ORIGINAL ARTICLE

Nosocomial diarrhoea in adult medical patients: the role of *Clostridium difficile* in a North Italian acute care teaching hospital

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Key words

Clostridium difficile-associated diarrhoea • Hospital • Nosocomial diarrhoea • Prevalence

Summary

Background. *The number of patients with severe Clostridium difficile-associated diarrhoea (CDAD) increases. Health care facilities are requested to establish rates of nosocomially acquired CDAD (N-CDAD) to understand the impact of control or prevention measures, and the burden of N-CDAD on health care resources.*
Objective. *Aim of the single-center surveillance project was to establish local prevalence rates of N-CDAD in adult acute care medical patients.*
Methods. *For a period of at least one year, all diarrhoeal stools from inpatients of a general internal medicine ward were tested for Clostridium difficile toxin A. Case record files were retrospectively analysed and questionnaires were completed for patients with positive stool assays who met the case definitions.*
Results and discussion. *During the surveillance period, 2,610 medical patients had been acutely hospitalized. Stools had been submitted to the hospital laboratory from 163 patients (6.2%) because of diarrhoea and were screened for Clostridium difficile cytotoxin. Complete data sets were available for analysis from 150 patients. Of 137 identified potential cases, 77 (56.2%) met the case definitions for nosocomial diarrhoea. Thirteen of the patients with nosocomial diarrhoea (16.9%) were detected positive by the Clostridium difficile toxin A assay. The overall prevalence of N-CDAD among inpatients was 8.7 cases/100 diarrhoeal stools. The mean number of N-CDAD cases was 62.3 cases/100,000 patient days and 5 cases/1,000 patient admissions. The mean age of N-CDAD patients was 79.4 years (range 71 to 92). All patients were given broad-spectrum antibiotics before acute diarrhoea developed. Four patients died for reasons not directly related to N-CDAD which confirms increased disease severity as an important risk factor.*
Conclusions. *This single-center surveillance project, which established N-CDAD rates at frequencies currently reported from international surveys, is useful as benchmark and will help in understanding patterns and impact of N-CDAD at the regional level.*

Introduction

Clostridium difficile-associated diarrhoea (CDAD) is an increasing health problem throughout Europe, Canada, and the United States with mortality rates rising. An increasing number of patients develop this illness in the community, although many with CDAD were recently discharged from a healthcare setting suggesting an acquisition of infection in the hospital environment [1]. The use of gastric acid-altering drugs that facilitate intestinal transit of the bacteria, antibacterial drugs that deplete colonic flora and presence of inflammatory bowel disease are identified risk factors for CDAD [1]. Although the majority of patients remain asymptomatic following acquisition of *Clostridium difficile*, it is still the most commonly identified cause of nosocomial (N) diarrhoea [2].
CDAD surveillance includes multi-centre national studies, description of periodic outbreaks or endemic situations in health care facilities, survey of elderly people, and study of specific wards, eg, medical and surgical [3]. However, it is useful to survey specifically N-CDAD cases, because they represent illness that may be prevented by hospital infection prevention and control practices. Consequently, the nosocomial acquisition of *Clostridium difficile* may represent inadequate infection control practices [4]. This underscores the importance of instigating measures to monitor the prevalence of N-CDAD, and implementing and assessing the efficacy of any prevention or control practices.
There are only few Italian studies in the literature that examine the role of N-CDAD infections [5-10]. Therefore, a single-site N-CDAD prevalence project was undertaken with the intent to contribute with the data to health care facility N-CDAD prevalence rates that could be inserted in future benchmark data for other Italian health care facilities, and to assist with the development and evaluation of guidelines that may decrease the incidence and cost of N-CDAD within Italian health care facilities.

Methods

At the Central Hospital of Bolzano, an 800-bed academic teaching hospital of the Autonomous Province of

Bolzano, Italy, affiliated with the Medical University of Innsbruck, Austria, all inpatient stools submitted from the 2nd Division of Internal Medicine (60 beds; general internal medicine with specialized units for endocrinology and angiology; about 2,200 patients annually; mean length of stay 8.0 days) to the hospital laboratory in a liquid or semiformed condition were analysed for the presence of *Clostridium difficile* toxin by the method currently in use, ie, cytotoxin A assay, and/or for bacterial stool culture regardless of the clinical indication for the specimen. A "*Clostridium difficile* case" was defined to be any person with nosocomial diarrhoea and stool containing *Clostridium difficile* cytotoxin. The patients' charts were reviewed to determine whether the patient met the case definition of N-CDAD, which was acute onset of > 3 loose stools per day that persisted for at least 2 days [7]. In addition, all CDAD cases had to fulfill one criterium to ensure that it was a case of N-CDAD: the symptoms occurred two days or more after admission.

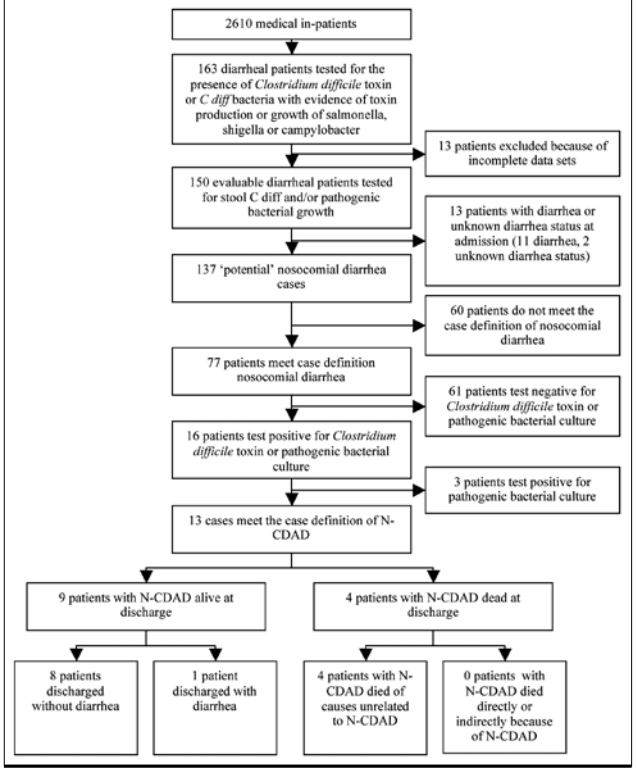
Data were collected between January 1, 2007 and January 12, 2008. In addition to the results of *Clostridium difficile* toxin A testing (Vidas® C. difficile Toxin A, Biomérieux) and bacterial culture for Salmonella / Shigella and *Campylobacter sp.*, further information was collected, including sex, age, whether patient was on antimicrobial medications at the time of stool specimen collection, and details on the treatments of N-CDAD. Primary cases were followed until death or discharge; relapses or re-infections of N-CDAD were not systematically documented. The patients' outcome at discharge was recorded, as well as the length of stay or time to death. Deaths directly or indirectly attributed to N-CDAD were defined respectively as due to colitis (eg, hemorrhage or perforation) or complications that would not have occurred if N-CDAD had not developed (eg, dehydration, debilitation). Laboratory information collected included the time period over which diarrhoeal stools were screened, and the total number of samples and patients tested. Duplicate specimens were not analyzed.

Results

During the surveillance period, 2,610 inpatients had been hospitalized at the general medical ward. Their mean age was 71.5 years with an overall range from 17 to 100 years (median 75 years). Stools had been submitted to the hospital laboratory from 163 patients (6.2%) because of diarrhoea in order to screen for *Clostridium difficile* cytotoxin (duplicate samples eliminated) and for pathogenic bacteria Salmonella, Shigella or Campylobacter (Fig. 1).

From the total of 163 samples, complete data sets were available for 150 patients and were analysed. Of 137 potential cases, 77 (56.2%) met the case definitions for nosocomial diarrhoea. Sixty (43.8%) cases did not meet the case definition of nosocomial diarrhoea because they did not meet the criteria to be considered nosocomially acquired, the diarrhoea did not persist for at least two days or the diarrhoea could be explained by other causes, such as chemotherapy. Thirteen of the patients with nosocomial diarrhoea (16.9%) were detected positive by

Fig. 1. Breakdown of the results of the nosocomial *Clostridium difficile*-associated diarrhoea (N-CDAD) prevalence surveillance project.



the *Clostridium difficile* toxin A assay, and three (3.9%) were found positive for stool pathogenic bacteria. Thus, the overall prevalence of N-CDAD among inpatients was 8.7 cases/100 diarrhoeal stools. The mean number of N-CDAD cases was 62.3 cases/100,000 patient days and 5 cases/1,000 patient admissions.

The characteristics of the patients with N-CDAD can be seen in Table 1. Seven patients (54%) with N-CDAD were female, while 6 (46%) were male. The mean age was 79.4 years with an overall range from 71 to 92 years, which was above the hospitalized patients average age ($p < 0.05$). The mean length of time from admission to onset of symptoms was 7.3 days with a range of 3 days to 16 days and a median of 8 days. The mean (± standard deviation) length of time from onset of symptoms to laboratory specimen collection was 2.9 (± 1.7) days. The mean length of stay (LOS) in hospital was 17.2 days with an overall range from 7 to 46 days again longer than the average LOS of the ward's patients. Four patients (31%) died for reasons that were unrelated to N-CDAD diarrhoea (two died of multiple organ failure due to severe sepsis of bacterial blood stream infection and pneumonia, respectively; one died of arrhythmia in cardiogenic shock because of decompensated chronic heart failure; and one of global respiratory insufficiency due to end-stage chronic obstructive pulmonary disease already on home oxygen therapy already for years); mean age of the patients who died was 82.2 years with an overall range from 79 to 84 years which was similar to the mean age of N-CDAD patients who survived (mean 78.1 years, range 67 to 92 years).

All patients with N-CDAD were on antibacterial medications at the time of stool specimen collection; 4 (30.8%)

Tab. I. Characteristics of patients of acute care nosocomial Clostridium difficile-associated diarrhoea (N-CDAD) participating in the 2007 retrospective surveillance program of a general medicine ward of the Central Hospital of Bolzano, Italy (n = 13).

Characteristic	Value
Mean age	79.4 years (Range from 71 to 92 years)
Sex	
Male	6 (46%)
Female	7 (54%)
Length of time from admission to acute onset of N-CDAD symptoms	Mean 7.3 days Median 8 days
Average length of stay (surviving cases)	Mean 17.2 days Median 16 days
Number of patients with N-CDAD receiving antibacterial medications at the time of stool specimen collection	13 (100%)

were on one antibiotic and 9 (69.2%) were on two or more antibiotics. Five patients (38.5%) with N-CDAD received concomitant antacid medications. Seven of the patients (54%) were given no antibiotics to treat N-CDAD either because of diarrhoea had ended spontaneously before arrival of test result, antibiotic therapy had been stopped and/or probiotics had been prescribed. The principal antibiotic used as therapy, oral metronidazole, was administered in 5 (38%) N-CDAD cases, intravenous metronidazole was administered in 1 case (8%), oral or intravenous vancomycin were not given.

Discussion

The prevalence of *Clostridium difficile* carriage in asymptomatic and otherwise healthy adult stool cultures is < 5% [11]. In contrast, the rate of carriage among hospitalised patients varies significantly and may be as high as 25% [12]. The present prevalence surveillance project identified 13 cases of N-CDAD among a total of 150 diarrhoeal patients analysed, thus, yielding a prevalence rate of 8.7%. The rates of CDAD as reported in the literature vary because they are based on different definitions of CDAD. According to recent recommendations the cases described here represent healthcare facility–onset, healthcare facility–associated (HO-HCFA) cases of CDAD [13]. A Canadian, multicentre, national point prevalence project on N-CDAD included nosocomial patients who had diarrhoea for at least two days that could not be explained by another cause, and a prevalence rate of 13% had been found [3]. Their selective case definition decreased the probability of false positives. The same case definition for N-CDAD was, therefore, also applied in the present study that was performed in adult patients from a medical ward. Thus, the observed prevalence rate of 8.7% is in the range of rates that was previously reported for medical ward patients which are known to have the highest frequencies of N-CDAD among the various health care facilities [3].

CDAD is reportedly more common among older individuals [14]. Age 50-80 years and age > 80 years were significantly associated with disease, and haemodialysis, non-surgical admission and increasing length of stay in the intensive care unit also being listed as risk factors [15]. In the current study, patients' age ranged from 67 to 92 years, among them 5 patients being 81 years or older. All patients were non-surgical. Haemodialysis and intensive care unit stay were not risk factors here due to the particular case mix of the medical ward under study.

In addition to increased severity of illness and increased age, prior antimicrobial use, particularly use of clindamycin, cephalosporins, and, more recently, fluoroquinolones and gastric acid suppressors are identified and proposed risk factors of CDAD, respectively [15, 16]. Not surprisingly, all patients with N-CDAD of the current survey had received antibiotic treatment at the time of stool specimen collection. However, the majority of patients with N-CDAD (61.5%) have not received antacid medications concomitantly. This observation might be interpreted in light of an ongoing controversy regarding the role of proton pump inhibitor treatment as a risk factor for CDAD [16, 17].

The morbidity and mortality associated with CDAD infections can be significant [18]. In the present project, four (30.8%) of the patients with N-CDAD died because of co-morbidities and complications unrelated to CDAD. This mortality rate reflects the particular case mix of the general medical ward under study with a high rate of acute medical illnesses and a median patient age above 70 years but not complications of CDAD. Mortality attributed to CDAD is much lower. Thus, in a 10-year surveillance project at one centre in the United States five of the 9,008 (0.6%) CDAD cases had identified CDAD as the primary cause of death [19]. Similarly, low mortality rates have been found in a Canadian surveillance project in 2001 of 1.5% [3]. Most likely, elevated disease severity which leads to increased mortality has also been a relevant risk factor for developing N-CDAD. It cannot be excluded, however, that, in our study, CDAD indirectly contributed to patient mortality.

As before, our acute medical health care facility did not know whether rates of N-CDAD were 'high' or 'low', the perception of whether N-CDAD is a problem does not appear to correspond with the observed rates of N-CDAD, according to nosocomial infection surveillance projects [3]. Not understanding what should be

acceptable rates of CDAD requires good benchmark data for comparisons and education. A recent Mediterranean survey from the Medical School of Bursa, Turkey, reported an incidence of nosocomial diarrhoea of 60 per 100,000 hospitalization-days and 5 per 1,000 patients' admissions; the incidence of N-CDAD was 26 per 100,000 hospitalization-days and 2.1 per 1,000 admissions [20]. A recent surveillance study including eight European countries and 112 laboratories reported the incidence of N-CDAD to be 1.1 case per 1,000 admissions [21]. This incidence is lower than those reported in North America [3]. The European study was a questionnaire-based survey including the Laboratory of Bacteriology, Istituto Superiore di Sanità, Rome, that suggest marked discrepancies between laboratories and also between countries regarding the criteria by which *C. difficile* is investigated for, and the methods and the strategies that are used for the diagnosis of *C. difficile* [21]. More than 90 percent of the participating European laboratories reported that they assay directly for *C. difficile* toxins in the stools, and among them an overall of 58 percent detect only toxin A [21], which was the case also in our study. However, literature on nosocomial diarrhoea is still difficult to compare also because of different definitions, different hygienic measures being used for patients with diarrhoea, and the presence of epidemics during the study period [22].

The current study may help to build up Italian benchmark rates that should assist hospital administration in decision making regarding the necessary infection control measures within their institutions.

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■ Received on December 22, 2008. Accepted on April 23, 2009.

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