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# VARYING RATES OF *CLOSTRIDIUM DIFFICILE*-ASSOCIATED DIARRHEA AT PREVENTION EPICENTER HOSPITALS

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## ABSTRACT

**BACKGROUND:** *Clostridium difficile*-associated diarrhea (CDAD) causes substantial healthcare-associated morbidity. Unlike other common healthcare-associated pathogens, little comparative information is available about CDAD rates in hospitalized patients.

**OBJECTIVES:** To determine CDAD rates per 10,000 patient-days and per 1,000 hospital admissions at 7 geographically diverse tertiary-care centers from 2000 to 2003, and to survey participating centers on methods of CDAD surveillance and case definition.

**METHODS:** Each center provided specific information for the study period, including case numbers, patient-days, and hospital characteristics. Case definitions and laboratory diagnoses of healthcare-associated CDAD were determined by each institution. Within institutions, case definitions remained consistent during the study period.

**RESULTS:** Overall, mean annual case rates of CDAD were

12.1 per 10,000 patient-days (range, 3.1 to 25.1) and 7.4 per 1,000 hospital admissions (range, 3.1 to 13.1). No significant increases were observed in CDAD case rates during the 4-year interval, either at individual centers or in the Prevention Epicenter hospitals as a whole. Prevention Epicenter hospitals differed in their CDAD case definitions. Different case definitions used by the hospitals applied to a fixed data set resulted in a 30% difference in rates. No associations were identified between diagnostic test or case definition used and the relative rate of CDAD at a specific medical center.

**CONCLUSIONS:** Rates of CDAD vary widely at tertiary-care centers across the United States. No significant increases in case rates were identified. The varying clinical and laboratory approaches to diagnosis complicated comparisons between hospitals. To facilitate benchmarking and comparisons between institutions, we recommend development of a more standardized case definition (*Infect Control Hosp Epidemiol* 2005;26:676-679).

*Clostridium difficile*-associated diarrhea (CDAD) causes substantial healthcare-associated morbidity in many hospitals. Patients who acquire CDAD require antibiotic therapy, contact isolation, and prolonged hospitalization and have a 20% rate of recurrence.<sup>1,2</sup> CDAD also imposes a significant financial burden on healthcare institutions, with an estimated cost of \$1.1 billion per year in the United States.<sup>3</sup> In addition, according to the Centers for Disease Control and Prevention (CDC), the annual rate of healthcare-associated CDAD has increased in recent years.<sup>4,6</sup>

Unlike other common healthcare-associated pathogens, such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*, there is little comparative information available about CDAD rates in hospitalized patients. Such data may be helpful for hospitals seeking to evaluate the effectiveness of their infection control and prevention programs and to benchmark their rates against national data.

To address the lack of comparative data, we determined the range of CDAD rates at Prevention Epicenter hospitals during the 4-year period from January 1, 2000, to December 31, 2003. In addition, these hospitals were surveyed on their methods of CDAD surveillance and case classification. The Prevention Epicenter is a consortium of seven academic medical centers funded by the CDC to address areas relevant to infection control and quality promotion.

## METHODS

Each Prevention Epicenter hospital provided specific information for the study period, including case numbers, patient-days, and hospital characteristics. All hospitals defined CDAD as a positive laboratory test result for a hospitalized, acute care patient with symptoms. Definition of symptoms ranged from physician designation of diarrhea alone to the full definition of the National Nosocomial Infections

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**TABLE 1**  
ANNUAL *CLOSTRIDIUM DIFFICILE* INCIDENCE RATES AND PERCENT CHANGE PER 10,000 PATIENT-DAYS AND PER 1,000 ADMISSIONS

	2000	2001	2002	2003	Mean	Annual % Change
Hospital A						
Rate per 10,000 patient-days	25.0	19.5	32.6	23.0	25.1	2.69
Rate per 1,000 admissions	13.7	9.8	16.9	12.0	13.1	1.48
Hospital B						
Rate per 10,000 patient-days	5.9	5.8	5.7	5.5	5.7	-2.22*
Rate per 1,000 admissions	3.5	3.4	3.3	2.4	3.1	-10.33
Hospital C						
Rate per 10,000 patient-days	4.0	5.9	3.0	4.2	4.3	-5.26
Rate per 1,000 admissions	4.0	5.2	2.6	3.4	3.8	-10.95
Hospital D						
Rate per 10,000 patient-days	9.2	9.9	7.1	8.7	8.7	-4.75
Rate per 1,000 admissions	6.7	6.9	4.9	5.9	6.1	-7.12
Hospital E						
Rate per 10,000 patient-days	22.0	16.0	20.0	20.9	19.7	0.78
Rate per 1,000 admissions	8.8	6.5	4.6	8.1	7.8	-0.99
Hospital F						
Rate per 10,000 patient-days	3.7	1.9	3.5	3.4	3.1	4.40
Rate per 1,000 admissions	5.4	2.7	5.2	5.1	4.6	5.01
Hospital G						
Rate per 10,000 patient-days	14.2	12.5	14.6	14.0	13.8	1.09
Rate per 1,000 admissions	9.6	8.7	9.9	9.5	9.4	1.10
Overall						
Rate per 10,000 patient-days	12.3	10.8	13.2	12.2	12.1	-0.53
Rate per 1,000 admissions	8.0	6.7	8.0	7.1	7.4	-3.29

\*The annual percent change differs from 0 to a statistically significant degree (two-sided  $P < .05$ ).

Surveillance System for nosocomial gastroenteritis with previous antibiotic exposure. Diagnostic tests differed among the various hospitals. Enzyme immunoassay (EIA) testing for toxins A and B was used by four centers; each of the remaining three centers used cytotoxicity assay, EIA for toxin A, or EIA for toxin B. One hospital switched in 2002 from cytotoxicity assay to EIA for toxins A and B, whereas another switched in 2003 from EIA for toxins A and B to cytotoxicity assay.

Prevention Epicenter hospitals were surveyed regarding their criteria for classifying CDAD cases. Relevant variables included the length of time between patient admission and the collection of incident diagnostic specimens; consideration of hospital exposure prior to collection of positive specimens; the interval between a previous hospitalization and the point at which CDAD was diagnosed; definition of recurrent cases and second incident cases; and categorization of outpatient cases.

The annual percent change was estimated by fitting a least squares regression line to the natural logarithm of the rate using calendar year as a regressor variable (model:  $y = mx + b$ , where  $y = \ln[\text{rate}]$  and  $x = \text{calendar year}$ ). The estimated annual percent change is equal to  $100 \times (e^m - 1)$ . The null hypothesis of the annual percent change being equal to 0 (ie, no increase or decrease in the rate) was tested. The hypothesis test statistic uses the  $t$  distribution of  $m \div SE_m$ , where  $SE$  is the standard error of  $m$  and the number of degrees of freedom is equal to the number of calendar years minus 2.<sup>7</sup> Data processing and analyses were performed using SPSS software (version 10.0; SPSS, Inc., Chicago, IL).

## RESULTS

The Prevention Epicenter hospitals comprise 5,300 beds with 1.3 million annual patient-days. Approximately 1,750 cases of CDAD occur in the Prevention Epicenter

**TABLE 2**  
**CLOSTRIDIUM DIFFICILE CASE DEFINITION COMPONENTS**

	Hospital A	Hospital B	Hospital C	Hospital D	Hospital E	Hospital F	Hospital G
Diagnostic test	Prior to 5/02, cytotoxicity assay; after 5/02, EIA for toxins A and B	Cytotoxicity assay for toxin B	EIA	EIA	EIA and culture on CCFA	EIA for toxin A	Cytotoxicity assay for toxin B
Criteria for healthcare-associated cases							
Hours after admission	> 48	> 48	> 48	> 48	> 48	> 48	≥ 72
Days from previous discharge date	≤ 60 for oncology patients only	≤ 30 and no previous positive assay in 6 mo	≤ 30	NA*	≤ 14	≤ 3	NA*
"Recurrent" cases counted as incidents	Yes	Yes	Yes	Yes	Yes	Yes	No
Time between cases	> 60 d	> 6 mo	> 30 d with resolution of symptoms	Different calendar year	Asymptomatic period	Asymptomatic period and no therapy for 72 h	NA
Outpatient cultures included in healthcare-associated rate	No	Yes, if ≤ 30 d since last discharge	No	No	No	Yes, if ≤ 3 d since last discharge	No

EIA = enzyme immunoassay; CCFA = cycloserine-cefoxitin-fructose agar; NA = not applicable.  
 \*Prior hospital admissions not accounted for.

hospitals each year, for mean annual rates of 12.1 cases per 10,000 patient-days (mean range, 3.1 to 25.1) and 7.4 cases per 1,000 admissions (mean range, 3.1 to 13.1). During the 4-year period, no significant changes in *C. difficile* rates were seen for the Prevention Epicenter hospitals collectively or by individual medical centers, with one exception. Hospital B experienced an annual percent change of -2.22 in the CDAD rate per 10,000 patient-days that was statistically significant (Table 1). No associations were identified between the diagnostic test or case definition used and the relative rate of CDAD per medical center.

Prevention Epicenter hospitals differed in their case definitions of healthcare-associated disease. Six centers considered a case to be healthcare associated if the incident diagnostic specimen was collected more than 48 hours after patient admission; one center required the specimen to be obtained at least 72 hours after admission (Table 2). The Prevention Epicenter hospitals also were not in agreement about whether a recent hospitalization should be given consideration when classifying a CDAD case as healthcare associated. Only five of the seven hospitals accounted for prior hospital admissions. Furthermore, the interval from a previous discharge to the start of symptoms was not uniform across institutions, ranging from 3 to 60 days. The definition of recurrent cases varied widely among the individual Prevention Epicenter hospitals and only some of the hospitals included outpatient cases in overall healthcare-associated rates (Table 2).

To examine how extensively case definition might affect case rates, chart reviews were performed for all incident

cases of CDAD at one Prevention Epicenter hospital during the 2-year period from January 1, 2002, to December 31, 2003 (n = 370).<sup>8</sup> Six different definitions of healthcare-associated CDAD were applied to this cohort and the resultant case numbers and rates were determined (Table 3). When the strictest definition of healthcare-associated disease (a positive test specimen collected 3 or more days after admission) was applied, the rate was 8.67 per 10,000 patient-days. When more inclusive criteria were used (a positive test result 3 or more days after admission or a previous hospitalization within 30 days of the first positive test result), the rate increased to 10.45 per 10,000 patient-days. With even more inclusive criteria (a positive test result more than 2 days after admission or a previous hospitalization within 30 days of the first positive test result), the rate rose to 11.33 per 10,000 days. Thus, the different definitions of healthcare-associated CDAD used by the Prevention Epicenter hospitals applied to a fixed data set resulted in a 30% difference in rates. Although these differences in definitions did not explain the wide variation of rates among the Prevention Epicenter hospitals, the variability in definitions complicates benchmarking.

## DISCUSSION

In contrast to a recent report from the CDC that evaluated an earlier time period, we did not find significant increases in CDAD case rates during our 4-year interval either at individual centers or in the Prevention Epicenter hospitals collectively.<sup>5,6</sup> These discrepant findings may be the result of differing methodologies. The CDC reports

calculated *C. difficile* rates using the International Classification of Diseases, 9th revision, code diagnoses per discharge, an approach that is influenced by additional factors not reflected in rates calculated using only laboratory and clinical hospital data. Alternatively, the hospital sample in this report may not be large enough to detect a national trend.

Direct comparisons among the Prevention Epicenter hospitals were hampered by several factors. First, the diagnostic tests used by the hospitals varied. No studies to date have shown that the use of different diagnostic tests for *C. difficile* has resulted in significant differences in CDAD rates. However, depending on the clinical and laboratory criteria used for the CDAD case definition, the sensitivities of cell culture cytotoxin detection and EIA toxin tests range from 67% to 100% and 63% to 99%, respectively.<sup>9</sup> Clinical and laboratory criteria for assessment of *C. difficile* did vary across the Prevention Epicenter hospitals. We cannot assess whether these differences had an appreciable impact on CDAD rates.

Second, the case definition for healthcare-associated CDAD for each hospital was unique, particularly regarding four variables. These include the duration of hospitalization prior to incident sample collection, the time from previous hospital discharge until the development of symptoms, and whether CDAD diagnosed in outpatients was included in surveillance. Moreover, the definitions of recurrent CDAD and second incident cases varied substantially. For institutions with relatively high numbers of readmissions, the definition used for differentiation of recurrent CDAD versus incident CDAD could have a greater impact on the final calculation of incident and healthcare-associated rates. Each of these variables may influence the rate a given hospital reports and so may affect evaluation of an infection control program.

Other study limitations include the suboptimal sensitivity and specificity of the various diagnostic CDAD stand-alone tests and that most of the Prevention Epicenter hospitals are large, mostly urban, tertiary-care teaching facilities that may not be representative of hospitals nationally.

The 7 Prevention Epicenter hospitals documented mean annual healthcare-associated CDAD rates of 12.1 cases per 10,000 patient-days and 7.4 cases per 1,000 admissions, with wide but stable variations between sites. The definitions of healthcare-associated disease used by the participating facilities varied considerably. Inherent subtleties are involved in the interpretation and comparison of infection rates across institutions (eg, patient case mix and potential ascertainment bias of more intensive surveillance programs). The variations in operational case classification outlined here only further hinder the efforts to interpret interinstitutional rate differences and preclude the establishment of a meaningful national benchmark. There is no standard case definition of healthcare-associated CDAD in the published guidelines.<sup>9-11</sup> We recommend that one be developed and that diagnostic tests and testing criteria be standardized to allow meaningful comparisons between hospitals. We also invite other medical centers to report healthcare-associated CDAD rates so that an expected annual rate of CDAD can be better defined.

**TABLE 3**  
IMPACT OF DIFFERENT DEFINITIONS OF HEALTHCARE-ASSOCIATED *CLOSTRIDIUM DIFFICILE*-ASSOCIATED DIARRHEA ON CASE RATES

Definition of Healthcare-Associated CDAD	No. of Cases	Rate per 10,000 Patient-Days
A = specimen $\geq$ 72 h after admission	225	8.67
B = A + specimen < 72 h after admission with hospitalization in previous 14 d (n = 32)	257	9.91
C = A + specimen < 72 h after admission with hospitalization in previous 30 d (n = 46)	271	10.45
D = specimen $\geq$ 48 h after admission	267	10.29
E = D + specimen < 48 h after admission with hospitalization in previous 14 d (n = 20)	287	11.06*
F = D + specimen < 48 h after admission with hospitalization in previous 30 d (n = 7)	294	11.33 <sup>†</sup>

CDAD = *C. difficile*-associated diarrhea.

\*Incidence rate ratio<sub>A,E</sub> = 1.28 (95% confidence interval [CI<sub>95</sub>], 1.07-1.52).

<sup>†</sup>Incidence rate ratio<sub>A,F</sub> = 1.31 (CI<sub>95</sub>, 1.10-1.54).

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