Clostridium difficile–Associated Diarrhea:
Epidemiological Data from Western Australia
Associated with a Modified Antibiotic Policy

Claudia Thomas,1,2 Mark Stevenson,2 D. James Williamson,3 and Thomas V. Riley1,4
Departments of 1Microbiology and 2Public Health, The University of Western Australia, 3Department of General Medicine, Sir Charles Gairdner Hospital, and 4Division of Microbiology, The West Australian Centre for Pathology and Medical Research, Nedlands, Perth, Western Australia

The incidence of Clostridium difficile–associated diarrhea (CDAD) has increased dramatically in hospitals worldwide during the past 2 decades. In Western Australia, this increase was most obvious during the 1980s, when there was also an increase in the use of third-generation cephalosporin antibiotics. A study of the epidemiology of CDAD and the use of third-generation cephalosporins during 1993–2000 was undertaken. From 1993 through 1998, the incidence of CDAD remained relatively stable (2–3 cases per 1000 discharges annually). Then, a significant decrease in the incidence occurred, from 2.09 cases per 1000 discharges (95% confidence interval [CI], 1.71–2.47) in 1998 to 0.87 cases per 1000 discharges (95% CI, 0.63–1.11) in 1999 (P < .0001); this decrease persisted into 2000. A decrease in third-generation cephalosporin use occurred during the period of the study because of changes in the prescribing policy. These findings suggest that a reduction in the use of third-generation cephalosporins can reduce the occurrence of CDAD.

Clostridium difficile is the most common cause of infectious hospital-acquired diarrhea in developed countries [1]. The spectrum of conditions caused by C. difficile varies from asymptomatic colonization to colitis that can progress to the more severe pseudomembranous colitis. Complications include colonic perforation and death [2]. Because of increased awareness and better diagnostic tests, most infections with C. difficile do not progress to pseudomembranous colitis, and the more general term “C. difficile–associated diarrhea” (CDAD) is often used to describe this infection. Many authors have documented an increased incidence of CDAD during recent years, and several health care centers worldwide reported outbreaks of hospital-acquired diarrhea during the 1990s [3–7].

The most important determinants of CDAD are exposure to the organism in the hospital environment and exposure to antibiotics—in particular, third-generation cephalosporins and clindamycin [8]. Procedures that increase the chance of exposure to C. difficile have been identified as risk factors for CDAD [9, 10]. Elderly patients and patients with more-severe underlying disease are at an increased risk of developing CDAD [11]. Whether this is the result of a longer hospital stay—and, therefore, an increased opportunity to be exposed to antibiotics and organisms—is still not clear. Prevention and control of CDAD has been achieved through modification of infection-control practices, although with varying success [12]. More-effective measures have consisted of restricting antibiotic use in hospitals via the implementation or alteration of prescribing policies, but these measures have been reported in specific settings only and have primarily involved elderly patients [13–15].

Previously, we reported a gradual increase in the in-
Incidence of CDAD at Sir Charles Gairdner Hospital (SCGH; Perth, Western Australia) from 1983 through 1992 that correlated with increased use of third-generation cephalosporins [16]. The same laboratory testing procedures have been used at SCGH since 1983 [17], and this has allowed the long-term comparison of CDAD rates. In the present article, we describe the epidemiological characteristics of CDAD in SCGH for the period of 1993–2000 in the light of significant hospitalwide changes to antibiotic policy.

MATERIALS AND METHODS

This study was approved by the SCGH Human Research Ethics Committee.

Sources of data. SCGH is a 560-bed urban public teaching hospital that admits ~56,000 patients annually, with 300,000 outpatient and 35,000 emergency department visits per year. It is the state referral center for neurosurgery, liver transplantation, complex radiotherapy, and treatment of exotic infections.

The Western Australia Centre for Pathology and Medical Research (Nedlands, Perth) provides on-site microbiology services to SCGH. All SCGH patients in whom C. difficile was detected during the period of January 1993 through December 2000 were identified retrospectively via the computerized laboratory database. Information on the number of investigations for C. difficile performed by the laboratory was also extracted to assess changes in the rate of testing.

In addition, data were obtained from the hospital’s computerized patient account information system, The Open Patient Administration System (TOPAS). TOPAS records summary discharge data for all inpatient episodes using the codes of the International Classification of Diseases, 10th Edition (Australian modification; ICD-10-AM). Public hospitals in Western Australia use a unique Unit Medical Record Number (UMRN) that can be used to identify and match individual patient data from different sources. The date of birth and the sex of patients identified from the laboratory database were extracted from TOPAS and matched to the laboratory data using the UMRN. Denominators for incidence calculations were also obtained from TOPAS and the Hospital Morbidity Data System (Department of Health, Perth, Western Australia). Information regarding hospital use of third-generation cephalosporins (cefazidime, cefotaxime, and ceftriaxone) during 1993–2000 was obtained from different sources. The date of birth and the sex of patients identified from the laboratory database were extracted from TOPAS and matched to the laboratory data using the UMRN. Denominators for incidence calculations were also obtained from TOPAS and the Hospital Morbidity Data System (Department of Health, Perth, Western Australia). Information regarding hospital use of third-generation cephalosporins (cefazidime, cefotaxime, and ceftriaxone) during 1993–2000 was obtained from different sources.

Data analysis. CDAD cases were defined as having a positive laboratory test result, by either direct fecal cytotoxin in African green monkey kidney (VERO) cells or culture of C. difficile on cycloserine, cefoxitin, and fructose agar. Patients were counted only once each year. Stool samples from SCGH were tested for C. difficile using restricted criteria [18]—that is, if they fulfilled ≥1 of the following criteria: (1) stools were loose or watery, (2) RBCs or WBCs were present on microscopic evaluation of stool samples, (3) there was a history of antibiotic use, or (4) there was a history of inflammatory bowel disease. In addition, all patients who developed diarrhea after 48 h as inpatients were investigated for C. difficile infection [17].

The crude incidence of CDAD in the total hospital population for each year from 1993 through 2000 was calculated using the annual number of CDAD cases as the numerator and the number of patient discharges per year as the denominator. An alternative denominator, the number of “occupied bed days” (OBDs) per year, was also used to adjust the rate for changes in length of stay [19]. OBDs were calculated as the arithmetic difference between the “in-event date” (admission or transfer in) and the “out-event date” (separation or transfer out).

The overall age- and sex-specific incidence was calculated for the study period, and the age- and sex-adjusted annual incidence was determined using direct standardization with the 1998 Western Australian population. Ninety-five percent CIs for individual rates were obtained using single proportion estimates. Ninety-five percent CIs for the age- and sex-adjusted incidence were calculated using the weighted Poisson method [20]. To test for differences between rates, the z score for 2 proportions was used [21].

The annual laboratory testing rate for C. difficile was calculated as the proportion of all stool samples obtained from patients admitted to the study hospital that were investigated for C. difficile. This rate was calculated for each year from 1993 through 2000, and changes in the rate over time were tested using the χ² test for trend [21].

RESULTS

A total of 773 patients with stool samples that tested positive for C. difficile by culture or direct fecal cytotoxin testing were identified for the period of 1993–2000. The age and sex distribution of cases is shown in figure 1. The overall ratio of female to male patients for the 8-year study period was 1.33:1 (56.8% were female). The ratios of female to male patients for the various age groups were as follows: <20 years, 0.73:1; 20–29 years, 1.27:1; 30–39 years, 1.62:1; 40–49 years, 1.03:1; 50–59 years, 0.93:1; 60–69 years, 1.08:1; 70–79 years, 1.18:1; and ≥80 years, 2.58:1. In particular, patients in the ≥80-year-old age group were predominantly female, and the 30–39-year-old age group consisted of slightly more women than men. More than 60% of the patients were aged ≥60 years.

The overall incidence for the CDAD cohort was 1.88 cases per 1000 discharges (95% CI, 1.75–2.01). Women had a higher overall incidence during the study period of 2.14 cases per 1000 discharges (95% CI, 1.94–2.34), compared with 1.60 cases per 1000 discharges (95% CI, 1.43–1.78) for men; this difference
was statistically significant ($z = 3.99; P < .0001, 1\text{-tailed}$). The incidence was also higher among patients aged $\geq 60$ years: 2.34 cases per 1000 discharges (95% CI, 2.15–2.57), compared with 1.39 cases per 1000 discharges (95% CI, 1.23–1.55) for patients aged $< 60$ years ($z = 7.18; P < .0001, 1\text{-tailed}$). Women aged $\geq 60$ years had the highest incidence (2.81 cases per 1000 discharges [95% CI, 2.49–3.14]).

The annual crude incidence and the age-, sex-, and length of stay–adjusted incidence of CDAD for 1993–2000 are presented in figure 2. Each of these showed similar trends over the study period. Fluctuations in both the crude incidence and age- and sex-adjusted incidence were observed during 1993–1998, but they were not statistically significant, as indicated by the overlapping 95% CIs. A statistically significant decrease in the annual incidence of CDAD from 2.09 cases per 1000 discharges (95% CI, 1.71–2.47) in 1998 to 0.87 cases per 1000 discharges (95% CI, 0.63–1.11) was observed. This decrease persisted into 2000, with a rate of 0.70 cases per 1000 discharges (95% CI, 0.46–0.91). The age- and sex-adjusted rate decreased similarly, from 1.83 cases per 1000 discharges in 1998 (95% CI, 1.19–2.57) to 0.67 cases per 1000 discharges in 1999 (95% CI, 0.30–1.13; $z = 3.3; P < .0001, 1\text{-tailed}$).

Antibiotic use. Figure 3 shows the annual individual and total third-generation cephalosporin use, in grams, for 1993–2000. Data were incomplete for 1993 (data for 5 months were missing) and 1994 (data for 1 month were missing); for those 2 years, the average monthly amount was determined from the available data and used to estimate the annual use. Overall use of third-generation cephalosporin decreased from 20,000 g in 1993 to 1223 g in 2000. Use of ceftazidime and cefotaxime was discontinued in early 1997, and ceftriaxone remained the only third-generation cephalosporin in use from that time.

Testing rate. From 1993 through 1995, the annual laboratory testing rate for C. difficile infection was stable at 96%; it decreased to 92% in 1996. The testing rate fluctuated between 92% and 95% during 1996–1999, decreasing again to 88% in 2000. The overall decrease in testing rate observed from 1993 through 2000 was statistically significant ($\chi^2$ test for trend, 17.0; $P < .0001$).

DISCUSSION

Throughout the developed world, C. difficile infection remains an important cause of morbidity in hospitalized patients. With changes in healthcare practices due to shrinking budgets and shorter admission periods, any additional length of stay resulting from hospital-acquired infections such as CDAD has important consequences not only for patients but also for health care providers. CDAD has been shown elsewhere to significantly increase the length of hospital stay for patients, both at SCGH [22] and elsewhere [23, 24], which, in turn, contributes to increased costs to the hospital.

An epidemiological study of CDAD at SCGH published elsewhere reported a gradual increase in the incidence of CDAD during the 1980s and a corresponding increase in the amount of third-generation cephalosporins dispensed by the hospital pharmacy [16]. The continued use of the same laboratory testing procedures for diagnosis of C. difficile infection enabled a
similar study to be undertaken from 1993 through 2000, which revealed a statistically significant decrease in the incidence of patients with stool samples that tested positive for *C. difficile* by culture or direct fecal cytotoxin testing, from a peak of 65 patients per 100,000 OBDs to 20 patients per 100,000 OBDs by 2000. Such low rates have not been observed in the hospital since 1983. As with the other study, the change in incidence coincided with a change in third-generation cephalosporin use, which decreased to 1223 g by 2000. Although CDAD was initially associated with clindamycin use in the United Kingdom [8], clindamycin is infrequently used at SCGH [25].

The demographic characteristics of patients with CDAD in the present study remained similar to those described in the earlier study [16]. The highest incidence was reported among elderly women, and a high ratio of female to male patients was observed among patients aged >80 years and, surprisingly, 30–39 years. It is still not clear why more women than men get CDAD. There was no difference between the number of female and male admissions for 30–39-year olds, unlike the >80-year-old patients, for whom there was a clear excess of female admissions (data not shown).

Although a statistically significant decrease in the rate of laboratory testing for *C. difficile* was observed in 1999 and 2000 that coincided with the decrease in CDAD incidence, it is unlikely that an 8% decrease in the testing rate explains the 50% decrease in incidence. The testing rate for *C. difficile* for SCGH patients is particularly high (~90%) on the basis of the argument that inpatients who develop diarrhea should be primarily investigated for *C. difficile* infection [17]. The slight decrease in the testing rate could have resulted from shorter hospital stays, with fewer patients remaining in hospital long enough for a specimen to be obtained. Alternatively, shorter hospital stays reduce the chance of exposure to *C. difficile*, potentially reducing the number of CDAD cases. The average length of stay for multiday stay admissions at the study hospital was 7.9 days in 1996, and it had changed very little (to 7.59 days) by 2000. The number of single-day admissions increased steadily during this time, from 29,686 in 1996 to 36,232 in 2000, and the number of multiday admissions also increased—although only slightly—from 21,192 to 22,362. These changes are an unlikely explanation for the decrease in the testing rate. A more plausible explanation for the decrease may be the decreased number of *C. difficile* infections that occurred in the hospital. Infection-control practices must also be considered in light of a change in nosocomial infection rates. At SCGH, standard precautions are used for all patients with diarrhea. These precautions involve transfer to a single room with ensuite facilities and reinforcing hand-washing advice. There were no changes to these practices during the study period that could explain the dramatic decrease in the incidence of CDAD.

A limitation to the present study is that it measured the total hospital population incidence by identifying all *C. difficile*—
positive inpatients through the laboratory database. Therefore, community-acquired and hospital-acquired infections are included in the incidence, likely producing an overestimation of the rate of hospital infection. CDAD does occur in the community [26], but the rates appear to be low [27] and are likely to have minimal impact on the overall hospital incidence. A second limitation, which is the result of the retrospective nature of the study, is that the presence of diarrhea could not be confirmed, and a proportion of patients who tested positive may have been asymptomatic carriers. This proportion is likely to be small, however, because specific criteria for testing specimens for \textit{C. difficile} are in place [17, 18]. Finally, patients with toxin-negative, culture-positive stool samples were considered to have had CDAD, because direct fecal cytotoxin testing has low sensitivity. A study published elsewhere has demonstrated that 60% of samples with negative direct fecal cytotoxin test results yielded cytotoxin-positive \textit{C. difficile} on culture [16].

The decrease in ceftriaxone use was precipitated by a change in the hospital’s antibiotic prescribing policy in November 1998. An audit of ceftriaxone use among patients in the respiratory unit found that both significant overuse and inappropriate use of ceftriaxone were occurring. The antibiotic policy was changed to require approval from the microbiology department before any use of ceftriaxone, and ward stocks of ceftriaxone could no longer be maintained, except in the emergency department and the intensive care unit. This change resulted in a substantial decrease in the pharmacy’s issuing of ceftriaxone from 1999. Ceftriaxone is one of the cephalosporins most commonly associated with \textit{C. difficile} infection. This is thought to be related to high rates of biliary excretion, which produces high concentrations of ceftriaxone in the gut [28]. Several epidemiological studies have shown that there is an association between ceftriaxone use and \textit{C. difficile} colonization [29, 30] or CDAD [31–33], although it is not clear whether ceftriaxone is more significantly associated with CDAD than are other third-generation cephalosporins [25].

Changes in the antibiotic prescribing policy were implemented at SCGH because of growing concerns regarding third-generation cephalosporin–resistant organisms, but these changes resulted in a reduction in the rate of CDAD. This has several benefits apart from the obvious advantage of the decrease in patient morbidity. The decrease in third-generation cephalosporin use has provided economic savings to the hospital. The third-generation cephalosporins cost the hospital $266,687 (in Australian dollars) at their peak use in the 1995–1996 financial year and only $24,035 (in Australian dollars) in the 1999–2000 financial year. However, the cost of replacement antibiotics, such as fourth-generation cephalosporins and ciprofloxacin, needs to be considered. The reduction of nosocomial CDAD means savings in terms of the costs of diagnosis and treatment of the patient, as well as decreased costs that would have been incurred through additional length of stay in the hospital. Often, withdrawal of the associated antibiotic is sufficient to resolve an episode of CDAD; however, when treatment is required, metronidazole or vancomycin are the antibiotics of choice. The involvement of CDAD in contributing to the emergence of vancomycin-resistant enterococci [34] has limited the choice of antimicrobial treatment of CDAD.
to metronidazole only. Thus, with limited treatment choices available, the prevention of endemic CDAD is of considerable importance.

Several investigators have reported the successful control of CDAD after a reduction in the use of third-generation cephalosporin, although these reports have involved specific settings [13–15]. These studies, in addition to our own more general observations, contribute to a growing body of evidence that restriction of the use of third-generation cephalosporins in hospitals can effectively control outbreaks of CDAD and reduce endemic levels of infection.

**Acknowledgments**

We thank B. Allison, A. Witt, and Y.-C. Li (Information Systems, Western Australian Centre for Pathology and Medical Research, Perth), for the laboratory database extracts; L. Spargo and G. Cowley (Corporate Information Unit, Sir Charles Gairdner Hospital [SCGH], Perth, Western Australia) and R. Maris, T. Threlfall, and T. Satti (Health Statistics, Health Information Centre, Department of Health, Perth, Western Australia), for provision of patient discharge data; and R. Donnelly (Pharmacy Department, SCGH), for antibiotic prescription data.

**References**