Hospital-wide Restriction of Clindamycin: Effect on the Incidence of *Clostridium difficile*–Associated Diarrhea and Cost

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Background: Widespread antibiotic use has been associated with increases in both bacterial resistance and nosocomial infection.

Objective: To characterize the impact of hospital-wide clindamycin restriction on the incidence of *Clostridium difficile*–associated diarrhea and on antimicrobial prescribing practices.

Design: Prospective, observational cohort study.

Setting: University-affiliated Veterans Affairs Medical Center.

Patients: Hospitalized patients with symptomatic diarrhea.

Measurements: Clinical data on individual patients and data on antibiotic use were obtained from hospital pharmacy records. Hospital-wide use of antimicrobial agents was monitored. Isolates of *C. difficile* underwent antimicrobial susceptibility testing and molecular typing.

Results: An outbreak of *C. difficile*–associated diarrhea was caused by a clonal isolate of clindamycin-resistant *C. difficile* and was associated with increased use of clindamycin. Hospital-wide requirement of approval by an infectious disease consultant of clindamycin use led to an overall reduction in clindamycin use, a sustained reduction in the mean number of cases of *C. difficile*–associated diarrhea (11.5 cases/month compared with 3.33 cases/month; $P < 0.001$), and an increase in clindamycin susceptibility among *C. difficile* isolates (9% compared with 61%; $P < 0.001$). A parallel increase was noted in the use of and costs associated with other antibiotics with antianaerobic activity, including cefotetan, ticarcillin–clavulanate, and imipenem–cilastin. The hospital realized overall cost savings as a result of the decreased incidence of *C. difficile*–associated diarrhea.

Conclusions: Hospital formulary restriction of clindamycin is an effective way to decrease the number of infections due to *C. difficile*. It can also lead to a return in clindamycin susceptibility among isolates and can effect cost savings to the hospital.

This paper is also available at http://www.acponline.org.

Clostridium difficile is an important cause of nosocomial infection and is the organism most often linked to antibiotic-associated diarrhea and pseudomembranous colitis (1–3). As many as 25% of cases of nosocomial diarrhea may be caused by *C. difficile*, leading to increased hospital costs, morbidity, and mortality (2–5). Acquisition of *C. difficile* may result in asymptomatic carriage or more clinically significant manifestations, including antibiotic-associated diarrhea, colitis, pseudomembranous colitis, and toxic megacolon (6–9). The most frequently identified risk factor for the development of *C. difficile*–associated diarrhea is the antecedent use of antibiotics that alter the normal intrinsic colonic microflora. Antibiotics commonly associated with *C. difficile*–associated diarrhea include penicillins, cephalosporins, and clindamycin (2, 3, 10–12).

Previous attempts to control nosocomial outbreaks of *C. difficile*–associated diarrhea have included emphasis on handwashing, enforced barrier precautions, enhanced educational initiatives, and increased environmental cleaning (12–14). Recently, several investigations showed a substantial decrease in the incidence of *C. difficile*–associated diarrhea after hospital formulary restriction of clindamycin (11, 15). Aside from the issue of efficacy, hospital formulary control of antibiotics as a strategy to decrease the incidence of nosocomial infections raises several other questions. What effect does restriction have on the use of other antibiotics? Does restriction of certain classes of antibiotics lead to increased use of more expensive antimicrobial agents? Does formulary control save money? Does restriction affect the antimicrobial susceptibility of nosocomial isolates?

Beginning in 1993, our hospital had an unusually high number of cases of nosocomial *C. difficile*–associated diarrhea, which continued despite the use of barrier precautions, educational programs, and enhanced terminal cleaning of patient rooms. When our investigation identified clindamycin use as a significant risk factor among hospitalized patients, we instituted hospital-wide restriction of clindamycin as an infection control measure.

In this study, we investigated the effects of hospital formulary control on the incidence of *C. difficile*–associated diarrhea and the antimicrobial susceptibility of nosocomial isolates of *C. difficile*. We also

examined the overall economic impact of such restrictions on antibiotic use.

Methods

The Hunter Holmes McGuire Veterans Affairs Medical Center is a 703-bed tertiary care hospital affiliated with the Medical College of Virginia in Richmond, Virginia. Infection control at the hospital is directed by the hospital epidemiologist (a physician) and administered by four infection control nurses. The monthly incidence of *C. difficile*–associated diarrhea for the past 10 years is known because of the routine review of *C. difficile* cytotoxin assay results or stool cultures positive for *C. difficile* from patients with symptomatic diarrhea.

In November 1993, we initiated a prospective cohort study. All inpatients who had been hospitalized for at least 48 hours and had had stool samples sent to the microbiology laboratory for *C. difficile* cytotoxin assay were studied. Case-patients were defined as patients who had diarrhea (three or four loose [unformed] stools) within a 24-hour period, a history of antibiotic use within 8 weeks, and a positive result on a cytotoxin assay. Symptomatic patients with negative results on cytotoxin assay with or without a history of antibiotic use were designated as controls. Hospital charts, microbiological laboratory test results, and hospital pharmacy records were reviewed to obtain data on demographic variables; admitting service and diagnosis; documented infections; use of antibiotics before the onset of diarrhea; use of medications, including antacids, H_2 blockers, and stool softeners; concurrent medical illnesses; invasive procedures and devices placed during hospitalization; presence of nasogastric or feeding tubes; ambulation status; room type (single or multi-bed); discharge status; and time from admission to onset of diarrhea.

All stool samples were tested for cytotoxin production by using tissue cell culture assay (16). Stool specimens with positive results on cytotoxin assay were cultured on CCFA (cycloserine, cefoxitin, fructose) blood agar (17) and incubated under anaerobic conditions for 48 hours. Isolates were presumptively identified as *C. difficile* by colony morphology, Gram stain, and biochemical identification with the RapID ANA II system (Innovative Diagnostic Systems, Norcross, Georgia). All isolates presumptively identified as *C. difficile* underwent *C. difficile* cytotoxin assay to verify toxin production. Isolates of *C. difficile* were maintained in chopped-meat broth and were typed by using pulsed-field gel electrophoresis after restriction endonuclease digestion with *Sma*I (18). Pulsed-field gel electrophoresis of all isolates

was completed over 20 hours with ramped pulsed-field times (initial 1 second to final 20 seconds).

Antimicrobial susceptibility testing was done on all isolates by using an anaerobic agar dilution method according to guidelines from the National Committee for Clinical Laboratory Standards. Isolates were tested for susceptibility to clindamycin, metronidazole, and vancomycin and were considered resistant if the minimal inhibitory concentration (MIC) was greater than 4.0 μg/mL for clindamycin and vancomycin or greater than 1.0 μg/mL for metronidazole.

The Fisher exact test was used to test for differences in proportions. The means of continuous variables were compared by using the Student *t*-test. Risk factors among the patient groups were compared by using the Cochran–Mantel–Haenszel chi-square test. Two-sided *P* values less than 0.05 were considered statistically significant.

Results

The Outbreak

In September 1993, our hospital had the most cases of *C. difficile*–associated diarrhea (18 cases; 19 cases per 1000 discharges) seen since the introduction of surveillance for this condition. A review of hospital records showed a gradual increase in the number of cases of *C. difficile*–associated diarrhea since 1991 (**Figure 1**). The hospital averaged 4.3 cases of *C. difficile*–associated diarrhea per month in 1991 (4.5 infections per 1000 discharges), 6.4 cases per month in 1992 (6.5 infections per 1000 discharges), and 10.6 cases per month in 1993 (10.8 infections per 1000 discharges). The number of patients seen in the hospital between 1991 and 1996 was relatively constant, with a difference of less than 9% in the number of inpatient discharges per year over the entire period.

In response to the increasing number of cases of *C. difficile*–associated diarrhea, several control measures were instituted. All hospital staff were educated about the importance of barrier precautions and the appropriate isolation of patients with *C. difficile*–associated diarrhea. All patients identified as having *C. difficile*–associated diarrhea were placed in private rooms, and the use of barrier precautions was strictly enforced. Emphasis was placed on proper handwashing and the appropriate use of gloves. In addition, attempts were made to decrease environmental contamination with *C. difficile*; these attempts included terminal cleaning of the rooms of patients with *C. difficile*–associated diarrhea on selected wards. Despite these measures, the number of new cases of *C. difficile*–associated diarrhea remained high. In the
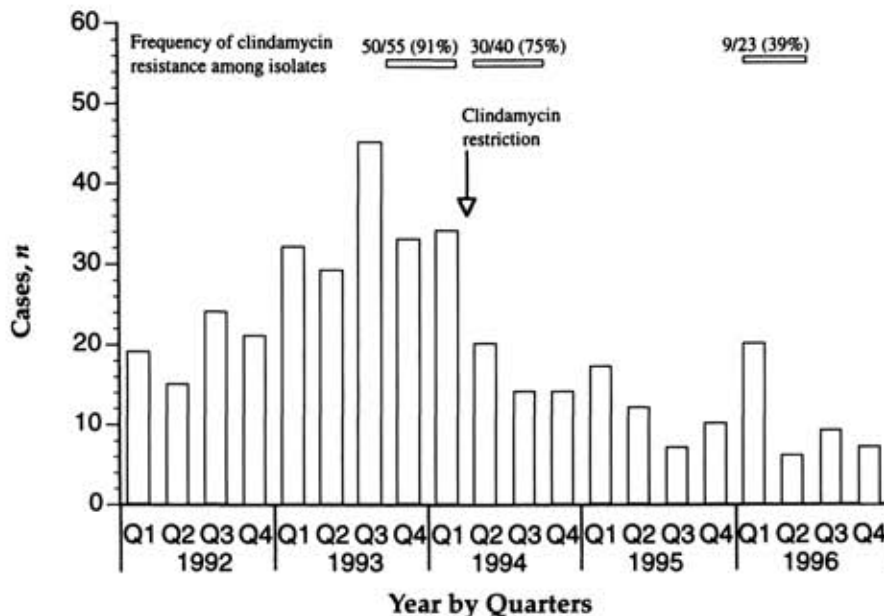
Figure 1. **Cases of *Clostridium difficile*–associated diarrhea, reported by quarter.** Hospital-wide restriction of clindamycin began in March 1994. The horizontal bars above the graph indicate periods during which antimicrobial susceptibility testing was done on *C. difficile* isolates; the frequency of clindamycin resistance is shown above the bars.

first 3 months of 1994, 11.3 cases per month occurred and 25% of all stool specimens sent to the microbiology laboratory for *C. difficile* toxin assay had positive results. In March 1994, 35% of all stool specimens sent for *C. difficile* toxin assay had positive results.

Over a 5-month period from November 1993 to March 1994, the microbiology laboratory received 159 stool samples for *C. difficile* toxin assay. Twenty-one of the samples were reported as "formed stool" and therefore were not satisfactory for testing. Of the remaining 138 samples, 52 (38%) were positive and 86 (62%) were negative for *C. difficile* toxin. Twenty percent of patients (10 of 50) had a relapse of *C. difficile*–associated diarrhea during the 5-month period.

Patients identified with *C. difficile*–associated diarrhea were found on all wards of the hospital. Most patients (73%) were on medical wards (17.5 infections per 1000 discharges), but patients with *C. difficile*–associated diarrhea were also found on surgical wards (1.6 infections per 1000 discharges); on neurology wards (5.2 infections per 1000 discharges); in intensive care units (10.5 infections per 1000 discharges); and in long-term care facilities, including a nursing home and a spinal cord injury unit (24.4 infections per 1000 discharges). All patients identified with *C. difficile*–associated diarrhea were initially treated with oral metronidazole; regimens varied from 250 mg given orally every 8 hours to 500 mg given orally every 6 hours.

Risk Factors for *Clostridium difficile*–Associated Diarrhea

We did a prospective cohort study of 138 consecutive patients admitted to the hospital between November 1993 and March 1994 to determine the risk factors associated with *C. difficile*–associated diarrhea in hospitalized patients with symptomatic diarrhea. Increased age, bedridden status, documented underlying infection, and increased antibiotic use were significantly associated with *C. difficile*–associated diarrhea. Patients with *C. difficile*–associated diarrhea were older than controls (71 years compared with 63 years; $P < 0.001$) and were more likely to be bedridden (86% compared with 54%; $P < 0.001$; odds ratio, 5.2). No statistically significant differences were seen for admitting diagnosis, admitting service, discharge status, or death within 1 year of the onset of diarrhea. Patients with *C. difficile*–associated diarrhea were more likely than controls to be on a general medical ward (56% compared with 44%). Symptomatic diarrhea occurred earlier in the hospitalization in controls than in patients with *C. difficile*–associated diarrhea; 60% of controls and 38% of patients with *C. difficile*–associated diarrhea developed diarrhea within 2 weeks of admission ($P = 0.009$). Controls were more likely to have diarrhea on admission (26% compared with 12%; $P = 0.047$; odds ratio, 1.46). In addition, patients with *C. difficile*–associated diarrhea had a greater incidence of bacteremia (19% compared with 3% [$P = 0.002$]; odds ratio, 6.6) and culture-proven urinary tract infection (56% compared with 35% [$P > 0.02$]; odds ratio, 2.3) compared with controls.

Patients with *C. difficile*–associated diarrhea were exposed to more antibiotics before they developed diarrhea than were controls (44.2 g compared with

15.6 g; $P = 0.001$). An analysis of patients with C. difficile–associated diarrhea showed that 67% of patients had received clindamycin before they developed diarrhea. At that time, clindamycin prescription in the hospital averaged 1119 g each month. Among antibacterial agents used in the hospital in 1993, clindamycin was the fifth most commonly used.

Antimicrobial Susceptibility and Typing of Nosocomial Isolates of Clostridium difficile

The antimicrobial susceptibilities of C. difficile isolated from November 1993 through March 1994 were compared with those of isolates obtained in 1987 through 1988 (Figure 2). Clinical isolates obtained in 1987 and 1988 and current clinical isolates were highly susceptible to both metronidazole and vancomycin. Forty-three percent of isolates from 1987 and 1988 were resistant to clindamycin (MIC > 4 µg/mL). In contrast, 91% of isolates collected from November 1993 to March 1994 were resistant to clindamycin (MIC$_{90}$ > 16 µg/mL) compared with 57% of those collected in 1987 and 1988 ($P < 0.001$). Fifteen clindamycin-resistant isolates collected in 1994 were examined by pulsed-field gel electrophoresis and found to be clonal (pattern A). Pulsed-field gel electrophoresis of isolates from 1987 and 1988 showed widely differing patterns, although 8 of 22 isolates (36%) were identified as clonal (pattern B). All isolates with restriction pattern B were susceptible to clindamycin.

Because of the widespread use of clindamycin and epidemiologic evidence indicating the presence of a clindamycin-resistant strain of C. difficile among nosocomial isolates, hospital-wide restriction of clindamycin was begun on 15 March 1994. Use of clin-

damycin after that date required approval by an infectious disease consultant.

Effects of Clindamycin Restriction

After the restriction of clindamycin, hospital-wide use of clindamycin decreased substantially. During the first 2 months of 1994, an average of 1119 g of clindamycin was used each month. In the first month after restriction, the hospital-wide use of clindamycin decreased to 170 g, a sixfold reduction. In the 5 months after restriction, the use of clindamycin averaged 151 g per month, an 87% reduction. Total hospital expenditures for clindamycin decreased from $35 000 in 1993 to less than $3000 in 1994, a 92% reduction. This reduction has been sustained; clindamycin expenditures in 1996 were 75% less than 1993 levels (Figure 3).

An obvious decrease in the number of patients with C. difficile–associated diarrhea occurred after the restriction of clindamycin was implemented (Figure 1). In the 12 months before clindamycin restriction, the hospital had a mean of 11.7 cases of C. difficile–associated diarrhea per month. In the 6 months after restriction, the mean number of cases of C. difficile–associated diarrhea per month decreased to 5.7 ($P = 0.001$). This reduction was sustained for the year after restriction, with a mean of 5.2 cases of C. difficile–associated diarrhea per month after the restriction of clindamycin ($P < 0.001$). In the second year after restriction, the number of cases of C. difficile–associated diarrhea decreased to 3.5 per month ($P < 0.001$). The number of stool specimens sent to the microbiology laboratory for C. difficile toxin assay decreased 20% after restriction, indicating an overall decrease in the incidence of symptomatic diarrhea. In addition, the percentage of stool specimens positive for C. difficile toxin decreased from 25% in the 3 months before restriction to 16.5% in the 3 months after restriction ($P < 0.001$).

Finally, after restriction, the percentage of nosocomial isolates of C. difficile resistant to clindamycin decreased (Figures 1 and 2). In the 6 months before restriction, 91% of isolates were resistant to clindamycin; in the 5 months after restriction, 75% of isolates collected were resistant ($P < 0.10$). This trend toward increasing susceptibility among nosocomial isolates of C. difficile has continued. Only 39% of isolates collected 20 months after the restriction of clindamycin were resistant to clindamycin ($P < 0.001$).

Effects of Clindamycin Restriction on Use of Other Antibiotics

The restriction of clindamycin offered a unique opportunity to study the effects of hospital formulary control on the prescribing practices of physi-
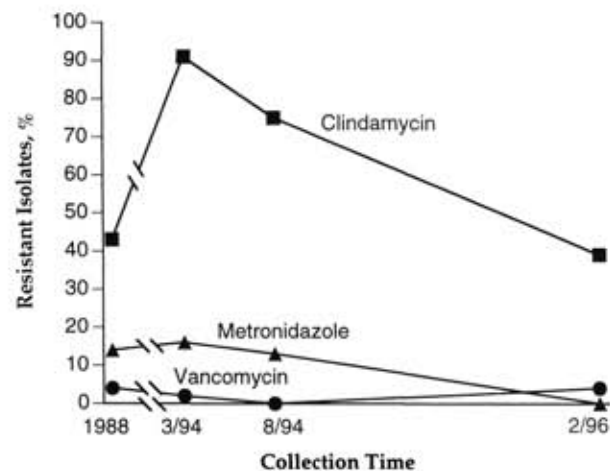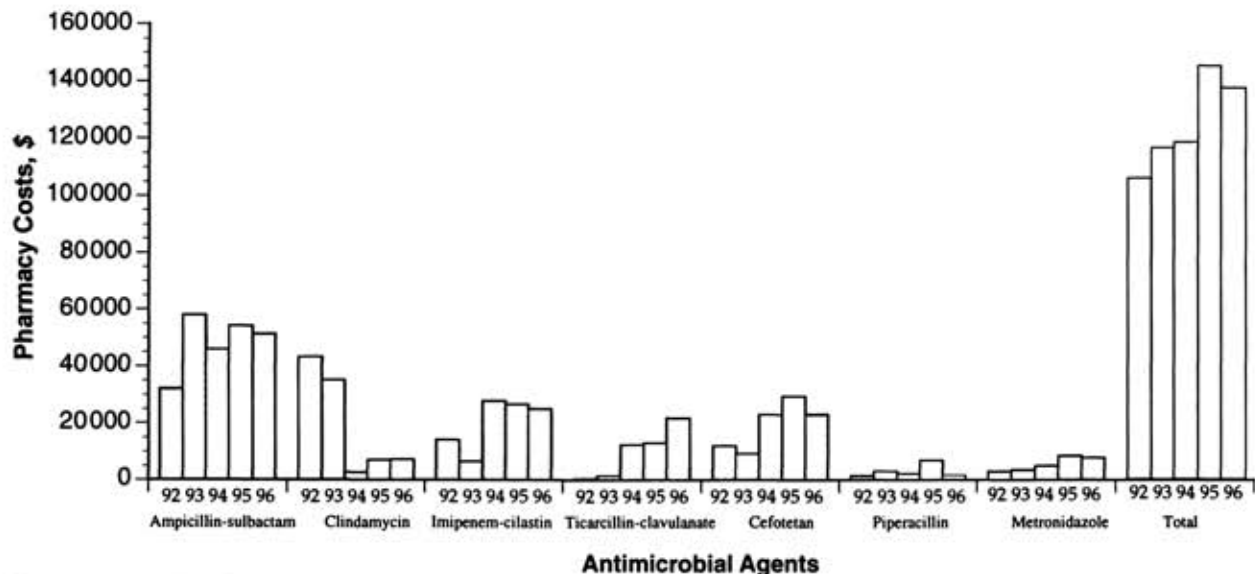

Figure 2. Antimicrobial resistance among Clostridium difficile isolates collected between 1987 and 1996. The percentage of isolates resistant to clindamycin, metronidazole, and vancomycin was determined by using the agar dilution method for nosocomial isolates collected from hospitalized patients over four separate time periods before and after the hospital-wide restriction of clindamycin began in March 1994.

Figure 3. Comparison of pharmacy costs, 1992 to 1996. Acquisition costs for the seven antimicrobial agents with anaerobic activity were collected from hospital pharmacy records. Totals for each year are shown on the right. Clindamycin restriction began in March 1994.

cians and on pharmacy costs. Because clindamycin has a limited antimicrobial spectrum, primarily for treatment of anaerobic infections, we followed the formulary expenditures for all parenteral antimicrobial agents with anaerobic activity (**Figure 3**).

In 1993, total pharmacy acquisition costs for clindamycin were $35 000. After restriction of clindamycin in the first quarter of 1994, acquisition costs for clindamycin for 1994 decreased 92% to $2695. This reduction in clindamycin use was offset by increases in expenditures for the other six anaerobic agents. Total acquisition costs for the seven agents had increased 15% by the end of the 4-year period. After restriction, the use of imipenem, ticarcillin–clavulanate, metronidazole, cefotetan, and piperacillin increased compared with 1993 levels. Only one agent, ampicillin–sulbactam, showed decreased use after restriction. In summary, total costs for antimicrobial agents with anaerobic activity increased despite the decrease in expenditures for clindamycin.

An analysis of the cost savings associated with the prevention of additional cases of *C. difficile*–associated diarrhea is shown in the **Table**. For each case of *C. difficile*–associated diarrhea prevented, we assumed a cost savings of $2000, based on the results of Kofsky and colleagues (4). This figure may be an overestimate of the actual costs associated with *C. difficile*–associated diarrhea because it was based on hospital charges, not costs. Unfortunately, few other estimates exist. Our analysis shows that in the 3-year period of clindamycin restriction, the costs of additional anaerobic agents exceeded the savings associated with the decreased use of clindamycin by $47 782. By using the peak incidence rate in 1993, before antibiotic restriction, we estimated that during the 3-year period of restriction, 237

cases of *C. difficile*–associated diarrhea were prevented. Each prevented case incurred $200 in additional antimicrobial costs ($47 782/237 cases). Thus, although we used $2000 as the estimate of the associated hospital cost savings in our cost analysis, any estimate exceeding $200 for each case of *C. difficile*–associated diarrhea prevented would result in a net savings to the hospital.

Discussion

We describe an outbreak of *C. difficile*–associated diarrhea that we believe was due in part to the widespread use of clindamycin and the presence of a clindamycin-resistant strain of *C. difficile*. The outbreak was characterized by a high level of clindamycin use in the hospital, the presence of a clonal strain of *C. difficile* among patients with *C. difficile*-

Table. Savings Associated with Clindamycin Restriction

Variable	1994	1995	1996
Reduction in clindamycin costs, $*	32 305	27 988	27 791
Additional costs for other anaerobic agents, $*†	(32 173)	(52 198)	(51 495)
Cases of *Clostridium difficile*–associated diarrhea prevented, *n*	57	93	87
Reduction in cases of *C. difficile*–associated diarrhea (number of cases of *C. difficile*-associated diarrhea prevented × 2000‡), $	114 000	186 000	174 000
Net savings, $	114 132	161 790	150 296

* Compared with 1993 figures.
† See text for description of anaerobic agents.
‡ Estimated excess costs attributed to each case of *C. difficile*-associated diarrhea (4).

associated diarrhea, and a high level of clindamycin resistance among nosocomial isolates. It continued despite the use of traditional infection control measures, including private rooms, handwashing, barrier devices, educational programs, and weekly environmental disinfection of patient rooms. Not until we restricted the use of clindamycin throughout the hospital did the number of cases of *C. difficile*–associated diarrhea diminish.

Hospital formulary restriction of antibiotics has previously been used successfully to control antibiotic-resistant nosocomial infections. The most extensive experience centers on the restriction of aminoglycosides (19–22). Beginning in the 1970s, investigators reported that "switching" aminoglycosides on the hospital formulary was an effective way to decrease aminoglycoside resistance among gram-negative organisms (19–22). Recently, hospital formulary restriction of clindamycin as a mechanism to control nosocomial *C. difficile*–associated diarrhea has been shown to be effective at other institutions (11, 15). Brown and associates (11) reported a decrease in the frequency of *C. difficile*–associated diarrhea at their institution after control measures, including earlier isolation and treatment of patients suspected of having *C. difficile*–associated diarrhea and hospital formulary restriction of clindamycin, were implemented. Pear and coworkers (15) documented a similar decrease in *C. difficile*–associated diarrhea after hospital formulary restriction of clindamycin in response to identification of a clindamycin-resistant strain of *C. difficile* in their hospital.

Neither of these studies, however, systematically studied the potential long-term effects of antibiotic restriction on either microbial flora or the overall antibiotic prescribing habits of physicians. It is possible that physicians merely substituted other, possibly more expensive, antibiotics for the one restricted, resulting in greater overall cost to the hospital. Pear and coworkers (15) noted that the restriction of clindamycin at their hospital was followed by an immediate increase in the use of amoxicillin–clavulanate and ampicillin–sulbactam but no change in the use of penicillin, imipenem, metronidazole, or ticarcillin–clavulanate. No cost data were provided. In addition, although a decrease in the prevalence of the epidemic strain of clindamycin-resistant *C. difficile* was reported, data on the antimicrobial susceptibility of nosocomial isolates after restriction were not.

To study the effect of clindamycin restriction on antibiotic susceptibility, we continued to prospectively collect isolates of *C. difficile* for 23 months after the restriction. We found a sustained decrease in the proportion of nosocomial isolates of *C. difficile* resistant to clindamycin from 91% during the peak of the epidemic to 39% during the last year of the observational period. Clindamycin resistance among *Clostridium* species is most often the result of the MLS_b type of resistance, which has been reported to be transposon-mediated (23). In the hospital environment, widespread clindamycin use would confer a selective advantage for persistence and spread of clindamycin-resistant *C. difficile*. Conversely, a reduction in the use of clindamycin would decrease this selective advantage. Our data indicate that antibiotic restriction can profoundly affect the antimicrobial susceptibilities of nosocomial pathogens. This is in accordance with several recent studies that have shown decreased resistance among several nosocomial pathogens (specifically, *Enterobacter cloacae* and *Pseudomonas aeruginosa*), after restriction of the use of third-generation cephalosporins and imipenem (24–27).

We found that restricting the use of clindamycin achieved the intended effect (a significant reduction in clindamycin use), but this was offset by increased use of several other antibiotics with anti-anaerobic activity: imipenem, cefotetan, ticarcillin–clavulanate, piperacillin, and metronidazole. Although it is difficult to prove the existence of a direct relation between these reciprocal changes through the review of pharmacy acquisition costs, the overall trend toward the increased use of these other agents is compelling. Additional explanations for this increased use could include factors unrelated to clindamycin restriction, such as greater awareness of certain agents. For example, ticarcillin–clavulanate was introduced to our formulary in 1992, and its use has increased each year since its introduction.

Overall, formulary restriction may be a cost-saving strategy. Although the cost savings realized by our pharmacy after the restriction of clindamycin were offset by the costs associated with the use of other, more expensive antibiotics, reduced costs associated with the substantial decrease in the frequency of *C. difficile*–associated diarrhea probably accounted for an overall savings to the hospital (**Table**). It has been estimated that each episode of *C. difficile*–associated diarrhea adds $2000 to $5000 to the costs of health care (4). In the first year of restriction, we projected that 57 cases of *C. difficile*–associated diarrhea were prevented, with a savings to the hospital of at least $114 000 (**Table**).

The addition of clindamycin restriction to effective standard infection control measures played an essential role in decreasing the number of cases of nosocomial *C. difficile*–associated diarrhea during this outbreak. Our analysis also indicates that hospital formulary control of clindamycin may be a cost-saving strategy, at least with regard to the overall costs associated with nosocomial infections due to *C. difficile*.

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