27% of infections classified as severe. Patients with CDI had a mean age of 70 years (SD, 14 years), a mean Charlson comorbidity index of 3.6 (SD, 2.0), a median length of stay of 33 days (interquartile range [IQR], 24–45 days), and a median time between admission and CDI diagnosis of 16 days (IQR, 9–23 days). The most commonly prescribed antibiotic preceding a CDI diagnosis was a cephalosporin, with median duration of 8 days (IQR, 4–14 days). In multivariate analysis, CDI was not significantly associated with the primary outcome (relative risk, 0.97; 95% CI, 0.59–1.58).

CONCLUSIONS. Incidence of CDI in an urban, university-affiliated LTACH was high. Future research should focus on infection prevention measures to decrease the burden of CDI in this complex patient population.

Infect Control Hosp Epidemiol 2017;38:294–299

Clostridium difficile is the most commonly reported pathogen to cause healthcare-associated infections in the United States.[1] *Clostridium difficile* infection (CDI) has been associated with increased cost of hospitalization, prolonged length of stay, and substantial infection-related morbidity and mortality.[2] For these reasons, *C. difficile* was designated as an "urgent threat" by the Centers for Disease Control and Prevention (CDC) in 2013, and significant research and quality improvement efforts have been invested in the prevention and control of CDI in acute-care hospitals. A limited number of studies have been conducted in post–acute-care settings and have focused primarily on nursing homes or skilled nursing facilities.[3–5]

Long-term acute-care hospitals (LTACHs) provide post-acute care to a complex patient population that is particularly susceptible to CDI. These facilities concentrate patients with multiple comorbidities, colonization with multidrug-resistant organisms, high rates of antibiotic use, and indwelling device use into 1 facility for extended periods of time. Others have noted that these characteristics make LTACHs the "perfect storm" for antibiotic resistance.[6] For the same reasons, LTACHs are also favorable environments for CDI. Given the mortality and morbidity associated with CDI, the impact of these infections in LTACHs may be considerable.

The role of LTACHs is also becoming increasingly important as the population ages and more patients are cared for in these facilities. 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 onward. However, few studies to date have examined the epidemiology, treatment, prevention, or outcomes of CDI in LTACHs.[7–9] We sought to describe the characteristics and impact of CDI in an urban, university-affiliated LTACH.

Affiliations: 1. Department of Medicine, Division of Infectious Diseases, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; 2. Department of Epidemiology and Biostatistics, College of Public Health, Temple University, Philadelphia, Pennsylvania.

[a]Authors of equal contribution.

Received August 2, 2016; accepted November 2, 2016; electronically published December 7, 2016

 0899-823X/2017/3803-0006. DOI: 10.1017/ice.2016.291

METHODS

Study Design

A retrospective matched cohort study was conducted from July 1, 2008, to October 1, 2015, to evaluate the association between LTACH-onset CDI and a composite outcome of 30-day readmission to an acute-care hospital, or mortality. The study was performed at a 38-bed LTACH affiliated with the University of Pennsylvania Health System (UPHS). All *C. difficile* stool testing for the LTACH was performed at the Clinical Microbiology Laboratory of the Hospital of the University of Pennsylvania. Stool samples were tested by immunoassay for glutamate dehydrogenase (GDH) antigen and toxins A and B. Discordant results were followed by a cytotoxicity assay between July 2008 and December 2010 and by nucleic acid amplification testing between December 2010 and October 2015.

Study Population

The catchment area for the LTACH is composed of tertiary and community hospitals within the city of Philadelphia. Theradoc clinical surveillance software (Premier, Salt Lake City, UT) was used to obtain a list of LTACH hospitalizations with positive *C. difficile* stool tests within the specified time period. All patients with LTACH-onset CDI during the study period were included. LTACH-onset CDI was defined as a positive *C. difficile* stool test occurring on day 4 or later of a patient's hospitalization at the LTACH. This definition was based on the National Healthcare Safety Network (NHSN) definition for healthcare-facility–onset CDI.[10] 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 using a recently derived and validated clinical prediction tool with 3 criteria: age ≥65 years, peak serum creatinine ≥2 mg/dL and peak peripheral leukocyte count ≥20,000 cells/μL.[11] Patients meeting 2 or more of these criteria were classified as having severe CDI.

Hospitalizations with LTACH-onset CDI were matched on a 1:1 basis with non-CDI hospitalizations based on LTACH length of stay prior to CDI diagnosis and concurrent LTACH admission. 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 of interest was a composite measure of readmission to an acute-care hospital or death within 30 days of CDI diagnosis. This study was approved by the institutional review board of the University of Pennsylvania and the Research Committee of Good Shepherd Penn Partners.

Data Collection

Patient data were obtained using Penn Data Store, a clinical data warehouse consolidating information from multiple clinical systems within UPHS. Data were collected on patient demographics, comorbidities, 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 ascertained for the period 5 days before to 2 days after collection of the stool sample. In rare cases for which Penn Data Store was unable to provide the necessary data, LTACH patient medical records were reviewed directly by the study investigators. Gastrointestinal procedures, including endoscopy and fecal microbiota transplant, were not performed at the LTACH during the study period. *International Classification of Disease, Ninth Revision* (ICD-9) admission codes were obtained from the LTACH admissions department. ICD-9 codes were used (1) to determine the presence of immunosuppression as defined by solid organ or hematopoietic stem cell transplant status, HIV infection with a CD4+ T-cell count of <200 cells/mm^3, or chronic corticosteroid use and (2) to calculate the Charlson comorbidity index (CCI).[12] The CCI was used as a marker for complexity of underlying illness.

Statistical Analysis

Descriptive statistics were calculated for baseline characteristics comparing patients with and without CDI. Mean or median and standard deviation (SD) or interquartile range (IQR) were summarized for continuous variables and frequencies (proportions) for categorical variables. Patient characteristics were compared across groups using the Student *t* test or the Mann-Whitney test for continuous variables, and χ^2 or Fischer's exact test for categorical variables. To account for the matched cohort study design, conditional Poisson regression was performed using a binary measure for the composite primary outcome as the dependent variable and CDI exposure as the primary independent variable, with calculation of relative risk (RR).[13] Bivariate analyses were performed to evaluate potential risk factors for the primary outcome.

Multivariate conditional Poisson regression was then performed. Variables with $P < .10$ on bivariate analysis and those considered clinically important were included in the final multivariate model. Subgroup analyses were performed to identify risk factors for the primary outcome among those patients with severe CDI, along with matched patients without CDI. Statistical analysis was performed using JMP software, version 12 (SAS, Cary, NC) and Stata, version 14.0 (StataCorp, College Station, TX).

RESULTS

A total of 150 hospitalizations with a positive *C. difficile* toxin were identified between July 1, 2008, and October 1, 2015. Overall, 130 hospitalizations (87%) met the definition for LTACH-onset CDI (Figure 1).

https://doi.org/10.1017/ice.0000-0.291 Published online by Cambridge University Press

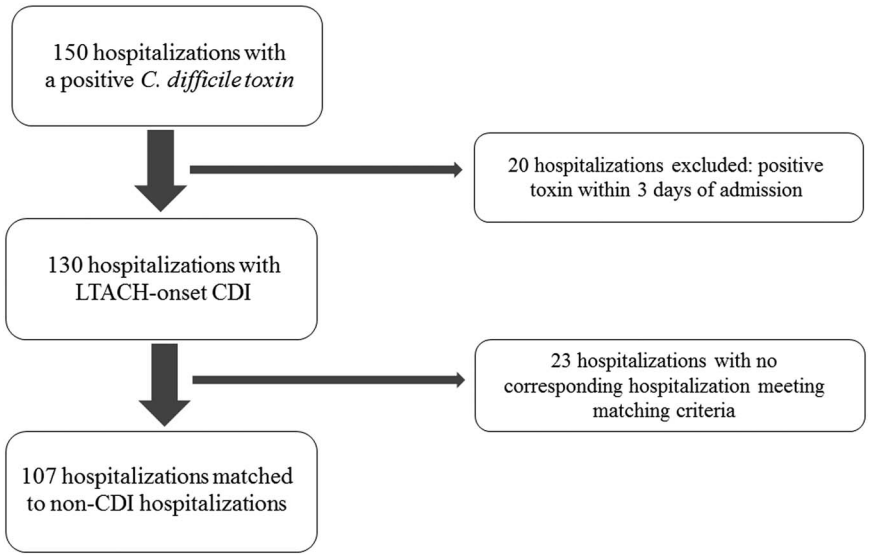

FIGURE 1. Flowchart detailing selection of CDI hospitalizations.

TABLE 1. Characteristics of Patients With LTACH-Onset *Clostridium difficile* Infection

Characteristic	No. (%) (n = 130)[a]
Age, y, mean (SD)	70 (14)
Female	64 (49)
Length of stay, d, median (IQR)	33 (24–45)
CDI severity score, mean (SD)	1 (1)
Albumin (g/dL), mean (SD)	2.3 (0.6)
Severe CDI[b]	34 (27)
Prior antibiotic use[c]	103 (79)
Prior fluoroquinolone use[c]	16 (12)
Prior cephalosporin use[c]	57 (44)
Respiratory failure	96 (74)
Inflammatory bowel disease	1 (0)
Pressure ulcer	65 (50)
Chronic kidney disease	54 (42)
Charlson comorbidity index, mean (SD)	3.6 (2.0)

NOTE. SD, standard deviation; CDI, *Clostridium difficile* infection.
[a]Unless otherwise indicated.
[b]Defined as ≥2 of the following criteria: age ≥65 years, serum creatinine ≥2 mg/dL, or peripheral leukocyte count ≥20,000 cells/μL.
[c]Administered between admission and CDI diagnosis.

The overall incidence of CDI was 21.4 cases per 10,000 patient days. The CDI incidence was relatively similar during each year of the study, with the exception of 2009 and 2010, when the rates were 46.7 per 10,000 patient days and 42.9 per 10,000 patient days, respectively. 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.

Table 1 shows the characteristics of patients with LTACH-onset CDI. Patients with LTACH-onset CDI had a mean age of 70 years (SD, 14), and a mean CCI of 3.6 (SD, 2). In total, 34 (27%) patients were classified as having severe CDI.

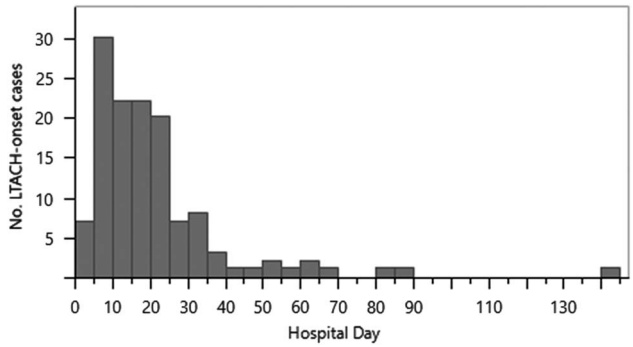

FIGURE 2. Time in days between admission to the long-term acute-care hospital and onset of *Clostridium difficile* infection.

In addition, 96 patients (74%) had respiratory failure, and 65 (50%) were noted to have a pressure ulcer on admission. The most common antibiotic class administered preceding CDI diagnosis was a cephalosporin, with a median duration of 8 days (IQR, 4–14 days). The median time from LTACH admission to onset of CDI was 16 days (IQR, 9–23 days) (Figure 2). Several outliers were noted, including 1 infection diagnosed on hospital day 140.

There were 23 hospitalizations with LTACH-onset CDI that could not be matched to hospitalizations without CDI and were not included in the analyses (Figure 1). Compared with the matched CDI cases, the unmatched CDI hospitalizations were had a longer median time between admission and CDI onset (34 days [IQR, 23–50 days] vs 14 days [IQR, 8–20 days]; $P < .01$), a longer median length of stay (46 days [IQR, 32–88 days] vs 32 days [IQR, 22–42 days]; $P < .01$), as well as a higher mean CCI score (4.3 [SD, 2.1] vs 3.4 [SD, 1.9]; $P = .04$).

Characteristics for matched patients with and without CDI are shown in Table 2. Patients with CDI were older than

https://doi.org/10.1017/ice.0000-0.291 Published online by Cambridge University Press

TABLE 2. Characteristics of Matched Patients With and Without *Clostridium difficile* Infection

Characteristic	CDI, No. (%) (N = 107)[a]	No CDI, No. (%) (N = 107)[a]	*P* Value
Age, mean (SD)	71 (14)	67 (14)	.049
Female	54 (50)	59 (45)	.49
Albumin, g/dL, mean (SD)	2.3 (0.6)	2.5 (0.7)	.15
Creatinine, mg/dL, mean (SD)	1.6 (1.5)	1.4 (1.4)	.43
Peripheral leukocyte count, mean (SD)[a]	16.1 (10.5)	10.6 (4.9)	<.01
Charlson comorbidity index, mean (SD)	3.4 (1.9)	3.9 (2.6)	.15
Respiratory failure	81 (76)	77 (72)	.53
Chronic kidney disease	40 (37)	29 (27)	.10
Liver disease	11 (10)	8 (7)	.47
Congestive heart failure	48 (45)	42 (39)	.41
Immunosuppression	7 (7)	18 (17)	.02
Pressure ulcer	53 (50)	44 (41)	.22
Length of stay, d, median (IQR)	32 (22–42)	28 (19–38)	.16
Prior antibiotic use[b]	81 (76)	82 (77)	.87
Prior fluoroquinolone use[b]	9 (8)	8 (8)	.80
Readmission to acute-care hospital within 30 d	36 (34)	34 (32)	.88
All-cause mortality within 30 d	13 (12)	11 (10)	.83
Primary outcome	41 (38)	39 (36)	.89

NOTE. SD, standard deviation; CDI, *Clostridium difficile* infection.
[a]Peripheral leukocyte count in thousands/mm^3.
[b]Administered between admission and CDI diagnosis.

patients without CDI (mean [SD], 71 [14] years vs 67 [14] years; $P = .049$) and had a higher peripheral leukocyte count (mean [SD], 16.1 [10.5] thousands/mm^3 vs 10.6 [4.9] thousands/mm^3; $P < .01$). A larger proportion of patients without CDI were immunosuppressed (17% vs 7%; $P = .02$).

Results of bivariate and multivariate regression analyses for the primary outcome of 30-day readmission to acute-care hospital or death are shown in Table 3. CDI was not a significant risk factor for the primary outcome on bivariate analysis (RR, 1.05 [95% CI, 0.68–1.63]; $P = .82$). The only significant risk factor on bivariate analysis was serum creatinine level (RR, 1.34 [95% CI, 1.02–1.77]; $P = .04$); CCI was borderline significant (RR, 1.15 [95% CI, 0.99–1.34]; $P = .06$). CDI remained nonsignificant in the multivariate model (RR, 0.97 [95% CI ,0.59–1.58]; $P = .90$). Increased serum creatinine level trended toward an increased risk for the primary outcome on multivariate analysis (RR, 1.28 [95% CI, 0.95–1.74]; $P = .10$).

A subgroup analysis was performed using data from those patients with severe CDI and their corresponding matched patients without CDI. As expected given the definition of severe CDI patients with severe CDI were older (mean [SD], 74 [7] years vs 65 [14] years; $P < .01$) and had higher peripheral leukocyte counts (mean [SD], 24.3 [16.5] thousands/mm^3 vs 11.4 [6.2] thousands/mm^3; $P < .01$) and higher serum creatinine levels (mean [SD], 2.72 [1.91] mg/dL vs 1.23 [0.28] mg/dL; $P < .01$). These patients also had a higher prevalence of chronic kidney disease (61% vs 25%; $P < .01$).

Results of regression analysis in the severe CDI subset were similar to the overall results. Severe CDI was not a significant risk factor for the primary outcome (RR, 1.89 [95% CI, 0.84–4.24]; $P = .12$). On bivariate analysis, CCI (RR, 1.37 [95% CI, 1.00–1.86]; $P = .047$) and serum creatinine level (RR, 1.84 [95% CI, 1.06–3.18]; $P = .03$) were significant risk factors for the primary outcome. Increased serum creatinine trended toward an increased risk for the primary outcome on multivariate analysis (RR, 1.73 [95% CI, 0.93–3.21]; $P = .08$).

DISCUSSION

Our study at an urban, university-affiliated LTACH found that the incidence of *Clostridium difficile* infection was 21.4 per 10,000 patient days over the course of 7.25 years. More than 25% of infections were classified as severe. Patients with CDI also had a prolonged length of stay (33 days) compared to the CMS-designated average LTACH length of stay of 25 days. 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.

The results of our study demonstrate a baseline incidence rate of CDI that was significantly higher than reported rates for acute-care hospitals. A majority of the study LTACH's admissions come from 3 neighboring acute care hospitals. These hospitals reported a pooled incidence rate of hospital-onset CDI of 9.3 per 10,000 patient days between September 2014 and October 2015 (CMS). 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.[14] Even after removing 2 years of data (2009 and 2010) from a potential CDI outbreak, the LTACH rate reported here is more than 2.5 times higher than the CDC's reported rate for

https://doi.org/10.1017/ice.0000-0.291 Published online by Cambridge University Press

TABLE 3. Bivariate and Multivariate Conditional Poisson Regression of Risk Factors for Composite Outcome of 30-Day Readmission or Mortality in LTACH Patients With and Without *Clostridium difficile* Infection

	Bivariate		Multivariate	
Risk Factor	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
CDI	1.05 (0.68–1.63)	.82	0.97 (0.59–1.58)	.90
Age	1.01 (0.99–1.03)	.39	…	…
Female	0.69 (0.38–1.26)	.23	…	…
Albumin	0.59 (0.28–1.22)	.16	…	…
Creatinine	1.34 (1.02–1.77)	.04	1.29 (0.95–1.74)	.10
Charlson comorbidity index	1.15 (0.99–1.34)	.06	1.07 (0.90–1.27)	.47
Congestive heart failure	1.63 (0.87–3.03)	.13	…	…
Respiratory failure	0.67 (0.34–1.31)	.24	…	…
Pressure ulcer	0.91 (0.51–1.65)	.76	…	…
Liver disease	1.2 (0.36–3.93)	.76	…	…
Immunosuppression	1.75 (0.73–4.17)	.21	…	…

NOTE. RR, relative risk; CI, confidence interval; CDI, *Clostridium difficile* infection.

acute-care hospitals. Furthermore, the proportion of cases classified as severe is approximately 2.5 times higher than the rate reported for acute-care hospitals in a study using the same definition (27% vs 10.9%).[11] These findings are concerning and highlight a significant LTACH burden of disease that has received little attention in the literature to date.

To our knowledge, only 3 studies have previously reported the incidence rate of CDI in the LTACH setting. In 2009, Goldstein et al[7] reported a CDI rate of 31.2 per 10,000 patient days over the course of 1 month at an 88-bed LTACH in Los Angeles. In addition, 2 other studies reported baseline CDI rates of 56.5 per 10,000 patient days and 31.5 per 10,000 patient days at LTACHs in the southeastern United States.[8,9] The CDI rates in the latter studies declined over the course of approximately 2 years to 31.5 per 10,000 patient days and 8.3 per 10,000 patient days, respectively, using multifaceted infection prevention programs. While the CDI rates reported in these studies are generally higher than the rate reported here, these studies are also limited by shorter time periods and potential outbreak situations.

The results of our study confirm 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, contact isolation precautions, hand hygiene (ideally with soap and water), and effective environmental disinfection. Such efforts should be intensified and standardized for the LTACH population.

Antibiotic stewardship warrants greater attention among LTACH patients. Although antibiotic use was not directly compared between the CDI and non-CDI groups, nearly 80% of patients with LTACH-onset CDI were found to have received antibiotics between their admission to the LTACH and their CDI diagnoses. Given that >50% of patients in acute-care hospitals receive an antibiotic during their inpatient stay,[15] it is likely that a large proportion of LTACH patients have received antibiotics during their preceding hospitalizations as well. A prior report by Gould et al[6] indicates that the rates of carbapenem and vancomycin use in LTACHs are higher than the 50th percentile of use for medical intensive care units (ICUs), and that fluoroquinolones, a class of antibiotics strongly associated with development of CDI, are administered at a rate comparable to the 90th percentile of use for medical ICUs. A "call to action" for antimicrobial stewardship in long-term care facilities, particularly LTACHs, was recently issued by Chopra and Goldstein.[16] The results of our study reinforce the need for such action.

Further studies are required to determine the source of acquisition for LTACH-onset CDI cases. Detailed epidemiological or molecular studies may reveal that a substantial proportion of 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 surveillance definitions may need to be adjusted. An argument for such changes has been made in the context of long-term care facilities.[17] Regardless of the source of acquisition, however, these cases remain potential sources of onward transmission and warrant specialized attention to infection prevention measures.

We found no significant association between CDI and the primary composite outcome of 30-day readmission or mortality. While the 30-day mortality rate in our study was within the range reported for hospital-onset CDI,[18–20] the risk of readmission to an acute-care hospital would depend significantly on the need for ICU-level care. Specifically, medical care delivered in an acute-care hospital non-ICU setting can generally be performed within the LTACH. The proportion of CDI cases requiring ICU-level care is likely to be small. Another potential explanation is that CDI plays a relatively insignificant role in the risk of hospital readmission when it occurs in the context of a severe comorbidity burden, as noted in the LTACH population. Along these lines, the mean CCI score for LTACH patients with CDI was higher than the scores reported for community-onset and hospital-onset CDI cases.[18,21] The mean length of stay was >30 days, and the rate of the

https://doi.org/10.1017/ice.0000-0.291 Published online by Cambridge University Press

primary outcome was high in both the CDI and non-CDI groups (38% and 36%, respectively)

Our study has several limitations. First, approximately 18% of hospitalizations with LTACH-onset CDI could not be matched to a non-CDI hospitalization. However, only 30% of unmatched patients met the primary outcome, compared with 38% among the matched CDI patients. Therefore, it is unlikely that our conclusions would have changed if all LTACH-onset CDI cases had been matched and included. Second, our dataset did not include information regarding proton-pump inhibitor or probiotic use, which may potentially have effects on CDI incidence. Third, for the primary outcome, we did not capture patients who were discharged to a lower level of care (eg, home, skilled nursing facility) and then readmitted to a non-UPHS hospital, or who expired in a non-UPHS setting. However, most admissions to the study LTACH are from UPHS-affiliated hospitals, and >85% of acute transfers from the LTACH are sent to UPHS-affiliated hospitals. Furthermore, differential admission rates between patients with CDI and patients without CDI to non-UPHS hospitals is unlikely. 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.

These findings outline the importance of future studies focusing on interventions, such as antimicrobial stewardship programs, to reduce the high incidence rate of CDI among LTACH populations. 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 complex group of patients.

ACKNOWLEDGMENTS

We would like to thank the Penn Data Store for their assistance in assembling the information used in this study.

Financial Support. No financial support was provided relevant to this article.

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article.

Address correspondence to Dr Jerry Jacob, Good Shepherd Penn Partners, 1800 Lombard St, Philadelphia, PA 19146 (jerry.jacob@uphs.upenn.edu)

REFERENCES

1. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care–associated infections. *N Engl J Med* 2014;370:1198–1208.
2. Lofgren ET, Cole SR, Weber DJ, Anderson DJ, Moehring RW. Hospital-acquired *Clostridium difficile* infections: estimating all-cause mortality and length of stay. *Epidemiology* 2014;25:570–575.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. Brakovich B, Bonham E, VanBrackle L. War on the spore: *Clostridium difficile* disease among patients in a long-term acute care hospital. *J Healthcare Qual* 2013;35:15–21.
9. Miller R, Simmons S, Dale C, Stachowiak J, Stibich M. Utilization and impact of a pulsed-xenon ultraviolet room disinfection system and multidisciplinary care team on *Clostridium difficile* in a long-term acute care facility. *Am J Infect Control* 2015;43:1350–1353.
10. National Healthcare Safety Network. Multidrug-resistant organism and *Clostridium difficile* infection module. Centers for Disease Control and Prevention website. http://www.cdc.gov/nhsn/pdfs/pscmanual/12pscmdro_cdadcurrent.pdf. Updated May 2016. Accessed Jun 17, 2016.
11. 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.
12. 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.
13. Cummings P, Mcknight Barbara. Analysis of matched cohort data. *Stata J* 2004;4:274–281.
14. McDonald LC, Lessa F, Sievert D, et al. Vital signs: preventing *Clostridium difficile* infections. *MMWR* 2012;61:157–162.
15. Fridkin S, Baggs J, Fagan R, et al. Vital signs: improving antibiotic use among hospitalized patients. *MMWR Morb Mortal Wkly Rep* 2014;63:194–200.
16. Chopra T, Goldstein EJC. *Clostridium difficile* infection in long-term care facilities: a call to action for antimicrobial stewardship. *Clin Infect Dis* 2015;60:S72–S76.
17. Mylotte JM. Surveillance for *Clostridium difficile*-associated diarrhea in long-term care facilities: what you get is not what you see. *Infect Control Hosp Epidemiol* 2008;29:760–763.
18. Hensgens MPM, Goorhuis A, Dekkers OM, van Benthem BHB, Kuijper EJ. All-cause and disease-specific mortality in hospitalized patients with *Clostridium difficile* infection: a multicenter cohort study. *Clin Infect Dis* 2013;56:1108–1116.
19. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. *N Engl J Med* 2015;372:825–834.
20. 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.
21. Khanna S, Pardi DS, Aronson SL, et al. The epidemiology of community-acquired *Clostridium difficile* infection: a population-based study. *Am J Gastroenterol* 2012;107:89–95.