# MORBIDITY, MORTALITY, AND HEALTHCARE BURDEN OF NOSOCOMIAL *CLOSTRIDIUM DIFFICILE*–ASSOCIATED DIARRHEA IN CANADIAN HOSPITALS

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## ABSTRACT

**OBJECTIVE:** To assess the healthcare burden, morbidity, and mortality of nosocomial *Clostridium difficile*–associated diarrhea (N-CDAD) in Canadian hospitals.

**DESIGN:** Laboratory-based prevalence study.

**SETTING:** Nineteen acute-care Canadian hospitals belonging to the Canadian Hospital Epidemiology Committee surveillance program.

**PATIENTS:** Hospitalized patients in the participating centers.

**METHODS:** Laboratory-based surveillance was conducted for *C. difficile* toxin in stool among 19 Canadian hospitals from January to April 1997, for 6 continuous weeks or until 200 consecutive diarrhea stool samples had been tested at each site. Patients with N-CDAD had to fulfill the case definition. Data collected for each case included patient demographics, length of stay, extent of diarrhea, complications of CDAD, CDAD-related medical interventions, patient outcome, and details of death.

**RESULTS:** We found that 371 (18%) of 2,062 tested patients had stools with positive results for *C. difficile* toxin, of whom 269 (13%) met the case definition for nosocomial CDAD. Of these, 250 patients (93%) had CDAD during their hospitalization, and 19 (7%) were readmitted because of CDAD (average readmission stay, 13.6 days). Forty-one patients (15.2%) died, of whom 4 (1.5% of the total) were considered to have died directly or indirectly of N-CDAD. The following N-CDAD–related morbidity was noted: dehydration, 3%; hypokalemia, 2%; gastrointestinal hemorrhage requiring transfusion, 1%; bowel perforation, 0.4%; and secondary sepsis, 0.4%. The cost of N-CDAD readmissions alone was estimated to be a minimum of $128,200 (Canadian dollars) per year per facility.

**CONCLUSION:** N-CDAD is a common and serious nosocomial infectious complication in Canada, is associated with substantial morbidity and mortality, and imposes an important financial burden on healthcare institutions (*Infect Control Hosp Epidemiol* 2002;23:137-140).

*Clostridium difficile*–associated diarrhea (CDAD) continues to be a leading cause of nosocomial diarrhea.[1-6] Despite this fact, and the knowledge that CDAD can manifest as severe disease in certain patients, the impact of nosocomial CDAD (N-CDAD) and its related morbidity and mortality in Canada remain to be objectively measured. To evaluate the prevalence of N-CDAD in Canada and its impact on patients and the healthcare system, we conducted a focused surveillance project among 19 Canadian hospitals, in 8 provinces, that participate in the Canadian Hospital Epidemiology Committee (CHEC). CHEC is a joint initiative by the Canadian Infectious Diseases Society and the Canadian Nosocomial Infection Surveillance Program (part of Health Canada). The epidemiology of N-CDAD among these institutions has been described previously.[7]

## METHODS

At participating CHEC hospitals, all inpatient stools that were submitted to the hospital laboratory in a liquid or semi-formed condition were screened for the presence of *C. difficile* cytotoxin by the method currently in use at that hospital (ie, cytotoxin assay or growth of *C. difficile* bacteria with evidence of toxin production). In addition, surveillance included the endoscopy laboratory, looking for patients with typical pseudomembranes on sigmoidoscopy or colonoscopy.

A *C. difficile* "potential" case was defined as any hospitalized individual with positive results for *C. difficile* cytotoxin, or with pseudomembranes by endoscopy. When a *C. difficile* potential case was identified, the hospital's infection control practitioner reviewed the patient's chart to determine whether the patient met the project's case definition of CDAD, which was consistent with the definition proposed by the Society for Healthcare Epidemiology of America: acute onset of loose stools that persisted for at least 2 days without an alternative explanation. In addition, all cases of CDAD had to fulfill one of two criteria required to ensure that CDAD was nosocomi-

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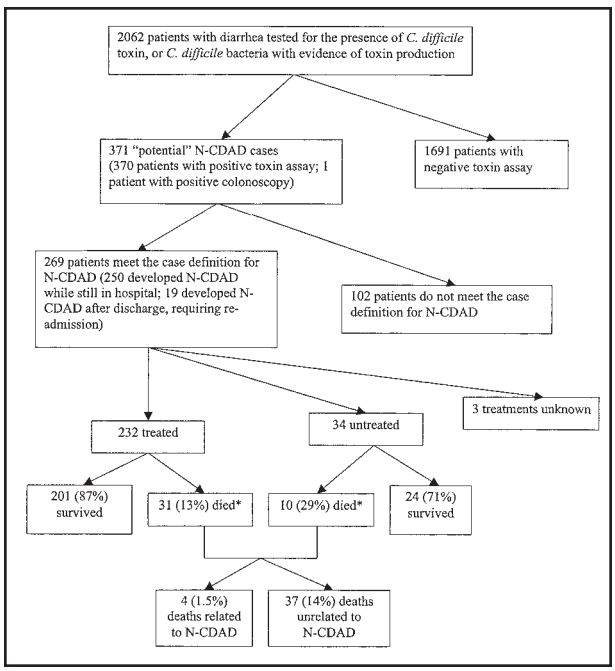


**FIGURE.** Patient distribution in the surveillance project on nosocomial *Clostridium difficile*–associated diarrhea (N-CDAD). *Odds ratio of not having received N-CDAD therapy among those who died: 2.7 (95% confidence interval, 1.1 to 6.6; $P < .05$).

ally acquired: symptoms starting 3 days or more after admission, or symptoms causing readmission of a patient who was discharged from the participating facility or any other healthcare facility within 1 month prior to the current admission date.

Participating sites collected data between January and April 1997 for 6 continuous weeks or until 200 consecutive diarrhea stool samples had been tested at each site. For patients who met the project's definition of having N-CDAD, further information was collected, including gender, date of birth, type of N-CDAD case (primary, relapse, or reinfection), location, treatment, and investigations done. Relapses were arbitrarily defined as cases that recurred within 2 weeks of the end of the previous treatment for N-CDAD, whereas reinfections were arbitrarily defined as cases that recurred after the patient had been asymptomatic for at least 2 weeks after the end of therapy for the previous episode. Primary cases were those that did not meet the definitions of relapse or reinfection.

Information was collected about each hospital, including the type of healthcare facility (adult, pediatric, or long-term), total number of hospital beds, total number of admissions, and total number of person-days in the survey period.

Data were entered into Epi Info (version 6.03; Centers for Disease Control and Prevention, Atlanta, GA), which was used to calculate descriptive statistics, odds ratios (Fisher exact test), *P* values, and 95% confidence intervals for this retrospective analysis.

## RESULTS

Nineteen healthcare facilities in 8 provinces participated in the N-CDAD surveillance project. Eighteen of the facilities had adult-care beds, 5 had long-term–care services, and 5 had pediatric services. Two centers had fewer than 200 beds, 6 had 200 to 399 beds, 3 had 400 to 599 beds, 1 had 600 to 799 beds, and 7 had more than 800 beds. The median duration of participation in the project was 42 days (range, 30 to 99 days).

All 19 participating sites used a toxin assay to detect *C. difficile*, but some routinely used more than one type of assay. Eleven sites used the cytotoxin B assay by means of cell culture, whereas 9 sites used enzyme immunoassay for toxin A or toxins A and B and 1 site used only latex agglutination for detection of *C. difficile* antigen. In addition to the toxin assay, 2 sites also processed stool for *C. difficile* culture and then tested these bacteria for toxin production.

The results of the surveillance for N-CDAD can be seen in the figure. During the surveillance period, 2,062 inpatient diarrhea stools were analyzed for *C. difficile* cytotoxin, of which 370 (17.9%) had positive results. One additional patient without diarrhea during this period had endoscopy that revealed the typical pseudomembranes of a *C. difficile* infection. Therefore, 371 (18%) of the inpatients were considered potential cases. Of these, 269 (72.5%) met the case definition for N-CDAD. The remaining 102 patients did not meet the case definition for several reasons, the most common being an absence of loose stools for 2 days or more. For the 269 patients, 264 had a positive result on cytotoxin assay, 4 had positive results for cultures with cytotoxin-producing *C. difficile* bacteria, and 1 was diagnosed by endoscopy alone. Two hundred fifty patients (93%) had N-CDAD while still in the hospital, and 19 patients (7%) were readmitted for their diarrhea after being discharged within the previous month.

The characteristics of the patients with N-CDAD are outlined in the table. Additional diagnostic or interventional procedures were performed for 7 patients (2.6%) because of N-CDAD symptoms. Complications related to N-CDAD occurred in 21 patients (8%), with some experiencing more than one complication: clinical dehydration, 8 patients (3%); hypokalemia, 6 (2%); mild gastrointestinal bleeding or ileus, 4 (1.5%); lower gastrointestinal bleeding requiring transfusion, 3 (1%); bowel perforation, 1; and secondary sepsis, 1.

Forty-one patients (15.2%) died during the surveillance period. Chart reviews for assessment of cause of death led to the judgment that 4 patients (1.5%) died directly or indirectly of the N-CDAD itself. The mean age of these 4 individuals (85.3 years) was not significantly different from the mean age of those who died of other causes (75.4 years). Twenty-three patients (9%) were deemed to have required an extension of their hospital stay due to N-CDAD, with the mean extension being 10 days (median, 7 days; range, 2 to 38 days). For the 19 patients who required readmission to an acute-care facility because of N-CDAD, the mean length of stay for that admission was 13.6 days (95% confidence interval, 5.8 to 21.4; range, 2 to 66 days).

Thirty-four patients did not receive specific therapy for their N-CDAD. These untreated patients were more likely to be located on a long-term–care floor (odds ratio, 2.85; 95% confidence interval, 1.2 to 6.6; $P < .05$) or on a surgical unit (odds ratio, 3.44; 95% confidence interval, 1.6 to 7.6; $P < .005$). Untreated patients with N-CDAD were also more likely to have died compared with those who received therapy for N-CDAD (29.4% vs 13.2%; odds ratio, 2.7; 95% confidence interval, 1.1 to 6.6; $P < .05$), as seen in the figure.

## DISCUSSION

In this large cross-Canada surveillance project, we found that N-CDAD remains an important hospital-acquired complication. It is likely that we underestimated the burden of N-CDAD, as it is known that the *C. difficile* cytotoxin assay used alone is less sensitive than stool culture for *C. difficile* with subsequent examination of the isolate for toxin production.[8]

In addition, we have objectively determined several measures of morbidity and the specific N-CDAD case-fatality rate for this population. Overall, 8% of the patients with N-CDAD suffered medical complications related to their diarrhea, including dehydration, intestinal hemorrhage, bowel perforation, and sepsis. Importantly, it was determined that 4 patients (1.5%) died directly or indirectly of N-CDAD. For ascertainment of mortality, the physician responsible for infection control was instructed to consider a death as related to N-CDAD "if the death in all likelihood would not have happened, had the N-CDAD not occurred." Although this ascertainment was subjective, the 4 cases cited were overt and probably underestimated the true mortality related to N-CDAD in the surveillance group. The case-fatality rate that we found is somewhat higher than the rate found in a 10-year surveillance project at one U.S. center,[3] where 5 (0.6%) of 908 patients had CDAD identified as the primary cause of death, but is similar to the 2% rate found in another recent study of CDAD.[9]

In addition to death, CDAD also imposes significant morbidity on many individuals and incurs considerable healthcare costs.[10-13] Jobe et al. reported that 5% of patients with CDAD required some type of reparative colon surgery, with an operative mortality rate of 30%.[14] Lipsett et al. noted that 0.4% of their ward patients with endemic CDAD required surgical intervention.[15] In our surveillance, 8% of 269 patients with CDAD suffered significant morbidity, 2.6% underwent a radiologic procedure to investigate their diarrhea (eg, abdominal series or abdominal ultrasound), and 1.9% underwent endoscopy due to their CDAD-induced symptoms.

Another important clinical aspect of N-CDAD is that increasing numbers of patients are being diagnosed as having it after being discharged from acute-care facilities. This is likely due to the overall trend to decrease lengths of stay in all surgical and medical areas. In our surveillance project, we identified 19 patients (7%) who required readmission to an acute-care facility because of N-CDAD. The reasons for readmission are variable. Many of these patients were elderly and fragile, leading to a general deterioration in their health with the advent of the diarrhea. The fever, electrolyte disturbances, dehydration, and fatigue that may accompany N-CDAD can often exacerbate other common medical conditions such as diabetes and cardiac insufficiency. In addition, the frequent episodes of diarrhea can put elderly or debilitated postsurgical patients at risk for falls, and can often lead to fecal incontinence due to the combination of bowel urgency and decreased patient mobility.

**TABLE**
CHARACTERISTICS OF THE PATIENTS WITH NOSOCOMIAL *CLOSTRIDIUM DIFFICILE*–ASSOCIATED DIARRHEA

| | |
|---|---|
| Female:male ratio | 1.3:1 |
| Mean age, y ($CI_{95}$) | 68.1 (65.6–70.6) |
| Type of N-CDAD (%) | |
| Primary | 86 |
| Relapse | 11 |
| Reinfection | 4 |
| Location of patient (%) | |
| Medical unit | 50 |
| Surgical unit | 25 |
| Intensive care unit | 9 |
| Long-term–care unit | 6 |
| Diagnostic or interventional procedures performed due to N-CDAD (no.) | |
| Radiographic abdominal views | 1 |
| Colonoscopy | 5 |
| Abdominal ultrasound | 1 |

N-CDAD = nosocomial *Clostridium difficile*–associated diarrhea; $CI_{95}$ = 95% confidence interval.

The current project found that an average hospital is likely to experience 10 readmissions per year due to the development of N-CDAD that manifests itself after the patient has been discharged. The estimated minimum cost of these readmissions was approximately $128,200 (in Canadian dollars; $85,000 in U.S. dollars) per hospital per year. This was based on our findings of an average length of stay of 13.6 days per N-CDAD readmission, a minimum cost of $900 (in Canadian dollars) per day per bed, an annual cost of antibiotic therapy for N-CDAD (assuming that 80% of patients received oral metronidazole and 20% received oral vancomycin) of $5,800 (in Canadian dollars), and a predicted mean of 10 readmitted N-CDAD cases (7% of all N-CDAD) per hospital per year. Additional costs would be incurred for physician visits, investigations, and ensuing complications (eg, dehydration, gastrointestinal bleeding, ileus, or sepsis). Of course, in addition to this economic cost and the coincident morbidity, one must also consider the human suffering involved.

N-CDAD continues to be a frequent and often severe complication of antibiotic administration in Canadian

healthcare facilities. Measures to reduce N-CDAD rates, including those that might seem expensive, are likely to be cost-effective because of the cost, readmission rate, morbidity, and mortality related to N-CDAD.

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