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Major Article

Burden of *Clostridium difficile* infection: Associated hospitalization in a cohort of middle-aged and older adults

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Background: *Clostridium difficile* is the principal cause of infectious diarrhea in hospitalized patients. The aim of this study was to describe and compare length of stay (LOS), costs, and in-hospital deaths for *C difficile* infection (CDI) and non-CDI hospitalizations, in a cohort of middle-aged and older Australians.
Methods: We used survey data from the 45 and Up Study, linked to hospitalization and death data. We calculated the average LOS and costs per hospitalization, and the proportion of in-hospital deaths for CDI and non-CDI hospitalizations. We then compared hospitalizations with CDI as a secondary diagnosis to non-CDI hospitalizations by stratifying hospitalizations based on principal diagnosis and then using generalized linear models to compare LOS and in-hospital costs, and logistic regression for in-hospital deaths, adjusting for age and sex.
Results: There were 641 CDI hospitalizations during 2006-2012. The average LOS was 17 days; the average cost per hospitalization was AUD 12,704; and in 7.3% of admissions (47 out of 641) the patient died. After adjusting for age and sex, hospitalizations with CDI were associated with longer LOS, higher costs, and a greater proportion of in-hospital deaths compared with hospitalizations with similar principal diagnosis but without CDI.
Conclusions: CDI places additional burden on the Australian hospital system, with CDI patients having relatively lengthy hospital stays and high costs.

Clostridium difficile is the principal cause of infectious diarrhea in hospitalized patients.[1] Globally, the incidence of *C difficile* infection (CDI) has increased significantly during the past decade, resulting in a considerable burden on health care systems. A recent systematic review of 45 CDI cost-of-illness studies confirmed a significant economic impact of CDI, and reported excess CDI costs ranging from $8,911-$30,049 per admission for hospitalized patients.[2] Most (84%) of the selected studies were from the United States and all focused on direct costs.[2]

In Australia, national surveillance for hospital-identified CDI has demonstrated increasing incidence since 2011,[3] although data on the burden of CDI-associated hospitalization are limited. One Australian study estimated that hospital-acquired *C difficile*-associated enterocolitis added AUD 19,745 to the cost of each hospital episode, making it among the most costly hospital-acquired conditions in public hospitals during 2007-2008.[4] However, this study focused on costs associated with hospital-acquired CDI, and the burden of all CDI hospitalizations was not reported. Our recent study found that the incidence of CDI hospitalization was 16.6 per 100,000 person-years in middle-aged and older Australians.[5] The aim of this study

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This research was completed using data collected through the 45 and Up Study (www.saxinstitute.org.au). The 45 and Up Study is managed by the Sax Institute in collaboration with major partner Cancer Council NSW and partners, including the National Heart Foundation of Australia (New South Wales Division); New South Wales Ministry of Health; New South Wales Government Family & Community Services—Careers, Ageing, and Disability Inclusion; and the Australian Red Cross Blood Service.
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was to describe and compare length of stay (LOS), costs, and in-hospital deaths for CDI and non-CDI hospitalizations, in a cohort of middle-aged and older Australians.

METHODS

Study population and data sources

We used data from the Sax Institute's 45 and Up Study, a prospective cohort study of healthy aging involving 267,153 men and women aged 45 years and older from the general population of the Australian state of New South Wales (NSW) (2006 population, 6.8 million persons).[6] Participants were randomly selected from the Medicare Australia database, which includes all citizens and permanent residents of Australia, and some temporary residents and refugees. Approximately 10% of the population of NSW aged 45 years and older was included in the final cohort. More details of the 45 and Up Study can be found elsewhere.[7]

The 45 and Up Study participants completed a mailed self-administered questionnaire and consent form. The baseline questionnaire is available at http://www.saxinstitute.org.au/ourwork/45-up-study/questionnaires. In this study, self-reported questionnaire data collected from 45 and Up Study participants at recruitment from 2006-2009 were linked to the NSW Admitted Patient Data Collection (date of recruitment-June 30, 2012), and the NSW Register of Births, Deaths, and Marriages (date of recruitment-June 30, 2012). The Admitted Patient Data Collection includes records of principal diagnosis for each admission, and up to 54 additional diagnoses contributing to the admission, coded using the ICD-10-Australian Modification.[8,9] These data also include the Australian Refined Diagnosis Related Group (DRG) code for each admission. Each DRG represents a class of patients with similar clinical conditions requiring similar hospital resources.[10] The NSW Centre for Health Record Linkage performed the data linkage independently of the study investigators and report false-positive and false-negative linkages of <0.5% and <0.1%, respectively.[11]

Case definition

Cases were defined as hospitalizations following the recruitment into the 45 and Up study with either the principal diagnosis or a secondary diagnosis of *C difficile* colitis (ICD-10-Australian Modification code A04.7). In Australia, CDI is diagnosed based on clinical features and presentation, along with diagnostic tests, including stool culture, polymerase chain reaction-based assays, cell-culture cytotoxicity assays, and enzyme immunoassays detecting *C difficile* glutamate dehydrogenase, and/or toxin A and/or B.[12]

Hospitalization outcomes

Outcomes included in-hospital deaths, LOS (discharge date minus admission date, plus 1 day for same-day admission), and costs of hospitalization. For patients who had been transferred between hospitals, relevant hospitalization records were merged to avoid double counting of unique hospitalizations. To estimate the costs of each hospitalization, we matched DRG codes of each hospitalization to DRG-based cost data from the National Hospital Cost Data Collection Public Sector Estimated Cost Weights Reports (NHCDC).[13] The NHCDC documents average costs per DRG, based on patient-cost and cost-modeled information. We used the average DRG-specific total costs per admission in the Round 14 (2009-2010) NHCDC (version 5.2 for admissions from January 2006-December 2009 and version 6.0x from admissions from January 2010-June 2012). Costs are reported in Australian dollars.

Patient characteristic variables

Sociodemographic information was obtained from the baseline questionnaire and included age (grouped as 45-54, 55-64, 65-74, 75-84, or ≥85 years), sex, annual household income (7 categories from AUD <20,000-70,000 or more per year), and region of residence (cities, inner regional, or outer regional/remote) based on the Accessibility/Remoteness Index of Australia.

Analysis

Participants were followed from the date of recruitment to June 30, 2012, the last date for which hospital data were available. Participants were excluded from the analyses if they had missing data on date of entry into study, or if they had any DRG code or cost information missing.

We first summarized the sociodemographic characteristics of the patients for all hospital hospitalizations in the study period, separately for CDI and non-CDI hospitalizations. We calculated the average LOS and costs per hospitalization, as well as the proportion of hospitalizations in which a patient died, separately for CDI and non-CDI hospitalizations, by age group. To compare outcomes of hospitalizations with CDI as a secondary diagnosis to hospitalizations without a secondary diagnosis of CDI, we further selected all the hospitalizations that fit into 4 major disease categories based on principal diagnosis (digestive disease, cardiovascular disease, neoplasm, and respiratory disease), and calculated the age-adjusted average LOS and costs, and the proportion with in-hospital deaths. Digestive disease, cardiovascular disease, neoplasm, and respiratory disease constituted the majority of principal diagnoses for which CDI was a secondary diagnosis in the study, and hence were chosen for this analysis. To compare the results, we used a generalized linear model assuming a negative binomial distribution for LOS and a gamma distribution for in-hospital costs, and logistic regression for in-hospital deaths. Exact logistic regression was used when sample size was < 5. All models were adjusted for age and sex. All analyses were carried out using Stata version 14.1 (Stata Corp, College Station, TX).

Ethics approval

Ethics approvals for this study were obtained from the University of New South Wales Human Research Ethics Committee, the NSW Population and Health Services Research Ethics Committee, and the Australian National University Human Research Ethics Committee. All participants provided written informed consent.

RESULTS

There were 641 hospitalizations with CDI during the study period. The average age at hospitalization was 76.7 ± 11.2 years, and 45% of patients were men. There were 712,178 hospitalizations without CDI and the average age of these patients was 70.4 ± 11.4 years, 53% were men. Table 1 summarizes the demographic characteristics of patients hospitalized with and without CDI during the study period.

Of those patients hospitalized with CDI, 7.3% (47 out of 641) died during hospitalization. The average number of days in hospital was 17 (interquartile range, 5-22 days), and the average cost per hospitalization was AUD 12,704 (interquartile range, AUD 4,998-AUD 13,356). In 35% (225 out of 641), CDI was classified as the principal diagnosis.

Table 2 compares the outcomes of hospitalization among patients hospitalized with CDI and those hospitalized without CDI during the study period, by age group. Compared with non-CDI hospitalizations, CDI-hospitalizations had greater average LOS, costs,