Canadian Nosocomial Infection Surveillance Program

Final Report

Clostridium difficile Associated Diarrhea in Acute-Care Hospitals Participating in CNISP: November 1, 2004 to April 30, 2005

September 5, 2007

Prepared by:

Denise Gravel
Senior Epidemiologist
Nosocomial and Occupational Infections Section
Blood Safety and Surveillance, Health-Care Acquired Infections Division
Public Health Agency of Canada

Dr. Mark Miller
Chair, Infection Prevention and Control
SMBD–Jewish General Hospital
Montreal, Quebec

Members of the *Clostridium difficile* Surveillance Working Group

David Boyd
National Microbiology Laboratory
1015 Arlington St.
Winnipeg, MB R3E 3R2
Tel: 204-789-2133
Email: david_boyd@phac-aspc.gc.ca

Denise Gravel (Co-chair)
Nosocomial and Occupational Infections
Public Health Agency of Canada
100 Eglantine Driveway, PL 0603E1
Ottawa, ON, K1A 0L9
Tel: (613) 841-3513
Email: denise_gravel@phac-aspc.gc.ca

Sharon Kelly
Health Care Corp. of St. John's
300 Prince Philip Drive
St. John's, NL, A1B 3V6
Tel: 709-777-3387
Email: sharon.kelly@hccsj.nl.ca

Dr. Mark Miller (Co-chair)
SMBD–Jewish General Hospital
3755 Cote St. Catherine, Suite G-139
Montreal, QC, H3T 1E2
Tel: (514) 340-8294
Email: mmiller@lab.jgh.mcgill.ca

Dr. Michael Mulvey
National Microbiology Laboratory
1015 Arlington St.
Winnipeg, MB R3E 3R2
Tel: 204-789-2133
Email: michael_mulvey@phac-aspc.gc.ca

Dr. Kathryn Suh
Children's Hospital of Eastern Ontario
401 Smyth Road
Ottawa, ON, K1H 8L1
Tel: (613) 737-7600 ext. 2491
Email: ksuh@cheo.on.ca

Dr. Michael Gardam
Toronto General Hospital
200 Elizabeth Street
New Clinical Services Building, 12C-1261
Toronto, Ontario, Canada M5G 2C4
Tel: (416) 340 3758
Email: michael.gardam@uhn.on.ca

Dr. Jim Hutchinson
Health Care Corp. of St. John's
300 Prince Philip Drive
St. John's, NL, A1B 3V6
Tel: (709) 777-7654
Email: jim.hutchinson@hccsj.nl.ca

Dr. Allison McGeer
Mount Sinai Hospital
1460-600 University Avenue
Toronto, Ontario, M5G 1X5
Tel: (416) 586-4800 Ext 3118
Email: amcgeer@mtsinai.on.ca

Dr. Dorothy Moore
Montreal Children's Hospital
2300 Tupper, Room C1243
Montreal, QC, H3H 1P3
Tel: (514) 412-4485
Email: dorothy.moore@muhc.mcgill.ca

Dr. Andrew Simor
Sunnybrook Health Sciences Centre
Room B103, 2075 Bayview Avenue
Toronto, ON, M4N 3M5
Tel: (416) 480-4549
Email: andrew.simor@sunnybrook.ca

Dr. Geoffrey Taylor
University of Alberta Hospital
2E4.11 Walter McKenzie Centre
8440-112 Street
Edmonton, AB, T6G 2B7
Tel: (780) 407-7786
Email: geoff.taylor@ualberta.ca

INTRODUCTION

Clostridium difficile associated diarrhea (CDAD) is the most frequent cause of nosocomial infectious diarrhea in industrialized countries [1-3], affecting more than 300,000 hospitalized patients yearly in the United States.[4-5] Clinical manifestations range from asymptomatic colonization, to severe diarrhea, pseudomembranous colitis, toxic megacolon and death.[6]

One of the earliest reports of more severe disease in patients with CDAD, many resulting in death, was in Pittsburgh, Pennsylvania in 2000.[7] Since the last half of 2002, several hospitals in Quebec have experienced a dramatic increase in the incidence, severity and number of relapses associated with CDAD.[8-12] Similar reports have been seen in other industrialized countries. [13, 14] An analysis of US hospital discharge data revealed that CDAD rates increased abruptly beginning in 2001, with a doubling of national rates from 2000 to 2003.[15] This increase was most prominent for patients 65 years of age and older. Reports also suggested that the attributable mortality rate (or fatality rate) had increased in recent years. Based on the data from Quebec, the attributable mortality rate for CDAD was estimated at 6.9%. [9]

Shortly after the appearance of reports of more severe disease in patients with CDAD, a previously unknown strain of *C.difficile* was identified. [9, 16] The strain is characterized as North American pulsed-field Type 1 with a restriction enzyme analysis type BI and PCR ribotype 027, hence the name NAP1/B1/027 (more commonly referred to as NAP1/027 or simply NAP1). In addition to the clostridial enterotoxin A and cytotoxin B, the main virulence factors of *C.difficile*, NAP1/BI/027 possesses an extra toxin known as the binary toxin. The role of this toxin remains unclear. More importantly, this strain has been shown, in vitro, to produce greater quantities of toxins A and B; due to an 18-base pair *tcdC* gene deletion. [9, 13, 16, 17] Although it is not known if these unique characteristics are responsible for the increased virulence, studies have found a definite association between NAP1/BI/027 and more severe disease, especially in older patients with CDAD. [18]

In this context, the Canadian Nosocomial Infection Surveillance Program (CNISP) elected to re-examine the incidence of CDAD in Canada with an emphasis on patient outcomes. The

objectives of the surveillance were to: 1) determine the incidence and burden of illness associated with CDAD in CNISP hospitals; 2) determine if there is an increase in severe outcomes (mortality and morbidity associated with CDAD) in 2005 compared to 1997; 3) characterize molecular subtype/toxinotype of *C.difficile* strains and determine if certain strains are associated with severe clinical outcomes; and 4) determine the geographic distribution of *C.difficile* isolates, including NAP1/027.

BACKGROUND

1997 N-CDAD Point Prevalence Surveillance Project

In 1997, the CNISP conducted a six week prospective surveillance study for healthcare-associated CDAD (HA-CDAD, formerly termed N-CDAD) within 19 health care hospitals in 8 Canadian provinces.[19] During this period; the participating hospitals tested all diarrheal stools from hospitalized patients for *C.difficile* toxin detection. Questionnaires were completed for patients with positive *C.difficile* assays who met eligibility criteria (diarrhea >2 days, symptoms occurred 3 days or more after admission, or symptoms causing readmission within one month of the current admission).

Among inpatients with diarrheal stools, 13% were caused by *C.difficile*. The incidence of healthcare-associated CDAD (HA-CDAD) cases was 6.63 cases per 10,000 patient days (95% CI 3.75-9.51) and 5.9 cases per 1000 patient admissions (95% CI 3.4-8.4). CDAD was found most frequently in older patients and those hospitalized more than 2 weeks in medical or surgical wards.

A sub-section of the initial project addressed morbidity, mortality and healthcare burden of healthcare- acquired CDAD in the same centers. Of the 269 patients that satisfied the HA-CDAD case definition, 41 (15.2%) died, 4 (1.5%) of these were attributable to CDAD. [20] The annual cost of HA-CDAD readmission for each center was estimated to be at least of $128,200. These reports were pivotal since they provided baseline rates to which other Canadian hospitals could compare and provided the only available information on healthcare burden of CDAD on

Canadian hospitals.

Increase in incidence, severity and relapse in Canadian hospitals

Recent reports have suggested an increase in incidence, severity and/or risk of relapse of CDAD in Canada. [8] Several health-care institutions in Quebec (located mostly in the southern region of the St-Lawrence River, Montreal and the Eastern Townships) are reporting increased incidence of nosocomial healthcare-associated cases, with average rates of 25 cases per 1000 admissions. [21]

An increase in the frequency of *C.difficile* toxin-producing strains at the Centre Hospitalier Universitaire de Sherbrooke lead to a 13 year review (January 1991-December 2003) of 1721 cases of CDAD in the Eastern Townships of Quebec. [12] From 1991/92 to 2001/02, the overall annual incidence of CDAD was stable with rates of 35 per 100,000 to 50 per 100,000. However, in 2003 the incidence increased to 160 per 100,000 with a rate of almost 900 per 100,000 for adults older than 65.

Severe colitis was defined as perforation, toxic megacolon, shock or death within 30 days of diagnosis. Using this definition, in 2003, an increase in the incidence of severe colitis when compared to previous years 1991-2002 (adjusted OR 2.2; 95% CI, 1.0-4.9) was reported.

Further study, conducted in 2005 in 88 Quebec hospitals found that severe disease was twice as frequent among patients with *C.difficile* strains possessing binary toxin genes and *tcdC* deletion compared to patients with strains lacking these characteristics. [18] This study was the first to describe the geographic dissemination of NAP1 strain in Quebec.

Starting in early 2006, a number of media reports have described outbreaks in areas outside of the Montreal region and in Ontario associated with severe disease in patients with CDAD; notably Gatineau, Quebec and Sault-Ste-Marie, Mississauga, and Belleville, Ontario. [21-23] To date, there have been no reported outbreaks in the western provinces or the Atlantic region.

Canadian Nosocomial Infection Surveillance Program

The CNISP is a collaborative effort of the Canadian Hospital Epidemiology Committee

(CHEC), a subcommittee of the Association of Medical Microbiologists and Infectious Disease (AMMI) and the Centre for Infectious Diseases Prevention and Control (CIDPC) of the Public Health Agency of Canada.

Established in 1994, the objectives of CNISP are to provide rates and trends on healthcare-associated (formerly nosocomial) infections at Canadian health care facilities thus enabling comparison of rates (bench-marks), and providing evidence-based data that can be used in the development of national guidelines on clinical issues related to healthcare-associated infections. At present, 49 sentinel hospitals from 9 provinces participate in the CNISP network. All CNISP hospitals have a university affiliation and provide primary, secondary, and tertiary care to adult and/or pediatric patients. Seven hospitals are stand-alone pediatric centers.

CHEC members participate in CNISP by working on sub-committees that direct the development, implementation and analysis of surveillance projects. CHEC members and their corresponding healthcare institution(s) participate voluntarily in CNISP projects by collecting standardized, case-by-case, non-nominal data on hospitalized patients at risk of healthcare-associated infections. The data is submitted to PHAC for compilation and analysis. All data is analyzed by region or larger geographical area. At no time is submitted data analyzed by individual hospital or site. The results of the CNISP surveillance projects are disseminated primarily through publications in peer-reviewed medical journals. The PHAC employees participate by co-authoring the manuscripts along with CHEC.

Members of the CNISP have collaborated successfully on a number of other surveillance projects including surveillance for methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin- resistant *Enterococcus* (VRE), and hemodialysis-associated blood stream infections, to name only a few. Although the patient populations examined in our surveillance activities are in major teaching hospitals and so likely not entirely representative of all hospitalized patients in Canada, the data obtained from our surveillance provide an important contribution to understanding the impact of healthcare-associated infections in patients admitted to Canadian hospitals.

METHODS

A prospective surveillance for CDAD was conducted among the patients hospitalized in Canadian acute-care hospitals participating in CNISP between November 1, 2004 and April 30, 2005. A total of 34 hospitals participated in the surveillance activity including one non-CHEC hospital from the province of Ontario. Of these, 16 hospitals admitted pediatric patients under the age of 18 years. All hospitalized patients 1 year of age and older meeting the case definition for CDAD were eligible for enrolment. Both community-acquired (CA-CDAD) and healthcare-associated (HA-CDAD) cases were included.

The following case definition was utilized for CDAD: 1) either diarrhea over 2 days; or fever, abdominal pain and/or ileuses with laboratory confirmation of a positive toxin assay for *C.difficile*; or 2) diagnosis of pseudomembranous colitis on colonoscopy, or histological/pathological diagnosis of CDAD. The infection was considered healthcare-associated if the patient's symptoms occurred at least 72 hours after admission; or symptoms resulted in readmission of a patient who had been hospitalized within the previous two months of the current admission date, and who was not a resident in a chronic care facility or nursing home. Patients who met the case definition for CDAD but did not meet the surveillance definition for healthcare-associated CDAD were considered to have acquired CDAD in the community.

Eligible patients were identified by daily review of stool *C.difficile* toxin assay results in the clinical microbiology laboratory as well as a review of relevant pathology reports or operating room records. The charts of patients with positive stool samples for *C.difficile* toxin were examined by experienced and trained infection control professionals or trained research personnel associated with each hospital. Basic demographic data was collected on all patients, including age and sex, admission date, type of patient ward where the patient was located on the day CDAD was identified, medical service, primary admitting diagnosis and co-morbidities. Information about CDAD included date of onset of diarrhea and date of the first positive specimen submission, initial treatment of CDAD, medical and treatment inventions, and complications.

Data regarding adverse events was collected 30 days after the diagnosis of a positive case and included death (all cause, and attributable to CDAD), ICU admission, surgery, bowel perforation, GI bleeding, toxin megacolon, dehydration, hypokalemia, and relapse. A relapse was defined as an episode of illness with onset of symptoms within 2 months of the end of the previous CDAD episode. All cases of death within 30 days of diagnosis of a CDAD episode were assessed by the CHEC member or a designated physician to determine if the death was attributable to CDAD. Cause of death was determined by the following criteria: 1) CDAD was directly related to the death of the patient; that is, the patient had no other underlying condition that would have caused death during this hospitalization; or 2) CDAD was indirectly related to death; that is, the CDAD contributed to the patient's death but was not the primary cause; or 3) the patient died but CDAD was not related to death.

Data was recorded for each new CDAD episode. An episode was defined as the time from onset of symptoms until the last day of antibiotic treatment. Episodes which did not meet the criteria for disease (i.e., positive test, but criteria for diarrhea or other symptoms not met), and relapses, were not included in the surveillance. Episodes occurring more than 2 months after the first episode were considered new episodes.

Data were collected and entered manually onto patient data extraction forms and forwarded to the PHAC for data entry and analysis. Information from the patient questionnaires was entered at the PHAC on a web-based data entry system (WEBBS) that mirrored the patient questionnaire. A unique identifier linked to the patient name was used only to identify patients at the participating hospital and was not transmitted to the PHAC. While this surveillance project was observational and did not involve any alteration in patient care, ethics approval was obtained at some of the participating hospitals.

Whenever possible, frozen stool specimens from patients with CDAD were forwarded to the National Microbiology Laboratory (NML) in Winnipeg for molecular characterization. *C.difficile* was isolated from the stools using an alcohol shock procedure. Toxigenic strains were confirmed using polymerase chain reaction (PCR) to detect *tcdA* and *tcdB* genes. PCR was also used to

confirm the species, detect variations in the *tcdC* gene and to detect the presence of the binary toxin (*cdtB*). Pulsed-field gel electrophoresis (PFGE) was used to type the strains. Antimicrobial susceptibilities to 12 antimicrobials were determined using agar dilution following Clinical Laboratory Standards Institute (CLSI) guidelines. Resistant breakpoints used were as follows: metronidazole >16 mg/L, vancomycin >16 mg/L, teicoplanin >16 mg/L, clindamycin >4 mg/L, ciprofloxacin >4 mg/L, levofloxacin >4 mg/L, gatifloxacin >4 mg/L, moxifloxacin >4 mg/L, cefazolin >16 mg/L, cefuroxime >32 mg/L, ceftriaxone >32 mg/L and cefotaxime >32 mg/L.

Statistical analysis

Incidence and rates of CDAD were calculated by province or region using patient admissions and patient-days for denominator. Mortality and case fatality rates were determined using the criteria described in the 'methods' section. Descriptive and univariate analyses were performed. To assess differences between patient populations, continuous variables were expressed by means and compared using the Student t-test and/or the Mann-Whitney test. Hospital stay was expressed by median and interquartile rank. Categorical variables were expressed as proportions and compared using the chi-square test and the Fisher's t-test when necessary. All tests were two-tailed, and a *P* value of less than 0.05 was considered statistically significant. Relative risks with corresponding 95% confidence intervals were calculated according to standard methods. Multivariate logistic regression model will be used to assess patient factors associated with a severe outcome. Severe outcome was defined as an admission to the intensive care unit for complications of CDAD, colectomy, and/or death, directly or indirectly related to CDAD. Variables will be selected for entry into the regression model if at least 10 of the patients had the characteristic and the variables were significantly associated with a severe outcome at a p-value less than or equal to 0.25 in the univariate analysis. The goodness-of-fit of the final model will be tested using the deviance test. Statistical analysis was conducted using SAS version 9.1 (SAS Institute, Cary NC).

RESULTS

Incidence and rates of CDAD

A total of 1842 patients with primary or recurrent CDAD were identified during the 6-month surveillance period. Of these, 1745 (95%) were adults 18 years of age and older and 97 (5%) were children 1 to 17 years of age. The source of the CDAD infection was found to be healthcare-associated (HA-CDAD) in 1493 (81%) of the patients and community-acquired (CA-CDAD) in 292 (16%) of the patients. Fifty-seven (3%) patients acquired the infection in a nursing home (Table 1.)

The overall national incidence and rate of HA-CDAD for during this 6-month period was 4.5 cases per 1000 patient admissions and 6.4 per 10,000 patient-days (Table 2). The incidence and rate were significantly higher in Quebec than the rest of Canada (11.1 vs. 3.9 cases per 1000 admissions and 11.9 vs. 5.7 cases per 10,000 patient-days, $p < 0.0001$). The rates are similar to those found in our previous study; 6.4 vs. 6.6 cases per 10,000 patient-days in 1997.

At 30 days following onset of CDAD, 237 patients had died from all causes for a mortality rate of 15.9 per 100 cases. Of these, 84 were directly (31 deaths (2.1%)) or indirectly (53 deaths (3.6%)) related to CDAD for a case fatality rate of 5.6% (Table 3). The fatality rate in Quebec was four times higher than the rest of the Canada combined (14.8% vs. 3.5%, $p < 0.0001$). Compared to the surveillance performed in 1997, the deaths directly or indirectly related to CDAD increased by almost 400% (5.6% vs. 1.5% in 1997, $p < 0.0001$). There were 4 deaths in children 1 to 17 years of age; 2 deaths were indirectly related to CDAD.

The data presented below describes the results found in adult patients 18 years of age and older with HA-CDAD.

HA-CDAD in Canadian adults

Of the total 1842 patients with CDAD, 1493 (81%) patients had HA-CDAD. Of these, 1430 (96%) were adults 18 years of age and older and 63 (4%) were children between 1 and 17 years of age (Table 1). The mean age of the adults was 70 ±16 years (range 18-101); 996 (70%) were 65 years of age and older; 735 (51%) were males (Table 4). The majority of the patients, 1242 (87%) were acute-care patients while the remaining 188 (13%) were long-term care

patients. The mean length of stay before onset of CDAD was 25 ± 50 days (median: 11 days). There was no difference in the mean length of stay between the adults 65 years of age and older and the adults 18 to 64 years of age.

At the time of the onset of HA-CDAD, 609 (43%) patients were on medical wards, 327 (23%) patients were on a surgical unit, and 142 (10%) patients were in an Intensive Care Unit (ICU). The remaining 352 (24%) were on other wards including oncology/hematology, long-term care wards and transplant units.

Patients 65 years of age and older were more likely to acquire CDAD on medical ward (48% vs. 30%, $p < 0.0001$), whereas the adults 18 to 64 years of age were more likely to have acquired CDAD on a surgical or oncology/hematology unit (28% vs. 21%, $p = 0.001$ and 7% vs. 2%, $p < 0.0001$; respectively).

Only 81 (6%) patients did not receive treatment for the episode of CDAD. Among the 1430 patients with CDAD, 1215 (85%) were prescribed Metronidazole, 230 (16%) received Vancomycin and 51 (4%) received Probiotics (Table 5). A total of 168 (12%) patients were receiving more than one drug. Patients 65 years of age and older were 1.5 times more likely to receive Vancomycin than patients aged 18 to 64 years (18% vs. 12%, $p = 0.0053$). Of interest, patients with CDAD in the province of Quebec were 9 times more likely to receive Vancomycin than all other provinces and regions combined (56% vs. 6%, $p < 0.0001$) (Table 6).

Adverse outcomes in patients with HA-CDAD

A total of 319 (22%) adult patients with HA-CDAD developed complications in the first 30 days following onset of CDAD; 104 (7.3%) patients had a severe outcome. Relapse was the most common complication occurring in 125 (9%) patients. Dehydration occurred in 84 (6%) patients; hyopkalemia was seen in 39 (3%) patients; and pseudomembranous colitis and/or gastrointestinal bleed not requiring transfusions was seen in 47 (3%) patients. Dehydration was more likely to be seen in the elderly patients 65 years and older (7% vs. 3%, $p = 0.005$) whereas gastrointestinal bleeding requiring blood transfusions were more likely to be seen in adults aged 18 to 64 years (2% vs. 0.7%, $p = 0.029$).

Thirty-one (2%) patients were admitted to the ICU for complications related to CDAD and 12 (1%) patients underwent a colectomy. In addition, 82 patients died, either directly or indirectly related to CDAD for a case fatality rate of 5.7%. The case fatality rate was 3.5 times higher in patients over the age of 65 years compared to the patients aged 18 to 64 years (7.3% vs. 2.1%, $p < 0.0001$).

In univariate analysis the following factors were associated with a severe outcome: age 65 years and older (RR 2.23, 95% CI 1.34-3.70, $p = 0.001$); being a long term care patient on any ward, having been admitted from a long term care facility or having acquired CDAD on a long term care unit (RR 1.77, 95% CI 1.14-2.78, $p =0.01$; RR 2.15, 95% CI 1.34-3.45, $p = 0.002$; and RR 1.97, 95% CI 1.01-3.86, $p = 0.05$, respectively); dementia (RR 1.88, 95% CI 1.10-3.24, $p = 0.02$); having received Vancomycin as initial treatment for CDAD (RR 2.60, 95% CI 1.97-3.45, $p < 0.0001$); and having had a change in the initial treatment for CDAD (RR 2.77, 95% CI 1.90-4.03, $p < 0.0001$) (Table 8). When compared to patients on all other units, patients on surgical units were less likely to have a severe outcome (RR 0.44, 95% CI 0.24- 0.79, $p < 0.004$). In addition, patients receiving Metronidazole as initial treatment were also less likely to have a severe outcome (RR 0.84, 95% CI 0.74-0.95, $p < 0.0001$).

Laboratory characterization of C.difficile isolates

During the 6-month surveillance, 2307 frozen stool specimens were submitted to NML for identification and characterization. Of these, 450 were duplicate specimens and were discarded. Laboratory analysis was completed on 1857 stool specimens; 488 of the 1857 were from patients who did not meet the case definition for CDAD and for which no patient information was collected. The laboratory data from the remaining 1369 was linked to the clinical database.

PFGE patterns of C.difficile isolates: HA-CDAD in adults

Of the 1430 patients with HA-CDAD, toxigenic *C.difficile* was found in the stool specimens of 1008 (70%) patients. In 280 (20%) patients, a stool specimen was not submitted to NML. In 101 (7%) patients, *C.difficile* was not isolated and in 41 (3%) non-toxigenic *C.difficile* was found. These patients all had a positive toxin assay as determined by the hospital

laboratory. The overall recovery rate for *C.difficile* was 91%.

Among the 1008 patients with complete laboratory workup, the hypervirulent strain NAP1/027 was isolated in 311 (31%) patients (Table 9). NAP1 was 1.3 times more likely to be found in patients 65 years of age and older compared to adults, 18 to 64 years of age (33% vs. 25%, $p = 0.006$) whereas NAP4 was more likely to be seen in younger adults (6% vs. 3%, $p = 0.003$). The second most predominant NAP subtype was NAP2, commonly termed "J-strain". The strain was recovered in the stool specimens of 283 (28%) patients with HA-CDAD. All other strains, not classified as a NAP subtype, accounted for the majority of the *C.difficile* strains isolated; over 115 distinct PFGE patterns were found. In addition, 316 (31%) of the strains were binary toxin positive and *tcdC* gene deletion positive; the vast majority of these were NAP1 (296 (29%)).

The NAP1/027 strain was found in every province and region of Canada (Table 10). The NAP1/027 was the most prominent strain in Quebec, isolated in 171 (76%) of the adult patients with HA-CDAD. The NAP1/027 strain was seen in 100 of 451 (22%) patients in Ontario and 22 of 111 (20%) patients in Alberta (Figure 1). The Atlantic region had the lowest incidence of NAP1/027, with the isolate found in only 5 of 103 (5%) of the adult patients with HA-CDAD. The most prominent NAP subtype in the Atlantic region was NAP2; isolated in 64 of 103 (62%) patients. This subtype was also the most frequently isolated NAP subtype in Ontario; found in 157 of 451 (35%) patients.

Antibiotic susceptibility of C.difficile: HA-CDAD in adults

Among the 1008 strains isolated in adults with HA-CDAD, there were no strains resistant to Metronidazole, Vancomycin, and Teicoplanin. All strains were resistant to Ciprofloxacin, Cefuroxime and Cefotaxime (Table 11). A total of 868 (86%) strains were resistant to Clindamycin, 957 (95%) resistant to Cefazolin and 747 (74%) resistant to Levofloxacin. The NAP1 strain was found more likely to be resistant to the fluoroquinolones than the other strains combined (Levofloxacin, 92% vs. 66%, $p < 0.001$; Gatifloxacin, 83% vs. 60%, $p < 0.001$ and Moxifloxacin, 83% vs. 60%, $p < 0.001$) whereas the NAP1 was more likely to sensitive to

Clindamycin (82% vs. 88%, $p = 0.02$).

Clinical outcome and presence of NAP1/027 strain

Adult patients with HA-CDAD were found to be twice as likely to develop a severe outcome if the NAP1/027 strain was isolated in their stool or die directly or directly related to the CDAD (12.5% vs. 5.9%, RR 2.12, 95% CI 1.65-2.59, $p = 0.0003$ and 12.5% vs. 5.9%, RR 2.34, 95% CI 1.50-4.11, $p < 0.0001$, respectively). The effect of the strain type was significantly associated with the age of the patient (Figure 2). In patients under the age of 60 years, strain type did not seem to be associated with severe outcomes. Over the age of 60 years (but not in the extreme elderly > 90 years of age), infection with NAP1/027 was highly associated with severe outcomes ($p = 0.03$). In the extreme elderly (≥ 90 years of age), severe outcomes were frequent, regardless of the strain type.

SUMMARY

The results from this surveillance project represent the most comprehensive surveillance of CDAD in Canada. This demonstrates that coordinated national attempts to survey CDAD, and more specifically, HA-CDAD; can be accomplished with excellent patient information and isolate recovery, given sufficient planning time and resources, to create a linked clinical-microbiological CDAD database. The information contained in this national database also represents the largest such database to exist in the developed countries including the US.

Our study demonstrates the wide variations in HA-CDAD among the participating hospitals. The underlying reasons remain as yet unclear although previous studies have suggested that antibiotic usage; the physical layout of the institution including the presence or absence of sinks for hand washing; and the infection prevention and control practices including isolation practices have played a role in the overall incidence of HA-CDAD. [3, 25, 26] Wide variations are also seen between provinces and regions in Canada. Ontario was found to have 40% more HA-CDAD cases (5.7 vs. 3.8 cases per 1000 admissions and 7.8 vs. 5.5 per 10,000 patient days, $p < 0.0001$); and Quebec has over twice the incidence of HA-CDAD compared to

other areas of the country (11.1 vs. 3.9 cases per 1000 admissions and 11.9 vs. 5.7 per 10,000 patient days, $p < 0.0001$). Overall, there is a small decrease in the mean incidence of HA-CDAD in Canada since 1997; however our surveillance has found a significant increase in the number of deaths related to CDAD and severe outcomes. Compared to the CNISP surveillance conducted in 1997, the incidence of deaths directly or indirectly related to CDAD has increased almost 4-fold (5.6 vs. 1.5%, $p < 0.0001$). [20] These results are comparable since we used the same methodology with this surveillance as was utilized in 1997. Furthermore, we found that the case fatality rates from CDAD were much higher in Quebec, followed by Ontario. Our findings support previously published reports describing increased fatality in Quebec. [18]

The presence of the NAP1/027 strain closely mirrors the HA-CDAD incidence and severe outcomes, across all provinces and regions. The "hypervirulent" NAP1/027 strain was found in eight provinces, but mostly in British Columbia, Alberta, Ontario, and Quebec. In our study, we found that the NAP1/027 strain leads to severe outcomes more frequently (approximately 3 times the incidence) in adults 60 to 90 years of age. Adults aged 90 and over were found to have a 14 to 16% attributable mortality, regardless of the strain. This data is remarkably similar to the Quebec outbreak data, in terms of the incidence of age-related CDAD attributable mortality. [18]

There are limitations to our study, primarily inherent to large multi-centre surveillance activities. First, although data collection was conducted by experienced and trained infection control professionals using standardized definitions, the data collection remained unmonitored and there may be inconsistencies between hospitals in identifying a CDAD. As the diagnosis of a CDAD is frequently based on laboratory findings, there may be some variability in the microbiological laboratory testing and identification of *C.difficile* at the different hospitals. Seasonal variations in CDAD incidence could influence the overall annual rates. Our surveillance was conducted during the peak CDAD months of November to April. In addition, although the hospital epidemiologist or another qualified physician determined the cause of death in patients with HA-CDAD; attribution of mortality; i.e. direct or indirect, is always subjective and can be interpreted differently from one clinician to another. Finally, the populations examined in this

survey were in major teaching hospitals and so likely not entirely representative of all hospitalized adult patients in Canada.

Despite these limitations, the data presented in this study are an important contribution to understanding the impact of CDAD in adults admitted to Canadian hospitals. The results are sufficiently robust to be used as baseline indicators for future comparisons. Follow-up surveillance in the same hospitals will allow us to follow the spread of *C.difficile* strains; more specifically the spread of NAP1/027, in Canada and assess the impact on the morbidity and mortality associated with CDAD. National surveillance also provide opportunities for interhospital collaboration that may lead to more standardized use of surveillance methodology, including application of definitions and case finding methods, and effective infection prevention and control measures.

NEXT STEPS

A multivariate logistic regression will be undertaken to evaluate the association between the variables and severe outcome and/or death related to HA-CDAD. Additional sub-analysis is currently underway, including (but not limited to): description of the pediatric patients between 1 and 18 years of age with CDAD; description of the CA-CDAD cases and case of CDAD in patients residing in nursing homes; and an evaluation of the *C.difficile* isolates from patients who did not meet the case definition for CDAD to determine if the strains are different than the strains isolated from patients who met the case definition for CDAD. The results in this report will be presented at the 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) Conference in Chicago, September 17- 20, 2007 and the 45th Infectious Disease Society of America (IDSA) Annual Meeting in San Diego, October 4-7, 2007.

Ongoing surveillance for CDAD

As of January 1st, 2007, surveillance for CDAD will be ongoing and mandatory in all hospitals participating in CNISP. CDAD surveillance will consist of monthly reporting of incidence and rates, and an annual two-month targeted surveillance for patient outcomes and

laboratory characterization of *C.difficile* isolates. The numerator will consist of all hospitalized patients meeting the case definition for CDAD except for children less than 1 year of age and patients residing on psychiatric and long-term care or awaiting placement units. Both community-acquired and hospital-acquired cases of CDAD will be counted. Denominator information will include total patient days, patient admissions, and total number of liquid stools submitted to microbiology laboratory. Whenever possible, denominator information will be obtained separately for pediatric and adult patients. The information received will be tabulated every four months and disseminated through the Nosocomial and Occupational Infections website at www.nosocomial.ca.

Once a year over a two-month consecutive period, a patient data collection form will be completed for on all patients meeting the case definition for CDAD and frozen stool specimens will be forwarded to NML for characterization. The annual period for the targeted surveillance will be determined each year at the CNISP meeting for the next calendar year. The targeted surveillance for 2007 will be from March 1st to April 30th. Patient information will include: age and sex, admission date, and type of patient ward where the patient is located on the day CDAD is identified. Information about CDAD will include date of onset of diarrhea or date of the first positive specimen submission. Data regarding adverse events will be collected 30 days after the diagnosis of a positive case, and will include death (all cause, and related to CDAD), ICU admission, and colectomy.

(2007 CNISP surveillance protocol available upon request)

ACKNOWLEDGEMENTS

The CDAD working group acknowledges the contribution of the following individuals who assisted with project management, data collection and data entry: Melinda Piecki, Katie Cassidy, John Koch, Emma Ongsansoy, Monali Varia, Mark Osmond, Stephanie Leduc, Louis Valiquette, and the Infection Control Professionals in each participating hospital.

REFERENCES

1. McFarland LV. Epidemiology of infectious and iatrogenic nosocomial diarrhea in a cohort of general medicine patients. *Am J Infect Control* 1995; 23(5): 295-305.

2. Kelly CP, Pothoulakis C, LaMont JT. Clostridium difficile colitis. *N Eng J Med* 1994; 330(4): 257-62.

3. Poutanen SM, Simor AE. *Clostridium difficile*-associated diarrhea in adults. *CMAJ* 2004; 171(1): 51-8.

4. McFarland LV, Mulligan ME, Kwok RY, Stamm WE. Nosocomial acquisition of *Clostridium difficile* infection. *N Engl J Med* 1989; 320(4): 204-10.

5. Johnson S, Clabots CR, Linn FV, Olson MM, Peterson LR, Gerding DN. Nosocomial *Clostridium difficile* colonization and disease. *Lancet* 1990; 336(8707): 97-100.

6. Kelly CP, LaMont JT. *Clostridium difficile* infection. *Annu Rev Med* 1998; 49: 375-90.

7. Muto CA, Pokrywka M, Shutt K, et al. A large outbreak of *Clostridium difficile* – associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased Fluoroquinolone use. *Infect Control Hosp Epidemiol* 2005; 26: 273-80.

8. Valiquette L, Low PE, Pepin J, McGeer A. *Clostridium difficile* infection in hospitals: a brewing storm. CMAJ 2004; 171(1): 27-9.

9. Loo VG, Poirier L, Miller MA, et al. A predominatly clonal multi-institutional outbreak of *Clostridium difficile* –associated diarrhea with high morbidity and mortality. *N Engl J Med* 2005; 2442-9.

10. Eggertson L, Sibbald B. Hospitals battling outbreaks of *Clostridium difficile. CMAJ* 2004; 171(1): 19-21.

11. Louie TJ, Meddings J. *Clostridium difficile* infection in hospitals: risk factors and responses. *CMAJ* 2004; 171(1): 45-6.

12. Pepin J, Valiquette L, Alary ME, et al. *Clostridium difficile* – associated diarrhea in a region of Quebec from 1991-2003: a changing pattern of disease severity. *CMAJ* 2004; 171(5): 466-72.

13. Warny M, Pepin J, Fang A, et al. Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. *Lancet* 2005; 366: 1079-84.

14. Kuijper EJ, Coignard B, Tull P. Emergence of *Clostridium difficile* – associated disease in North America and Europe. *Clin Microbiol Infect* 2006; 12 (Suppl 6): 2-18.

15. McDonald LC, Owings M, Jernigan D. *Clostridium difficile* infection in patients discharged from US short-stay hospitals, 1996-2003. *Emerg Infect Dis* 2006; 12: 409-15.

16. McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. *N Engl J Med* 2005; 353: 2433-41.

17. Blossom DB, McDonald LC. The challenges posed by reemerging Clostridium difficile infection. CID 2007; 45(25): 222-227.

18. Hubert B, Loo VG, Bourgault AM et al. Portrait of the geographic dissemination of the *Clostridium difficile* North American pulsed-field type 1 strain and the epidemiology of *C.difficile* – associated disease in Quebec. *Clin Infect Dis* 2007; 44: 238-244.

19. Hyland M, Ofner-Agostini M, Miller M, Paton S, Gourdeau M, Ishak M, N-CDAD in Canada: Results of the Canadian Nosocomial Infection Surveillance N-CDAD Prevalence Surveillance Project. *Can J Infect Dis* 2001; 12(2): 81-8.

20. Miller MA, Hyland M, Ofner-Agostini M, Gourdeau M, Ishak M. Morbidity, mortality, and healthcare burden of nosocomial *Clostridium difficile* – associated diarrhea in Canadian hospitals. *Infect Control Hosp Epidemiol* 2002; 23(3): 137-40.

21. Loo VG, Libman MD, Miller MA, et al. *Clostridium difficile*: a formidable foe. *CMAJ* 2004; 171(1): 47-8.

22. The Toronto Star: Lethal germ hits hospital; Bacteria strain behind 2,000 deaths in Quebec shows up in Mississauga, where 4 patients have died, 14 are treated. March 1, 2007.

23. The Globe and Mail. C.difficile widens its reach, Quebec official says. November 11, 2006.

24. The Globe and Mail. How bad is the C.difficile problem in Canadian hospitals? Is it getting worse? Better? No one really knows. Sure, there are anecdotal reports of outbreaks in individual hospitals, many of which keep close tabs on their in-house C.difficile. May 2, 2007.

25. McFarland LV, Beneda HW, Clarridge JE, Raugi GJ. Implications for the changing face of *Clostridium difficile* disease for health care practitioners. *Am J Infect Control* 2007; 35: 237-53.

26. Blossom DB, McDonald LC. The challenges posed by reemerging *Clostridium difficile* infection. *CID* 2007; 45: 222-7.

CNISP Hospitals that participated in the surveillance for CDAD; November 1, 2004 to April 30, 2005*

Victoria General Hospital
Victoria, British Columbia

Vancouver General Hospital
Vancouver , British Columbia

Peter Lougheed Centre (3 facilities)
Calgary , Alberta

University of Alberta Hospital
Edmonton , Alberta

Stollery Children's Hospital
Edmonton, Alberta

Health Sciences Centre (2 facilities)
St-John's, Newfoundland

QE II Health Sciences Centre
Halifax , Nova Scotia

I.W.K. Hospital for Sick Children
Halifax , Nova Scotia

Hospital for Sick Children
Toronto , Ontario

Mount Sinai Hospital
Toronto , Ontario

St-Joseph's Health Centre
Hamilton , Ontario

Peterborough General Hospital
Peterborough, Ontario

Children's Hospital of Eastern Ontario
Ottawa, Ontario

Health Sciences Centre (Adults)
Winnipeg , Manitoba

Hamilton Health Sciences (4 facilities)
Hamilton , Ontario

Health Sciences Centre (Paediatrics)
Winnipeg , Manitoba

London Health Sciences Centre (2 facilities)
London , Ontario

The Ottawa Hospital
Ottawa , Ontario

Royal University Hospital (2 facilities)
Saskatoon , Saskatchewan

Jewish General Hospital
Montréal, Québec

Montreal Children's Hospital
Montreal , Quebec

Maisonneuve-Rosemont Hospital
Montreal, Quebec

Sunnybrook and Women's College Health Science Centre
Toronto , Ontario

The Moncton Hospital
Moncton , New Brunswick

Kingston General Hospital
Kingston , Ontario

* 34 hospitals participated in the surveillance. Some CHEC sites have more than one facility.

Members of the Canadian Nosocomial Infection Surveillance Program as of January 1st, 2007.

David Boyd, National Microbiology Laboratory, Public Health Agency of Canada; Elizabeth Bryce Vancouver General Hospital, Vancouver, BC; John Conly, Foothills Medical Centre Calgary, Alta; Gordon Dow, The Moncton Hospital, Moncton, NB; John Embil, Health Sciences Centre Winnipeg, Man; Joanne Embree, Health Sciences Centre, Winnipeg, Man; Sarah Forgie, Stollery Children's Hospital, Edmonton, Alta; Charles Frenette, Hôpital Charles LeMoyne, Longueil, Que; Michael Gardam, University Health Network, Toronto, Ont; Denise Gravel, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada; Elizabeth Henderson, Peter Lougheed Centre, Calgary, Alta; James Hutchinson, Health Sciences Centre, St. John's, Nfld; Michael John, London Health Sciences Centre, London, Ont; Lynn Johnston, Queen Elizabeth II Health Sciences Centre, Halifax, NS; Pamela Kibsey, Victoria General Hospital, Victoria, BC; Joanne Langley, I.W.K.Health Science Centre, Halifax, NS; Mark Loeb, Hamilton Health Sciences Corporation, Hamilton, Ont; Anne Matlow, Hospital for Sick Children, Toronto, Ont; Allison McGeer, Mount Sinai Hospital, Toronto, Ont.; Sophie Michaud, CHUS-Hôpital Fleurimont, Sherbrooke, Que; Mark Miller, SMBD-Jewish General Hospital, Montreal, Que; Dorothy Moore, Montreal Children's Hospital, Montreal, Que; Michael Mulvey, National Microbiology Laboratory, Public Health Agency of Canada; Marianna Ofner-Agostini, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada; Shirley Paton, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada; Virginia Roth, The Ottawa Hospital, Ottawa, Ont; Andrew Simor, Sunnybrook and Women's College Health Sciences Centre, Toronto, Ont; Jacob Stegenga, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada; Tammy Stuart, Canadian Field Epidemiology Program, Public Health Agency of Canada; Kathryn Suh, Children's Hospital of Eastern Ontario, Ottawa, Ont; Geoffrey Taylor, University of Alberta Hospital, Edmonton, Alta; Eva Thomas, Children's and Women's Health Center, Vancouver, BC; Nathalie Turgeon, Hôtel-Dieu de Québec du CHUQ, Que; Mary Vearncombe, Sunnybrook and Women's College Health Sciences Centre, Toronto, Ont; Joseph Vayalumkal, Canadian Field Epidemiology Program, Public Health Agency of Canada; Karl Weiss, Maisonneuve-Rosemont Hospital, Montreal, Que; Alice Wong, Royal University Hospital, Saskatoon, Sask.; Dick Zoutman, Kingston General Hospital, Kingston, Ont.

Table 1: Source of CDAD infection among the patients enrolled in the surveillance, N = 1842.

Source of CDAD	All patients N = 1842	Adults =>18 years n = 1745 (95%)	Children 1 to < 18 years n = 97 (5%)
Healthcare-associated	1493 (81%)	1430 (82%)	63 (65%)
Nosocomial, my hospital	1421	1361	60
Nosocomial, other hospital	71	68	3
Unknown	1	1	0
Community-acquired	292 (16%)	258 (15%)	34 (35%)
No known healthcare contact	128	114	14
Admitted > 2 months ago	97	85	12
Home care	19	18	1
Information missing	48	41	7
Nursing home, household contact	57 (3%)	57 (3%)	0

Table 2: Incidence and rates of HA-CDAD by province or region among hospitalized patients 1 years of age and older, N= 1493.

Province/Region	Cases*	Admissions	Per 1000 admissions	Patient-days	Per 10,000 patient-days
British Columbia	131	42,197	3.1	279,911	4.7
Alberta	175	79,145	2.2	386,575	4.5
Sask/Manitoba	69	25,214	2.7	184,153	3.8
Ontario	693	122,734	5.7	893,970	7.8
Quebec	283	25,610	11.1	237,794	11.9
Atlantic	142	37,549	3.8	366,243	3.9
Overall	1493	332,449	4.5	2,348,646	6.4

* Includes only the patients identified with HA-CDAD.

Table 3: Mortality and fatality rates for patients with HA-CDAD at 30 days after onset of disease, N = 1493.

Province/Region	Cases	All deaths	Mortality rate per 100	Directly related	Indirectly related	Fatality rate per 100
British Columbia	131	22	16.8	1	7	6.1
Alberta	175	16	9.1	1	1	1.1
Sask/Manitoba	69	10	14.5	1	0	1.5
Ontario	693	110	15.9	7	22	4.2
Quebec	283	64	22.6	20	22	14.8
Atlantic	142	15	10.6	1	1	1.4
Overall	1493	237	15.9	31	53	5.6

* Definitions: Mortality rate = death from all causes 30 days after onset of CDAD;
Fatality rate (or case fatality rate) = deaths directly or indirectly related to CDAD 30 days after onset.

Table 4: Description of the adult patients with HA-CDAD, N = 1430.

Patient characteristics	All patients, N = 1430	18-64 years, n = 434	65 and older, n = 996	*P* value
	No. (%)	No. (%)	No. (%)	
Mean age at onset ± SD (median, range)	70 ± 16 73 (18-101)	50 ± 12 (54)	79 ± 8 (78)	
Male	735 (51%)	238 (55%)	497 (50%)	NS
Mean length of stay before onset ± SD (median)	25 ± 50 (11)	25 ± 57 (8)	25 ± 46 (12)	NS
Type of patient				
Acute care	1242 (87%)	415 (96%)	827 (83%)	<0.0001
Long term care	188 (13%)	19 (4%)	169 (17%)	
Admitted from				
Home	1073 (75%)	346 (80%)	727 (73%)	0.0068
Another hospital	175 (12%)	65 (15%)	110 (11%)	0.0369
Long term care facility	127 (9%)	11 (3%)	116 (12%)	<0.0001
Other	55 (4%)	12 (3%)	43 (4%)	NS
Location at onset				
Medicine	609 (43%)	130 (30%)	479 (48%)	<0.0001
Surgery	327 (23%)	123 (28%)	204 (21%)	0.0011
Intensive care unit	142 (10%)	53 (12%)	89 (9%)	NS
Home	92 (6%)	33 (8%)	59 (6%)	NS
Long-term care	58 (4%)	5 (1%)	53 (5%)	0.0002
Oncology/Hematology	53 (4%)	31 (7%)	22 (2%)	<0.0001
Combined Med/Surgical	45 (3%)	16 (4%)	29 (3%)	NS
BMT/Transplant Unit	22 (2%)	18 (4%)	4 (0.4%)	<0.0001
Other	82 (5%)	25 (6%)	57 (6%)	NS
Chronic disease *				
Diabetes	331 (23%)	82 (19%)	249 (25%)	0.0118
Heart disease	514 (36%)	76 (18%)	438 (44%)	<0.0001
Lung disease	327 (23%)	57 (13%)	270 (27%)	<0.0001
Cancer	290 (20%)	125 (29%)	165 (17%)	<0.0001
Liver disease	62 (4%)	38 (9%)	24 (2%)	<0.0001
Kidney disease	229 (16%)	63 (15%)	166 (17%)	NS
Dementia	101 (7%)	5 (1%)	96 (10%)	<0.0001
Immunocompromised	120 (8%)	72 (17%)	48 (5%)	<0.0001
Other	338 (24%)	103 (24%)	235 (24%)	NS

* May have more than one chronic disease

Table 5: Description of the treatments and medical interventions for adult patients with HA-CDAD, N = 1430.

Patient characteristics	All patients, N = 1430	18-64 years, n = 434	65 and older, n = 996	*P* value
	No. (%)	No. (%)	No. (%)	
Initial CDAD treatment*				
No treatment	81 (6%)	28 (7%)	53 (5%)	NS
Metronidazole PO or IV	1215 (85%)	381 (88%)	834 (84%)	0.0487
Vancomycin	230 (16%)	52 (12%)	178 (18%)	0.0053
Cholestyramine	18 (1%)	3 (0.7%)	15 (2%)	NS
IVIG	3 (0.2%)	0	3 (0.3%)	NS
Probiotics	51 (4%)	13 (3%)	38 (4%)	NS
Other interventions				
Discontinued antibiotics	181 (13%)	68 (16%)	113 (11%)	0.0238
Endoscopy	51 (4%)	21 (5%)	30 (3%)	NS
Surgical consult	44 (3%)	18 (4%)	26 (3%)	NS
Infectious disease or GI consult	12 (1%)	2 (0.5%)	10 (1%)	NS
Initial treatment changed	246 (17%)	63 (15%)	183 (18%)	NS
Reason treatment changed				
Failure to respond	145 (10%)	28 (7%)	117 (12%)	0.0023
Intolerance to antibiotic	21 (2%)	10 (2%)	11 (1%)	NS
Complications	12 (1%)	2 (0.5%)	10 (1%)	NS
Inappropriate treatment	58 (4%)	17 (4%)	41 (4%)	NS

* No patients received Fucidin, Bacitracin, or Linezolid; patients may be on more than one treatment

Table 6: Initial treatment for CDAD among the patients with HA-CDAD by province or region, N = 1430.

Initial treatment for CDAD	British Columbia n = 128 No. (%)	Alberta n = 153 No. (%)	Sask/Man n = 67 No. (%)	Ontario n = 664 No. (%)	Quebec n = 282 No. (%)	Atlantic n = 136 No. (%)
No treatment, n = 81	6 (5%)	15 (10%)	1 (2%)	30 (5%)	19 (7%)	10 (7%)
Metronidazole, n = 1215	117 (91%)	132 (86%)	66 (99%)	622 (94%)	159 (56%)	119 (88%)
Vancomycin, n = 230	5 (4%)	15 (10%)	1 (2%)	36 (5%)	159 (56%)	14 (10%)
Other, n = 67*	2 (2%)	3 (2%)	0	37 (6%)	23 (8%)	2 (2%)

* Cholestyramine, IVIG, and/or Probiotics. Patients may be on more than one therapy.

Table 7: Frequency of adverse outcomes among the adult patients with HA-CDAD in the first 30 days following onset of disease, N = 1430.

Patient characteristics	All patients, N = 1430 No. (%)	18 -64 years, n = 434 No. (%)	65 and older, n = 996 No. (%)	*P* value
Complications from CDAD	319 (22%)	88 (20%)	231 (23%)	NS
Type of complication				
Relapse	125 (9%)	39 (9%)	86 (9%)	NS
Bowel perforation	1 (0.1%)	1 (0.2%)	0	NS
GI bleed, transfusion	16 (1%)	9 (2%)	7 (0.7%)	0.029
Toxic megacolon	17 (1%)	3 (0.7%)	14 (1%)	NS
Bacteraemia	22 (2%)	7 (2%)	15 (2%)	NS
Dehydration	84 (6%)	14 (3%)	70 (7%)	0.005
Hyopkalemia	39 (3%)	11 (3%)	28 (3%)	NS
Other*	47 (3%)	15 (3%)	32 (3%)	NS
Admitted to ICU	31 (2%)	7 (2%)	24 (2%)	NS
Colectomy	12 (1%)	4 (1%)	8 (1%)	NS
Death, all causes	233 (16.3%)	35 (8.1%)	198 (19.9%)	< 0.0001
Death, related to CDAD†	82 (5.7%)	9 (2.1%)	73 (7.3%)	< 0.0001
Directly related	31	1	30	
Indirectly related	51	8	43	
Severe outcome†	104 (7.3%)	17 (3.9%)	87 (8.7%)	0.0013

* Pseudomembraneous colitis and/or gastrointestinal bleed not requiring transfusions

† Severe outcome defined as admission to ICU, colectomy and/or death, directly and indirectly related to CDAD. 21 patients had more than one severe outcome.

Table 8: Univariate analysis of the variables associated with severe outcome in patients with HA-CDAD, N = 1430.

Variable	No. of patients	Severe outcome n = 104		RR* (95% CI)	*P* value
		No.	%		
Adults 65 and older	996	87	8.7	2.23 (1.34-3.70)	0.0013
Adults 18 to 64 years of age	434	17	3.9	Ref	
Long term care	188	22	11.7	1.77 (1.14-2.78)	0.0121
Acute care	1242	82	6.6	Ref	
Age of the patient by decade†					
90+ years	84	11	13.1	1.92 (1.05-3.51)	0.0342
80 -89 years	311	35	11.3	1.61 (1.21-2.16)	0.0022
70-79 years	418	27	6.5	0.88 (0.63-1.23)	0.4465
60-69 years	275	17	6.2	0.84 (0.54-1.31)	0.4383
50-59 years	163	5	3.1	0.40 (0.17-0.96)	0.0281
40-49 years	86	3	3.5	0.46 (0.15-1.43)	0.1633
18-39 years	93	6	6.5	0.88 (0.39-1.96)	0.7525
Admitted from					
Home	1073	62	5.7	0.49 (0.34-0.71)	0.0002
Another hospital	175	18	10.3	1.50 (0.92-2.43)	0.1013
Long term care facility	127	18	14.2	2.15 (1.34-3.45)	0.0017
Other	55	6	10.9	1.53 (0.70-1.05)	0.2849
Location at onset					
Medicine	609	47	7.8	1.11 (0.77-1.61)	0.5769
Surgery	327	12	3.7	0.44 (0.24-0.79)	0.0043
ICU	142	15	10.6	1.53 (0.91-2.57)	0.1116
Home	92	11	12.0	1.72 (0.96-3.10)	0.0737
Long-term care	58	8	13.8	1.97 (1.01-3.86)	0.0509
Oncology/Haematology	53	2	3.8	0.51 (0.13-2.01)	0.4262
Combined Med/Surgical	45	0	0.0	-	0.0716
BMT/Transplant Unit	22	1	4.6	0.62 (0.09-4.25)	1.0000
Other	82	8	9.8	1.37 (0.69-2.72)	0.3776

* Abbreviations: RR, relative risk; CI, confidence interval; PO, per os; IV, intravenous; ID, infectious disease; GI, gastroenterology.
P value: Chi-square or Fisher's exact test where appropriate.
† Comparing each category to all others

Table 8 (cont.): Univariate analysis of variables associated with severe outcome in patients with HA-CDAD, N = 1430.

Variable	No. of patients	Severe outcome n = 104 No.	%	RR* (95% CI)	*P* value
Chronic disease†					
Diabetes	331	30	9.1	1.35 (0.90-2.02)	0.1524
Heart disease	514	41	8.0	1.16 (0.79-1.69)	0.4426
Lung disease	327	29	8.9	1.30 (0.87-1.97)	0.2058
Cancer	290	18	6.2	0.83 (0.50-1.34)	0.4337
Liver disease	62	7	11.3	1.59 (0.77-3.28)	0.2130
Kidney disease	229	17	7.4	1.09 (0.62-1.69)	0.9236
Dementia	101	13	12.9	1.88 (1.10-3.24)	0.0246
Immunocompromised	120	8	6.7	1.00 (0.94-1.06)	0.8500
Other	338	24	7.1	0.97 (0.62-1.50)	0.8891
Initial treatment for CDAD					
No treatment	81	9	11.1	0.97 (0.91-1.02)	0.1708
Metronidazole (PO or IV)	1215	75	6.2	0.84 (0.74-0.95)	<0.0001
Vancomycin	230	39	16.9	2.60 (1.97-3.45)	<0.0001
Others	67	5	7.5	1.03 (0.43-2.50)	0.8128
Initial treatment changed	246	38	15.5	2.77 (1.90- 4.03)	<0.0001
No change	1184	66	5.6	Ref	
Other medical interventions					
Discontinued antibiotics	181	14	7.7	1.07 (0.64-1.78)	0.7978
Surgical consult	44	17	38.6	8.03 (4.52-14.24)	<0.0001
Endoscopy	51	3	5.9	0.80 (0.25-2.51)	0.6979
ID or GI consult	12			-	
Province or region					
British Columbia	128	10	7.8	1.08 (0.58-2.00)	0.8053
Alberta	153	5	3.3	0.43 (0.18-1.03)	0.0436
Sask/Manitoba	67	4	6.0	0.81 (0.30-2.18)	0.6742
Ontario	664	35	5.3	0.71 (0.53-0.93)	0.0067
Quebec	282	47	16.7	2.55 (2.00-3.25)	<0.0001
Atlantic	136	3	2.2	0.29 (0.09-0.89)	0.0168

* Abbreviations: RR, relative risk; CI, confidence interval; PO, per os; IV, intravenous; ID, infectious disease; GI, gastroenterology.
P value: Chi-square or Fisher's exact test where appropriate.
† Comparing each category to all others, patients may have more than one chronic disease and treatment/intervention.

Table 9: Molecular characterization of C*.difficile* isolated from the stool specimens of the patients with HA-CDAD, N = 1008.

Strain characteristics	All patients, N = 1008 No. (%)	18 -64 years, n = 289 No. (%)	65 and older, n = 719 No. (%)	*P* value
PFGE Small Patterns				
NAP1/027*	311 (31%)	71 (25%)	240 (33%)	0.0062
NAP2 (J-strain)	283 (28%)	75 (26%)	208 (29%)	NS
NAP3	11 (1%)	3 (1%)	8 (1%)	NS
NAP4	36 (4%)	16 (6%)	20 (3%)	0.0331
NAP5	3 (0.3%)	1 (0.4%)	2 (0.3%)	NS
NAP6	31 (3%)	15 (5%)	16 (2%)	0.0137
Other patterns	333 (33%)	108 (37%)	225 (31%)	NS
Binary toxin+ *tcdC* gene deletion+	316 (31%)	77 (27%)	239 (33%)	0.0412
NAP1/027 Binary toxin+ *tcdC* gene deletion+	296 (29%)	68 (24%)	228 (32%)	0.0099

Table 10: Distribution of the NAP PFGE subtypes isolated in stool specimens of the patients with HA-CDAD by province or regions, N = 1008.

NAP PFGE subtype	British Columbia n = 81 No. (%)	Alberta n = 111 No. (%)	Sask/Man n = 37 No. (%)	Ontario n = 451 No. (%)	Quebec n = 225 No. (%)	Atlantic n = 103 No. (%)
NAP1, n = 311	10 (12%)	22 (20%)	3 (7%)	100 (22%)	171 (76%)	5 (5%)
NAP2, n = 283	16 (20%)	25 (23%)	8 (22%)	157 (35%)	13 (6%)	64 (62%)
NAP3, n = 11	0	0	0	10 (2%)	1 (0.4%)	0
NAP4, n = 36	1 (1%)	3 (2%)	5 (14%)	21 (5%)	5 (2%)	1 (1%)
NAP5, n = 3	0	0	0	2 (0.4%)	0	1 (1%)
NAP6, n = 31	4 (5%)	5 (5%)	0	12 (3%)	3 (1%)	7 (7%)
All Others, n = 333	50 (62%)	56 (51%)	21 (57%)	149 (33%)	32 (14%)	25 (24%)

Table 11: Frequency of resistance to select antimicrobial agents of C*.difficile* isolated from the stool specimens of the patients with HA-CDAD by PFGE small patterns, N = 1008.

Antimicrobial agent*	All strains, N = 1008 No. (%)	NAP1, n = 311 No. (%)	NAP2, n = 283 No. (%)	NAP 3, n = 11 No. (%)	NAP4, n = 36 No. (%)	NAP5, n = 3 No. (%)	NAP6, n = 31 No. (%)	All others, n = 333 No. (%)
Clindamycin	868 (86%)	256 (82%)	280 (99%)	10 (91%)	22 (61%)	3 (100%)	27 (87%)	270 (81%)
Fluoroquinolone								
Levofloxacin	747 (74%)	287 (92%)	276 (98%)	10 (91%)	8 (22%)	3 (100%)	8 (26%)	155 (47%)
Gatifloxacin	672 (67%)	259 (83%)	276 (98%)	10 (91%)	3 (8%)	3 (100%)	0 (0%)	121 (36%)
Moxifloxacin	673 (67%)	258 (83%)	277 (98%)	10 (91%)	4 (11%)	3 (100%)	0 (0%)	121 (36%)
Cephalosporin								
Cefazolin	957 (95%)	310 (99%)	283 (100%)	9 (82%)	35 (97%)	3 (100%)	29 (94%)	288 (86%)
Ceftriaxone	658 (34%)	245 (79%)	276 (98%)	7 (63%)	10 (28%)	3 (100%)	3 (10%)	114 (34%)

* No strains were resistant to Metronidazole, Vancomycin or Teicoplanin.
All strains were resistant to Ciprofloxacin, Cefuroxime and Cefotaxime.

Table 12: Frequency of severe outcomes among the adult patients with HA-CDAD in the first 30 days following onset of disease according to the strain type, N = 1008.

Strain characteristics	All, N = 1008	Death,* n = 66 No. (%)	RR (95%CI)	*P* value	Severe outcome, n = 80 No. (%)	RR (95%CI)	*P* value
NAP1/027	311	34 (10.9)	2.34 (1.50-3.79)	<0.0001	39 (12.5%)	2.13 (1.40-3.24)	0.0003
All others	697	32 (4.6)	Ref		41 (5.9%)		
NAP2 (J-strain)	283	9 (3.2)	0.41 (0.20-0.81)	0.0069	13 (4.6%)	0.49 (0.28-0.86)	0.0142
Others including NAP1	725	57 (7.7)	Ref		67 (9.2%)		
NAP1/Binary toxin/*tcdC* deletion	296	34 (11.4)	2.55 (1.50-4.11)	<0.0001	38 (12.8)	2.17 (1.33-3.35)	0.0002
Others	712	32 (4.5)	Ref		42 (5.9)	Ref	

* Death directly or indirectly related to HA-CDAD

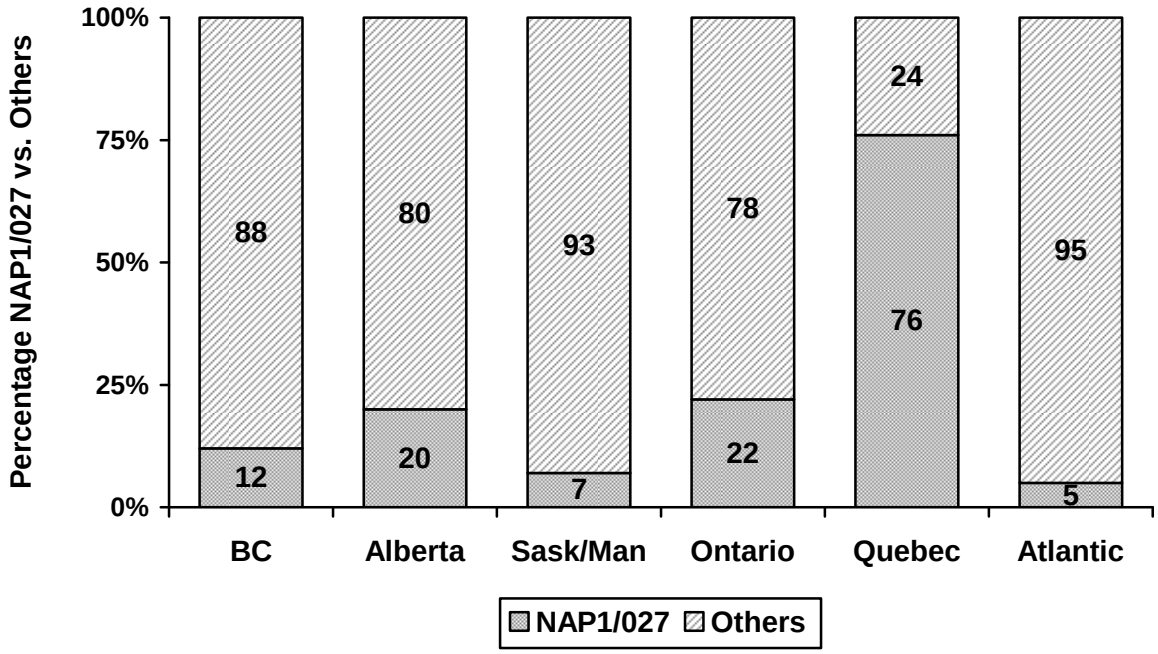

Figure 1: Distribution of *C. difficile* NAP1/027 in adults with HA-CDAD, by province or region (n=1008)

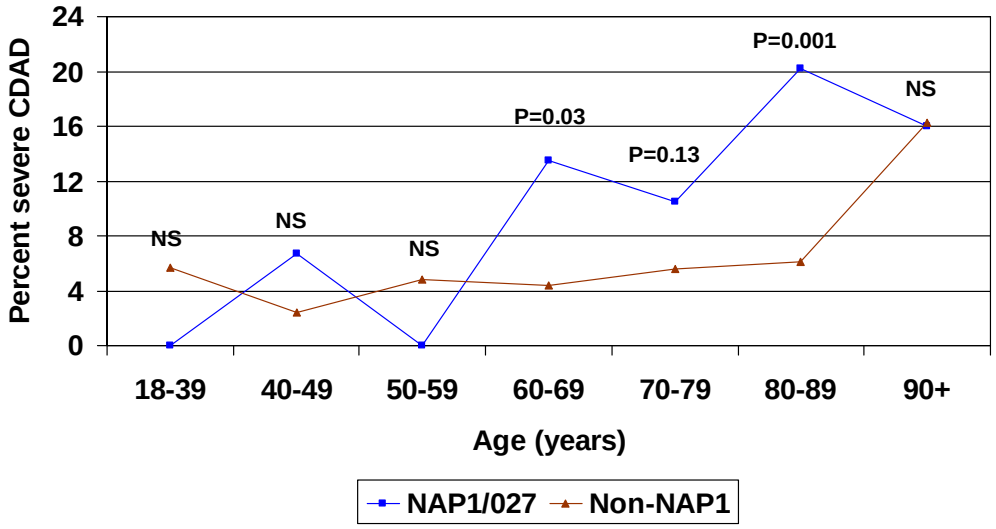

Figure 2: Effect of strain type on severe outcomes, by age, N =1008