Environmental Control to Reduce Transmission of *Clostridium difficile*

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Restrictive antibiotic policies and infection control measures have been shown to reduce the incidence of *Clostridium difficile*–associated diarrhea (CDAD) among hospitalized patients. To date, the role of environmental disinfectants in reducing nosocomial CDAD rates has not been well studied. In a before-and-after intervention study, patients in 3 units were evaluated to determine if unbuffered 1:10 hypochlorite solution is effective as an environmental disinfectant in reducing the incidence of CDAD. Among 4252 patients, the incidence rate of CDAD for bone marrow transplant patients decreased significantly, from 8.6 to 3.3 cases per 1000 patient-days (hazard ratio, 0.37; 95% confidence interval, 0.19–0.74), after the environmental disinfectant was switched from quaternary ammonium to 1:10 hypochlorite solution in the rooms of patients with CDAD. Reverting later to quaternary ammonium solution increased the CDAD rate to 8.1 cases per 1000 patient-days. No reduction in CDAD rates was seen among neurosurgical intensive care unit and general medicine patients, for whom baseline rates were 3.0 and 1.3 cases per 1000 patient-days, respectively. Unbuffered 1:10 hypochlorite solution is effective in decreasing patients' risk of developing CDAD in areas where CDAD is highly endemic. Presumed mechanisms include reducing the environmental burden and the potential for *C. difficile* transmission among susceptible patients.

Clostridium difficile–associated diarrhea (CDAD) is the most common cause of nosocomial diarrhea [1]. Risk factors include increasing age [2, 3], severity of underlying illness [2], gastrointestinal surgery and procedures [2–5], use of electronic rectal thermometers [6], prior use of antimicrobials [2, 3, 7, 8], and proximity to other patients infected with *C. difficile* [9]. *C. difficile* is found on floors and other environmental surfaces in rooms of symptomatic and asymptomatic patients [9–13]. Contamination of hospital environments was first reported in 1979 [14]. Nosocomial spread is well documented, and health care workers may transmit *C. difficile* via transient hand carriage [9–11].

Infection control measures that prevent horizontal transmission of *C. difficile* include glove use [9, 15], use of chlorhexidine in hand washing [9], and replacement of electronic rectal thermometers with single-use disposable thermometers [6]. Restrictive antibiotic policies appear to reduce the incidence of CDAD among hospitalized patients [16–18]. Environmental disinfectants may also reduce the incidence of CDAD [19, 20]. Unbuffered hypochlorite solution has been shown to decrease environmental contamination with *C. difficile* in hospital rooms [12]. However, it is uncertain whether routine cleaning of hospital rooms with environmental disinfectants will decrease the incidence of CDAD. The purpose of our study was to evaluate whether the routine use of hypochlorite solution can reduce the incidence of CDAD on defined geographic units in an acute care hospital.

Methods

Design. A before-and-after intervention study was designed to compare CDAD rates among hospitalized patients in different geographic units. Hospital rooms of patients with CDAD were cleaned with 2 environmental disinfectants: quaternary ammonium solution for the first 9 months and hypochlorite solution for the subsequent 9 months. Patients with diarrhea during hospitalization were evaluated for the presence of CDAD, and corresponding disease rates for the 2 study periods were adjusted for other potential risk factors.

Participants. The study population included all patients in the bone marrow transplantation unit, the neurosurgical intensive care unit (ICU), and a general medicine unit at Barnes-Jewish Hospital, a 2-campus tertiary care facility licensed for 1287 beds and affiliated with Washington University School of Medicine. All patients admitted to the bone marrow transplantation unit from 1 July 1995 through 31 December 1996 and the neurosurgical ICU or general medicine unit from 1 November 1995 through 31 March 1997 were identified via the hospital's informatics database. The study was initiated in the bone marrow transplantation unit because of sus-

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tained high rates of CDAD (9 cases per 1000 patient-days). The study was then expanded to a general medicine unit and a neurosurgical ICU, where CDAD rates were historically between 1 and 3 cases per 1000 patient-days, respectively. The CDAD rates for these 3 geographic units were higher than baseline hospital rates, at 0.8 cases per 1000 patient-days, which was similar to hospital-based CDAD rates reported for our region [21].

Interventions. From 1 April 1996 through 30 June 1997, environmental surfaces in the rooms of bone marrow transplantation patients for whom a *C. difficile* toxin assay was positive were cleaned routinely with hypochlorite instead of quaternary ammonium solution. In the remaining rooms in the units, cleaning with quaternary ammonium solution was continued. Nursing and housekeeping managers and staff were instructed about the purpose and procedure for using hypochlorite, by the infection control specialist, and the housekeeping staff was instructed to use 1:10 hypochlorite solution that was mixed fresh daily.

Adherence to the new hypochlorite protocol was monitored by the infection control specialist, who periodically contacted the housekeeping staff to determine whether they were aware of the CDAD status of patients and if hypochlorite was being used properly to clean patient rooms. This periodic contact with housekeeping staff has been a protocol standard for the past 5 years in our hospital. The same hypochlorite protocol was used in the neurosurgical ICU and a general medicine unit from 1 August 1996 through 31 March 1997. During the postintervention period in the bone marrow transplantation unit, an outbreak of vancomycin-resistant *Enterococcus faecium* afforded additional opportunity to study reversion of the hypochlorite protocol.

Data measures. Demographic, antimicrobial, and antineoplastic exposure data were obtained for each patient. Antimicrobial drug exposures during the patient's hospitalization were estimated by 4 different categorical variables. These exposures were calculated as the total number of days of antimicrobial drug therapy, total number of grams of antimicrobial drug, spectrum of antimicrobial activity on gastrointestinal flora, and aggregate exposure to the most commonly used antibiotics (vancomycin, ceftriaxone, and ceftazidime). For the determination of the spectrum of antimicrobial activity, patients were classified according to exposure to agents effective against gram-negative, gram-positive, anaerobic, or fungal pathogens. Antineoplastic drug exposure was defined collectively as selective treatment with agents that have been reported to increase the risk of *C. difficile* infection. These antineoplastic agents were cytoxan, doxyrubicin, methotrexate, and fluorouracil [22].

The total numbers of days and grams of antineoplastic exposure were not available from the informatics database for the entire study period. Antimicrobial and antineoplastic drug exposures were calculated for the 60 days prior to the onset of CDAD for infected patients and the 60 days prior to discharge for patients without CDAD.

Nosocomial CDAD was defined by the positivity of a physician-ordered stool assay for *C. difficile* toxin (Bartels cytotoxicity assay for toxins; Bartels, Issaquah, WA) at least 48 h after the patient was admitted to 1 of the 3 geographic units. Patients admitted to the 3 units during these periods were not routinely screened for *C. difficile* colonization via the culture-detection method. At our hospital, nondiarrheal specimens are not routinely sent for detection of *C. difficile* toxin but are processed for toxin production upon request. Patient-days at risk were counted from 48 h after the patient was admitted to the unit until the date of CDAD diagnosis or unit discharge (for CDAD-negative patients). We computed the unit- and time-period–specific CDAD rates by dividing the total number of cases of nosocomial CDAD by the total number of patient-days, for each unit and study period. CDAD rates were reported as number of cases of nosocomial CDAD per 1000 patient-days at risk.

All data were obtained from the hospital's informatics databases, GermWatcher/GermAlert (GW/GA) [23, 24] and DoseChecker [25]. GW/GA classifies final microbiology culture reports according to National Nosocomial Infection Surveillance (NNIS) criteria and sorts cultures on the basis of the likelihood that they represent nosocomial infections. GW computes site-specific nosocomial infection rates for significant organisms, and GA identifies epidemiologically significant organisms (e.g., *C. difficile*). Improved case-finding through use of GW/GA facilitated timely infection-control intervention. DoseChecker is an automated pharmacy database that offers trend analyses of frequently prescribed drugs, including antimicrobial and antineoplastic agents [25].

Data analysis. To measure the effectiveness of hypochlorite solution in reducing the incidence of CDAD, an extended Cox proportional hazards model [26] was used to estimate the hazard ratio (HR) for each unit. The HR represents the patient's risk of developing CDAD during the period when the new hypochlorite protocol was in effect, relative to the patient's risk before the protocol was initiated. Potential confounders included age, race, sex, and antimicrobial and antineoplastic exposures as time-dependent variables. All analyses were completed with use of SAS software, version 6.12 for Windows NT (SAS Institute, Cary, NC) [27].

Results

All admissions. There were 293 patients admitted to the bone marrow transplantation unit, 1278 patients admitted to the neurosurgical ICU, and 2881 patients admitted to the designated general medicine floor of the hospital. Twenty-nine percent of the bone marrow transplantation patients, 8% of the neurosurgical ICU patients, and 23% of the general medicine patients had $\geq$2 admissions to the hospital during the 18-month study period. The number of total admissions for the 3 units represented 5% of 83,705 admissions to the hospital for the same period.

Baseline characteristics of all patients admitted to the 3 defined geographic units were similar for the 9-month periods before and after initiation of the new hypochlorite protocol (table 1). Overall, bone marrow transplantation patients were younger than neurosurgical ICU and general medicine patients and were more likely to be white and to have received antimicrobial and antineoplastic drugs during their hospitalization. In addition, there were differences in the frequencies of antimicrobial exposure for bone marrow transplantation patients (88% preintervention vs. 95% intervention; $P = .01$), the percentages of white patients treated in the neurosurgical ICU (66% preintervention vs. 71% intervention; $P = .05$), and the

Table 1. Characteristics of 3 patient populations before and after initiation of the use of hypochlorite solution for disinfecting environmental surfaces in patient rooms.

Characteristic	Bone marrow transplantation patients			Neurosurgical ICU patients			General medicine patients		
	Before intervention, 07/95–03/96 (n = 197)	After intervention, 04/96–12/96 (n = 226)	P	Before intervention, 11/95–07/96 (n = 678)	After intervention, 08/96–04/97 (n = 740)	P	Before intervention, 11/95–07/96 (n = 1972)	After intervention, 08/96–04/97 (n = 1998)	P
Sex, male	96 (49)	117 (52)	.53	336 (50)	377 (51)	.60	827 (42)	849 (42)	.72
Race, white	165 (86)	201 (90)	.24	442 (66)	523 (71)	.05	842 (43)	830 (42)	.46
All antimicrobials given[a]	173 (88)	215 (95)	.01	575 (85)	619 (84)	.55	1322 (67)	1308 (65)	.30
Spectrum of antimicrobial activity[a]									
Gram-negative bacteria	170 (86)	211 (93)	.02	509 (75)	580 (78)	.14	1074 (54)	1071 (54)	.59
Gram-positive bacteria	161 (82)	205 (91)	.01	563 (83)	608 (82)	.66	1212 (61)	1195 (60)	.29
Anaerobic bacteria	95 (48)	144 (64)	.001	152 (22)	162 (22)	.81	469 (24)	401 (20)	.01
Fungi	39 (20)	98 (43)	.001	21 (3)	31 (4)	.28	111 (6)	106 (5)	.65
Selected antimicrobials given[b]	163 (83)	191 (85)	.62	287 (42)	283 (38)	.12	668 (34)	675 (34)	.95
Selected antineoplastics given[c]	88 (45)	100 (44)	.93	1 (<1)	4 (1)	.21	20 (1)	27 (1)	.33
Age, mean y (SD)	43 (13)	44 (12)	.67	54 (19)	56 (19)	.20	63 (19)	62 (19)	.36
Total antimicrobial days, mean (SD)[b]	12 (11)	12 (10)	.68	7 (8)	7 (10)	.93	4 (5)	4 (5)	.06
Total antimicrobial grams, mean (SD)[b]	30 (27)	29 (24)	.65	20 (25)	20 (28)	.89	9 (13)	8 (11)	.19
Exposure days, mean (SD)[d]	15 (16)	16 (12)	.68	7 (8)	8 (15)	.27	4.3 (7)	3.8 (5)	.01

NOTE. Data are no. (%) of patients unless otherwise indicated.

[a] Exposure to all antimicrobials from hospital admission to date of positive *C. difficile* assay (for infected patients) or until discharge (for uninfected patients).

[b] Exposure to vancomycin, ceftriaxone, and/or ceftazidime from hospital admission to date of positive *C. difficile* assay (for infected patients) or until discharge (for uninfected patients).

[c] Exposure to cytoxan doxyrubicin, methotrexate, and/or 5-fluorouracil from hospital admission to date of positive *C. difficile* toxin assay (for infected patients) or discharge (for uninfected patients).

[d] Number of days from hospital admission to date of positive *C. difficile* toxin assay (for infected patients) or discharge (for uninfected patients).

average length of stay for general medicine patients (4.3 days preintervention vs. 3.8 days intervention; $P = .01$).

During the 9 months prior to the use of hypochlorite solution, CDAD rates were 8.6, 3.0, and 1.3 cases per 1000 patient-days for bone marrow transplantation, neurosurgical ICU, and general medicine patients, respectively (table 2). After the initiation of the hypochlorite protocol, CDAD rates decreased significantly to 3.3 cases per 1000 patient-days (HR, 0.37; 95% CI, 0.19–0.74) for bone marrow transplantation patients but did not change significantly for patients in the other 2 units. Risk adjustment did not affect the risk estimates, although exposure to antineoplastic drugs (HR, 2.8; 95% CI, 1.3–5.8) independently increased the risk of CDAD for bone marrow transplantation patients.

Exposure to the most commonly used antimicrobial regimens (of vancomycin, ceftriaxone, and ceftazidime) increased the risk of CDAD for neurosurgical ICU patients (HR, 2.5; 95% CI, 1.0–6.2) and general medicine patients (HR, 2.2; 95% CI, 0.9–5.3). Antimicrobial drug exposures, assessed by spectrum of antimicrobial activity, did not affect the risk estimates for any of the 3 patient populations. Overall, hospital CDAD rates remained constant at 0.8 cases per 1000 patient-days during the 9-month periods before and after the intervention.

First admissions. Patient data for the study were restricted to first admissions during the 18-month study period, to determine whether the protective effect from using hypochlorite solution as an environmental disinfectant was due to multiple admissions that might have diluted the intervention rates for each unit. There were no remarkable differences in patients' baseline characteristics or CDAD rates when the data were restricted to first admissions rather than sequential admissions during the study period (data not shown). For bone marrow transplantation patients, in the preintervention period, the CDAD rate per 1000 patient-days was 9.5, versus 3.0 during the intervention period. The adjusted risks of developing CDAD after the introduction of hypochlorite solution, relative to the preintervention period, were 0.31 (95% CI, 0.14–0.69), 0.91 (95% CI, 0.42–1.96), and 1.25 (95% CI, 0.38–4.15) for the bone marrow transplantation, neurosurgical, and general medicine units, respectively.

Postintervention period for bone marrow transplant recipients. Although the hypochlorite protocol was discontinued for patients on the neurosurgical ICU and general medicine floor in April 1997, the protocol was continued for bone marrow transplantation patients through June 1997. Vancomycin-resistant *E. faecium* was first detected in the bone marrow transplantation unit during September 1995, and the incidence rate continued to climb before and after the intervention with hypochlorite solution. Subsequently, a different environmental cleaning protocol with use of quaternary ammonium solution was implemented in the bone marrow transplantation unit to reduce the potential spread of vancomycin-resistant *E. faecium* and CDAD. The new protocol required daily application of quaternary ammonium solution to all environmental surfaces for a 5-min contact time, followed by vigorous rubbing.

The CDAD rate remained at 3.2 cases per 1000 patient-days

Table 2. *Clostridium difficile*–associated diarrhea rates, hazard ratios (HRs), and 95% CIs for 3 hospitalized patient populations before and after the use of hypochlorite solution as an environmental disinfectant.

	Preintervention period			Postintervention period				
Unit	*n*	Patient-days	Rate per 1000 patient-days	*n*	Patient-days	Rate per 1000 patient-days	HR	95% CI
Bone marrow transplantation	26	3008	8.6	12	3583	3.3	0.37	0.19–0.74
Neurosurgical ICU	15	5048	3.0	16	6027	2.7	0.93	0.46–1.90
General medicine	11	8456	1.3	11	7510	1.5	1.11	0.48–2.56

NOTE. *n,* Number of patients diagnosed with *Clostridium difficile*–associated diarrhea.

through June 1997. The vancomycin-resistant *E. faecium* incidence rate declined during the postintervention period, but the CDAD rate increased to 8.1 cases per 1000 patient-days (figure 1). After confirmation of this unexpected increase in the CDAD rate, the hypochlorite protocol was reinstituted in the bone marrow transplantation unit in July 1998 in rooms with CDAD patients, and the rate again declined to 3.4 cases per 1000 patient-days for the period from July through October 1998. Vancomycin-resistant *E. faecium* rates remained low during this 5-month period.

Protocol compliance. Although protocol compliance was not observed directly, nursing and housekeeping staffs were surveyed to determine the perceptions of compliance with the new hypochlorite protocol. Staff members completed a questionnaire that asked the following questions: (1) Was housekeeping notified of the *C. difficile* status of patients' rooms? (2) How often was housekeeping observed by monitors cleaning a room? (3) How often was the bleach protocol used in daily cleaning of *C. difficile*–affected rooms? Likert scale responses to the questions included "every time," "75%–99%," "50%-74%," "<50%," "never," and "don't know." Responses for each question were assigned weights of 100, 75, 50, 25, and 0, respectively. Overall, compliance with environmental cleaning was higher for the neurosurgical ICU (87%) than the bone marrow transplantation (68%) and general medicine (65%) units. Furthermore, there were no complaints by patients, family, or staff regarding the noxious effect of the 1:10 hypochlorite solution after implementation of the bleach protocol.

Discussion

Our data show a protective effect of hypochlorite solution against CDAD acquisition in an area of high endemicity in an acute care hospital. The CDAD rate for bone marrow transplantation patients declined impressively, from 8.6 cases to 3.3 cases per 1000 patient-days, after the switch from quaternary ammonium to 1:10 hypochlorite solution; it returned to 8.1 cases per 1000 patient-days after the switch back to the original disinfectant. The plausible mechanism for decreased nosocomial transmission is reduced environmental burden and, hence, reduced *C. difficile* transmission among susceptible patients. Unbuffered 1:10 hypochlorite solution has been shown to reduce the frequency of positive *C. difficile* cultures from 31% to 16% and the mean number of colony forming units per positive culture from 5.1 to 2.0 in patient rooms [12]. It is unlikely that the reduction in the CDAD rate among bone marrow transplantation patients was due to improved cleaning strategies, given the resurgence of incidence during the postintervention, nonbleach period, when the protocol required a 5-min dwell time for the quaternary ammonium solution, followed by vigorous rubbing of all hard surfaces until dry.

It is notable that the hypochlorite solution did not reduce the patients' risk of developing CDAD in other hospital units where CDAD rates were <3.0 cases per 1000 patient-days. One alternative explanation for the lack of reduction in CDAD rates for these 2 units could be less-vigorous environmental cleaning in them than in the bone marrow transplantation unit, but this is not supported by our protocol compliance data, which showed the highest compliance for disinfection of ICU rooms. Likewise, one may argue that the threshold for physician-based CDAD orders was higher for the bone marrow transplantation unit than for the other 2 units because of the perceived severity of illness and longer length of stay of these patients. Although physicians were not intentionally blinded to the intervention study, it is unlikely that they would have modified their practice for ordering CDAD toxin assays before or after the intervention with hypochlorite solution. We may have underestimated the CDAD rates for patients in the ICU and general medicine units, but this would have occurred equally for both study periods.

Our findings support those of other investigators who have reported that prior use of antimicrobial and antineoplastic agents increase the risk of CDAD among hospitalized patients [2, 3, 7, 8, 28]. In this study, there was a 2-fold increase in CDAD risk for neurosurgical ICU and general medicine patients exposed to antimicrobial agents and a 2-fold increase in CDAD risk among transplantation patients exposed to selected antineoplastic drugs. This increase in risk is presumably due to an alteration in gastrointestinal flora resulting from such treatment. Given the high exposure rates of all patients to antimicrobial agents, we may not have been able to detect an associated risk of the antimicrobial agents' spectrum of activity with CDAD.

There are several limitations to our study. Most important, at the time of admission, we were unable to evaluate colonization with *C. difficile,* a potential source of nosocomial *C. difficile* infections [29, 30]. Additional research would be needed

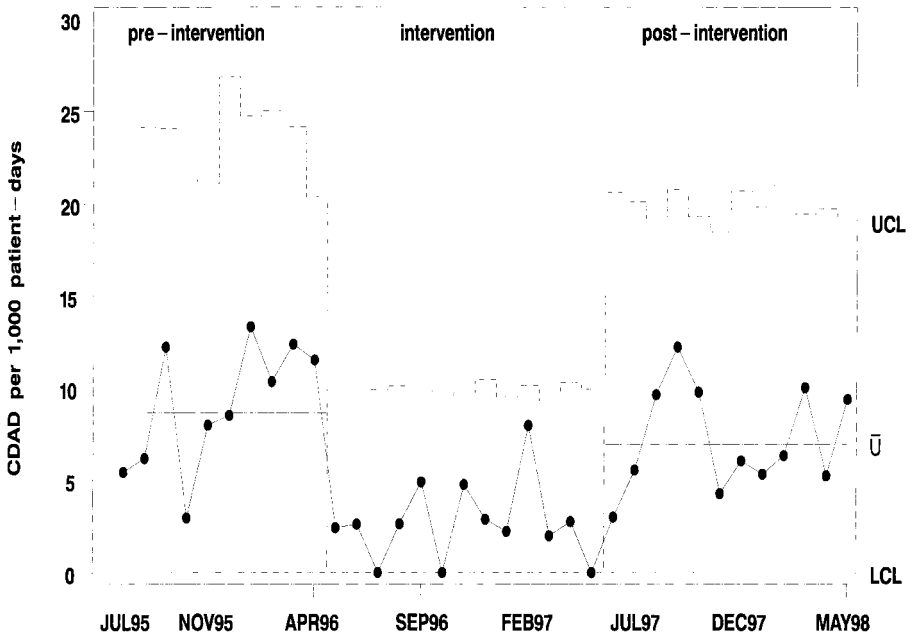

Figure 1. Monthly rates of *Clostridium difficile*–associated diarrhea (CDAD) among bone marrow transplantation patients hospitalized from July 1995 through May 1998 (subgroup sizes: minimum, 235 patients; maximum, 504 patients). LCL, lower control limit; UCL, upper control limit; Ū, CDAD rate.

to determine the effectiveness of hypochlorite solution or other environmental disinfectants in reducing exposure to and colonization with *C. difficile.* Second, we did not have information on whether patients in the study were more likely to have gastrointestinal surgery or nasogastric tubes or procedures [2-5] during the preintervention versus intervention period. However, there is no reason to believe that there were significantly more patients requiring this type of surgery or such procedures during the study periods. Third, the proximity of patients with CDAD to each other was not measured beyond geographic unit–specific locations. Given the limitations of our informatics system, data were not available on sequential patients in rooms of prior CDAD patients.

Fourth, since our data harvest, an original report of combination chemotherapy with ifosfamide, carboplatin, and etoposide has linked treatment with an 8% incidence of CDAD [31]. Although no bone marrow transplantation patients received treatment with this protocol, some patients in our cohort received etoposide. Finally, although nursing and housekeeping staff members reported that housekeepers were probably not in full compliance with the hypochlorite protocol, failure to clean the rooms with hypochlorite solution during the intervention period would have only masked any protective effect from environmental disinfection.

Overall, our findings confirm an association of unbuffered 1:10 hypochlorite solution with reduced CDAD rates in a unit with a high prevalence rate. Given the uncertainty of the corrosive impact of routine use of this solution, our hospital now uses this solution daily in rooms of patients with confirmed CDAD where unit rates are >3 cases per 1000. Daily environmental cleaning with a 1:10 hypochlorite solution in areas of high endemicity at acute–health care settings is a practical and inexpensive addition to the short list of effective measures that can reduce the spread of nosocomial pathogens.

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