Secular Trends in Hospital-Acquired *Clostridium difficile* Disease in the United States, 1987–2001

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We reviewed *Clostridium difficile*–associated disease (CDAD) data from the intensive care unit (ICU) and hospital-wide surveillance components of the National Nosocomial Infections Surveillance System hospitals during 1987–2001. ICU CDAD rates increased significantly only in hospitals with >500 beds ($P < .01$) and correlated with the duration of ICU stay ($r = 0.82; P < .05$). Hospital-wide (non-ICU) rates increased only in hospitals with <250 beds ($P < .01$) and in general medicine patients versus surgery patients ($P < .0001$). CDAD predominated in general hospitals versus other facility types, and rates were significantly higher during winter versus nonwinter months ($P < .01$). Thus, prevention efforts should be targeted to high-risk groups in these settings.

*Clostridium difficile*–associated disease (CDAD) is the major hospital-acquired gastrointestinal infection in the United States [1]. Risk factors associated with hospital-acquired CDAD include antimicrobial use, advanced age, laxative use, antineoplastic chemotherapeutic agent use, bowel colonization with *C. difficile*, production of toxin A, renal insufficiency, or gastrointestinal surgery or procedures [1, 2]. Over the past several years, a wide variety of reports have been published of outbreaks or perceived or real increases in the incidence of CDAD in the United States. Therefore, we conducted this study to determine secular trends in the incidence of CDAD in National Nosocomial Infections Surveillance System (NNIS) hospitals.

**SUBJECTS AND METHODS**

**Study population.** NNIS is the oldest source of data in the United States on hospital-acquired infections [3]. Previously, NNIS data were collected from 4 standardized surveillance components: adult and pediatric in-
tensive care units (ICUs), surgical units, high-risk nur-
series, and hospital wide. Hospital-wide data reflected all non-ICU inpatients and was distinct from the ICU component. In 1998, the hospital-wide component was replaced by a standardized antimicrobial use and resistance component. We analyzed data reported during January 1987 to December 2001 for the ICU component and during January 1987 to December 1998 for the hospital-wide component. For the ICU component, we evaluated the association between the occurrence of CDAD and number of beds in the ICU, medical device use, and duration of ICU stay. For the hospital-wide component, we studied CDAD in the medicine, surgery, obstetrics and gynecology, pediatrics, and neonatal medicine services. For both components, additional risk factors evaluated included hospital size (<250 beds, 250–500 beds, or >500 beds) and teaching status.

**Case definition.** The NNIS system definition of hospital-acquired gastroenteritis requires that patients meet either of the following 2 criteria [4]: (1) acute onset of diarrhea (liquid stools for >12 h) with or without vomiting or fever (temperature $>38^\circ$C) and no likely noninfectious cause; and (2) at least 2 of the following symptoms: nausea, vomiting, abdominal pain, fever $>38^\circ$C, or headache, and at least 1 of 5 specified types of positive laboratory confirmatory tests [4]. Patients who met the above case definition were deemed to have CDAD if they had a positive stool culture and/or toxin assay for *C. difficile*. Thus, our analyses en-
Figure 1. Annual Clostridium difficile–associated disease rates for hospitals with >500 beds, by intensive care unit surveillance component (National Nosocomial Infections Surveillance System, 1987–2001).

RESULTS

During 1987–2001, the number of participating hospitals increased from 90 to 340. For ICU data, 52% were reported by hospitals with >500 beds, 35% by hospitals with 250–500 beds, and 12% by hospitals with <250 beds. The percentage of hospitals reporting hospital-wide data decreased from 86% in 1987 to 10% in 1998. This decrease in hospital-wide reporting did not vary by the number of beds (28% were reported by hospitals with >500 beds, 49% by hospitals with 250–500 beds, and 23% by hospitals with <250 beds).

ICU data, stratified by hospital type, were reported by general hospitals (90%), children’s hospitals (5.2%), Veterans Administration hospitals (4.7%), and women’s hospitals (0.1%). Thus, this report overwhelmingly reflects the trend of CDAD in general hospitals. During 1987–2001, ICUs recorded a total of 14,136,364 ICU patient-days and 7008 patients with CDAD. During 1987–1998, the hospital-wide component recorded 5,959,517 patient discharges and 7280 patients with CDAD.

ICU component. During 1987–2001, the ICU CDAD rate increased significantly only in hospitals with >500 beds ($P < .01$; figure 1). This trend was not observed at hospitals with <250 beds. The CDAD rate in teaching versus nonteaching hospitals were similar (5.1 vs. 4.4 cases /10,000 patient-days; $P < .05$). Correlates with CDAD included mean duration of ICU stay ($r = 0.82; P < .05$) and rates of medical device use ($r = 0.63; P < .05$).

Hospital-wide component. Hospital-wide CDAD rates (per 10,000 discharges) increased significantly ($P < .01$) only in hospitals with <250 beds, were significantly higher in teaching versus nonteaching hospitals (13.0 vs. 11.7 cases; $P < .0001$), and were highest in the medical service (18.9 cases), followed in decreasing order by the surgical (15.6 cases), gynecology (6.0 cases), pediatrics (2.8 cases), obstetrics (1.0 cases), and neonatal (0.5 cases) services. CDAD rates in the medical service were significantly greater than those in the surgical service ($P < .0005$).

Seasons and geography. CDAD rates in ICUs were highest during the winter months (January to March) and decreased during the nonwinter months (April to December; figure 2). When we stratified the data by winter months versus the rest of the year, winter rates were consistently higher for each year of the study period ($P < .01$). The rate of ICU CDAD varied by geographic region (range, 1.1 infections/10,000 patient-days in the West south-central region to 7.9 infections/10,000

Rate calculations. ICU CDAD incidence density rates were expressed as the number of patients with CDAD per 10,000 patient-days; hospital-wide incidence rates were expressed as the number of patients with CDAD per 10,000 patient discharges. We stratified the data by US geographic region, as defined by the American Hospital Association, and examined the seasonal occurrence of CDAD in ICUs during 1987–2001.

Data analysis. Data were analyzed by use of PC SAS software (version 6.12; SAS Institute). Incidence densities were compared by use of the $z$ test. Linear regression lines were fitted to determine trends in CDAD rates over the respective study periods, and the $t$ test was used to determine the significance of these trends. Pearson’s coefficient was calculated for correlation analyses.
patient-days in the mid-Atlantic region of the United States [figure 3]). When we further stratified the data and compared the CDAD rates from the regions, the trend in hospitals from the Northeast mirrored the nationals trends described above. This trend was not observed for the other regions.

**DISCUSSION**

The present study indicates that, during 1987–2001, hospital-acquired CDAD increased significantly in the ICUs of NNIS hospitals with \( \geq 500 \) beds and that the occurrence of CDAD was significantly associated with longer duration of patient ICU stay and use of medical devices. In addition, the hospital-wide data indicate increasing rates in hospitals with \( \geq 250 \) beds and that medical-service patients are at greater risk of contracting CDAD versus patients in other services.

Most of the published CDAD incidence data in the United States pertain to studies conducted in single, acute-care, medical institutions and suggest that CDAD is an increasing problem. In a 1999 editorial, Gorbach [5] underscored the fact that many observers had noted a steady increase in the number of cases of CDAD over the past 15 years. In contrast, there is a paucity of similar data from multicenter surveillance systems, such as NNIS. It has long been recognized that the risk of acquiring CDAD is a function of length of hospital stay [6] and that rates of colonization of inpatients with *C. difficile* may be as high as 50% for patients hospitalized \( \geq 4 \) weeks, which suggests acquisition from personnel, patients, or the environment [7]. Although health-care workers play a substantial role in the transmission of the *C. difficile* spores through transient hand carriage, person-to-person spread of *C. difficile* within the hospital setting can occur through a variety of routes, including direct patient-to-patient contact or transmission between patients via the hands of health-care workers [1]. In addition, patients could acquire the organisms directly or indirectly from the contaminated environment [8].

The upward trend in CDAD incidence rates that we documented could have been caused by \( \geq 1 \) of the following factors: increases in antimicrobial use in US hospitals, increases in ICU patient census, increased sensitivity of diagnostic testing, or some uncharacterized factor conducive to the proliferation of *C. difficile* spores in the environment. Published results from single-center studies have attested to an increase in the institutional use of antimicrobials during the 1990s [9, 10]. However, until recently, antimicrobial usage data were not collected or aggregated in most single-center or multicenter surveillance systems. Because NNIS hospitals only started reporting antimicrobial use data in 1999, there were insufficient data at the end of 2001 to enable proper study of the relationship between antimicrobial use and CDAD occurrence. However, our observation that patients were more likely to acquire CDAD in the medical service versus other inpatient services is consistent with the expectation that extensive antimicrobial prescribing occurs in the medical services of hospitals.

Although there was a general decrease in the total number of beds in NNIS hospitals during the 1990s, the number of ICU beds increased during the same period [11]. This increase in the numbers of ICU beds during the study period would suggest a potentially larger number of patients admitted to ICUs, accommodation for greater numbers of severely ill patients, and increased antimicrobial use. More recently, Kyne et al. [12] established that patients with CDAD are significantly
more likely to have a higher underlying disease severity score (Horn’s index) after admission. Our analyses confirmed that duration of ICU stay and rates of medical device use, which are surrogate markers for severity of illness, were significant correlates with CDAD rates. The increasing trend of CDAD rates in the hospital-wide component at smaller NNIS hospitals might be a reflection of the fact that many small hospital do not have ICUs; therefore, at-risk patients have to be located in hospital-wide wards or, perhaps, because smaller hospitals are less likely to have a designated infection control department or hospital epidemiologist.

During 1987–2001, there was overall seasonal variation in CDAD occurrence in ICUs, with higher rates during the winter versus nonwinter months (figure 2). Plausible reasons for the higher winter rates include persistence of viable spores during the colder months, increased patient census that results in overcrowding in ICUs, reduced nurse-to-patient ratios as a result of staffing problems, or greater severity of illness scores among patients admitted during winter. Also, because hospitals tend to admit higher numbers of patients with respiratory infections during winter months, one would naturally expect a parallel increase in antimicrobial use, a major risk factor for CDAD, during that time of the year. We ascertained higher rates of CDAD at NNIS hospitals in the Northeast. This finding is consistent with a selection bias arising from overrepresentation of NNIS data from large teaching hospitals in the Northeast. This inference is underscored by the fact that only hospitals from the Northeast had CDAD trends that mirrored the national profile.

If the increasing trends are indeed caused by the proliferation of spores in the hospital environment, an organized hand hygiene program could theoretically reduce CDAD rates. Some investigators feel that alcohol gels are unlikely to be of use for control of *C. difficile*, because alcohol is actually used as an enrichment factor in growth medium to enhance *C. difficile* recovery [13]. Thus, handwashing with soap and water, instead of alcohol gels, might be the preferred hand hygiene method for prevention.

The present study had several limitations. First, because the number of NNIS hospitals increased 4-fold during 1987–2001, with a significant increase in the number of hospitals collecting and reporting ICU data and a concomitant decrease in the number of hospitals collecting hospital-wide data, NNIS data reflect an intrinsic selection bias toward patients in the ICUs, who would have been more likely to receive antimicrobials or invasive devices. Such a bias would have resulted in more CDAD being ascertained and reported. Second, the sensitivity of microbiological tests for *C. difficile* improved over the course of the study period and could have contributed to higher detection rates of *C. difficile* and its toxins. Third, we ascertained

Figure. 3. Incidence density (per 10,000 patient-days) of *Clostridium difficile*-associated disease, by region and intensive care unit surveillance component (National Nosocomial Infection Surveillance System, 1987–2001).
CDAD rates by use of a surveillance rather than a clinical case definition for hospital-acquired gastroenteritis. More precise multicenter surveillance and characterization of CDAD will require a more specific clinical case definition [1]. Fourth, NNIS data did not contain information on the laboratory methods (i.e., culture, toxin assay, or both) used to detect C. difficile. Fifth, we combined data from individual ICUs when a hospital had >1 ICU. This constituted a surveillance bias, because rates of CDAD and device use are known to be dependent on ICU type [14]. Last, hospital-wide rates are not amenable to risk adjustment and, therefore, are not meaningful for national comparison [14].

In summary, our results suggest that, during 1987–2001, rates of CDAD increased significantly in the ICUs of large NNIS general hospitals. During the same time, hospital-wide CDAD rates increased in smaller NNIS hospitals, particularly in the medical services. Prevention efforts should be targeted to high-risk groups in these settings to reduce environmental contamination with C. difficile, to enhance hand hygiene practices, and to reduce antimicrobial exposures.

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References