Clostridium difficile outbreak in Costa Rica: control actions and associated factors

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ABSTRACT

Objective. *To describe interventions implemented during a nosocomial outbreak of* Clostridium difficile *in a general hospital in Costa Rica from December 2009 to April 2010 in order to achieve outbreak control and the factors determined to be associated with* C. difficile *infection.*

Methods. *Laboratory-confirmed cases of* C. difficile *were analyzed to describe the outbreak pattern and intervention measures implemented. Cases were selected and recruited in a case-control study. Controls were selected from the same services and time period as the cases. Evaluated exposures included underlying medical conditions and treatments administered before the onset of symptoms.*

Results. *The mean ages in case and control groups were 62.3 and 55.3 years, respectively. Control measures included a hand-hygiene campaign, deep disinfection of hospital surfaces, strict isolation of cases, use of personal protection equipment, and restriction of antibiotic use. The adjusted attributable risks associated with the outbreak were diabetes [odds ratio (OR) 3.4, 95% confidence interval (CI) 1.5–7.7], chronic renal failure (OR 9.0, 95% CI 1.5–53.0), and prescribing ceftazidime (OR 33.3, 95% CI 2.9–385.5) and cefotaxime (OR 20.4, 95% CI 6.9–60.3).*

Conclusions. *Timely implementation of control measures resulted in reduced infection transmission and successful control of the outbreak. Conditions associated with* C. difficile *infection were similar to those found in previously described outbreaks of this bacterium.*

Key words *Clostridium difficile;* enterocolitis; Costa Rica.

Clostridium difficile–associated diarrhea (CDAD), caused by the ingestion of *C. difficile* spores, has been recognized as an increasingly common nosocomial infection (1). It is defined as the presence of diarrheal disease and a positive toxin assay (2). Several *C. difficile* outbreaks have been described in the literature and have been associated with various factors, including decreased immunocompetence and administration of drugs, particularly fluoroquinolones, cephalosporins, and proton-pump inhibitors (3–6).

Such outbreaks have been scarcely documented in Latin American countries, with the exception of the outbreaks described in Brazilian intensive care units. A previous *C. difficile* outbreak of the BI/NAP1 strain was documented in Costa Rica in 2009. The organism was identified in more than half of the isolated strains (7). However, such prior reports have been limited in their description of the infectious agent and their characterization of the infection control strategies implemented in intensive care

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units, and they have not extensively explored factors associated with the outbreak in critical care patients, especially with regard to underlying conditions (8).

In 2010, a non-BI strain *C. difficile* outbreak was identified in a general hospital in Costa Rica, which affected the medical and surgical wards. The aim of this investigation was to describe the infection control strategies implemented in this case and to determine the factors associated with the outbreak.

MATERIALS AND METHODS

The affected facility was a Costa Rican tertiary care hospital with 563 beds and an average of 24 000 discharges annually. The hospital provides medical, surgical, and gynecologic services to a population of approximately 850 000.

A *C. difficile* outbreak was reported in this hospital in December 2009, with an initial increase in the monthly incidence rate of CDAD from a baseline of 0.3 to 0.6 case per 10 000 patient-days to 2.4 cases per 10 000 patient-days during the outbreak.

A descriptive analysis of *C. difficile* was conducted to characterize disease patterns between January 2009 and June 2011. An unmatched case-control study was performed from December 2009 to April 2010.

Selection of subjects

Selected patients were the CDAD cases reported during the outbreak period. The working definition of CDAD was all patients with diarrheal disease (more than two episodes of watery stools in 24 hours) 72 hours after hospital admission who did not have diarrheal symptoms upon admission, confirmed with a positive *C. difficile* test. It was necessary to exclude patients with diarrhea before the first 72 hours of hospitalization or those with diarrhea as the cause of admission in order to eliminate possible community *C. difficile* cases in accordance with the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America (9).

Selection of control subjects

Control subjects were randomly selected among patients hospitalized during the same time period as the case subjects. The neonatology, gynecology, obstetrics, and outpatient surgery wards, which did not report cases, were excluded from the selection process. To avoid including false-negative *C. difficile* cases, exclusion criteria were patients with diarrheal disease as the reason for admission. Patients who developed diarrheal disease during the hospital stay due to etiologic agents or conditions other than *C. difficile* were also excluded. The *C. difficile* toxin detection test used had a sensitivity of 95.2%; to improve it, patients with diarrhea not related to *C. difficile* were excluded.

The control sample frame was the patient hospitalization information system and random selection was done by sample random command from Stata 10.1 (Stata Corporation, College Station, Texas, United States of America, 2009).

As a result, data collection was substantially cheaper and easier for the controls than for the case samples; therefore, the selected number of controls per case was six, which is higher than the standard recommended four controls per case for reasonable study efficiency (10).

Evaluation of exposures

Exposures were obtained based on several information sources. General patient features, medical history, and hospitalization data were collected from the hospital information system. Drug prescription data were obtained from the hospital drug information system, while the associated symptom and mortality data were collected from the nosocomial infection surveillance system.

The nosocomial infection surveillance system collects data for routine surveillance of all wards and is collected by nurses, who record information related to nosocomial infections, procedures, and medical conditions of affected patients. All data sets were integrated to a master data set.

Length of hospitalization was determined as the entire hospitalization period for control subjects and from the first day of hospitalization to the date of onset of symptoms for case subjects.

The window of exposure was defined as a period of three weeks preceding the date of onset of symptoms for case subjects and three weeks before the date of discharge for control subjects. The window period was defined based on the unknown incubation period of *C. difficile* and the 12-day average hospitalization stay in the affected hospital.

Laboratory analysis

C. difficile toxin was determined by testing fresh stool 1 hour after sample collection. An Immuno Card toxin A&B (Meridian Bioscience, Inc., Cincinnati, Ohio, United States of America) was used as the *C. difficile* toxin detection test.

Toxin-positive isolates were confirmed by culture and the isolates were recovered by placing inoculating loops of stool samples onto cefoxitin cycloserine fructose agar plates (Oxoid Ltd., Basingstoke, United Kingdom). The isolates were identified by the rapid ID32A system (bioMérieux, Inc., Durham, North Carolina, United States of America) and polymerase chain reaction amplification of the triosephosphate isomerase gene. The isolates were typed by pulsed-field gel electrophoresis and fragments of *tcdA*, *tcdB*, *tcdC*, and *cdtB* genes were amplified by polymerase chain reaction with oligonucleotides. All isolates were positive for the *tcdA* and *tcdB* and non-BI strain.

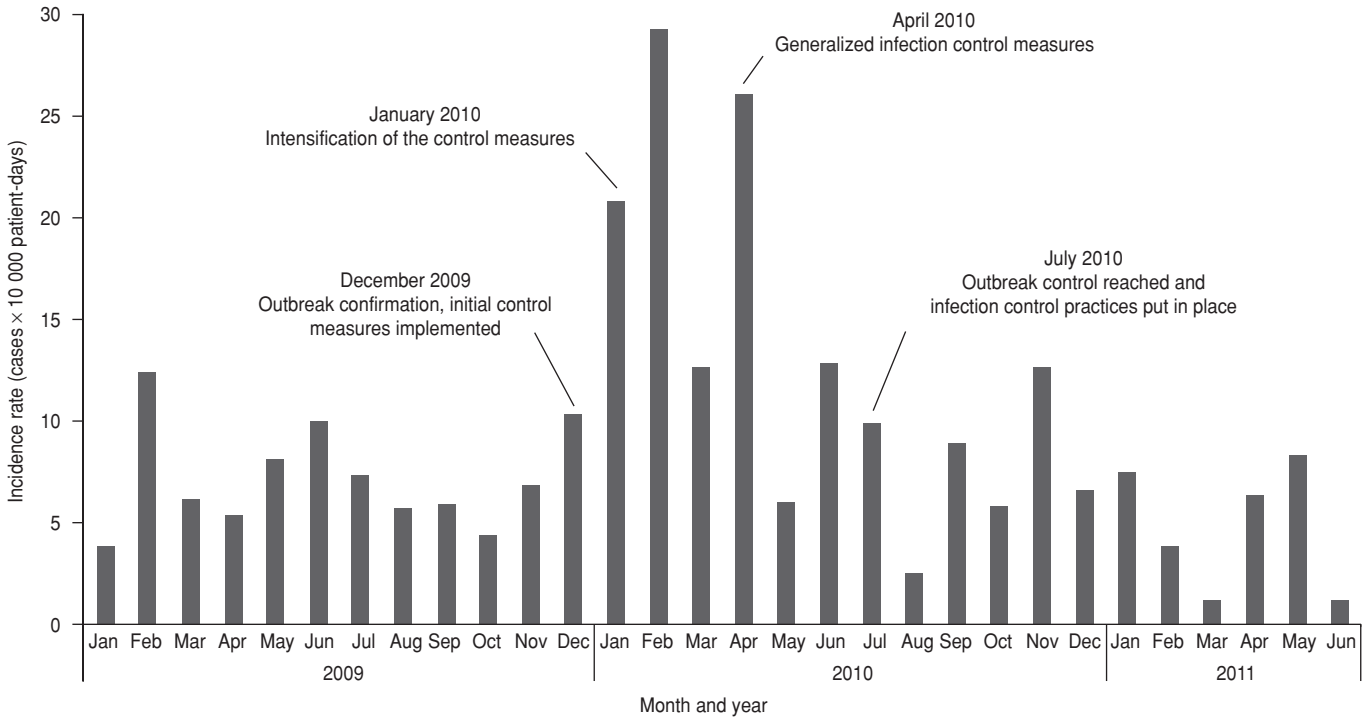
Data analysis

A descriptive analysis of general variables by group was initially conducted. The comparison of general features between cases and controls was done with the chi-square test for categorical variables and the *t*-test for comparison of means.

The odds ratio (OR) was calculated to estimate the likelihood of association between the evaluated exposures and the development of CDAD. The conditions associated with CDAD were then assessed with a bivariate model. An adjusted OR was estimated with a logistic regression model for variables that demonstrated association or that were identified as confounders. Backward stepwise regression was then performed and variables with a P value > 0.20 were excluded.

All estimations were calculated with Stata 10.1 at a significance level of 0.05. Ethical approval was not necessary for this investigation, in accordance with the country's bioethical regulations at the time of the start of the outbreak investigation, and the patients' confidentiality was maintained during the study, with a unique code assignment by the hospital control infection committee. The final version of the manuscript was evaluated and approved to be submitted for publication by the Caja Costarricense de Seguro Social (CCSS) bioethical office.

FIGURE 1. *Clostridium difficile* incidence rate by month and year, Costa Rican General Hospital, 2009 to June 2011



The data from this investigation are the property of CCSS, the public health care provider of the Costa Rican government.

RESULTS

General overview of the outbreak

During the outbreak period, a total of 84 cases were identified on the medical and surgical wards. The usual incidence rate of 3.1 to 6.7 cases per 10 000 patient-days increased 5-fold, with 24.3 cases per 10 000 patient-days in February 2010.

The outbreak was confirmed in the last week of December 2009, and initial control measures based on the CCSS *C. difficile* outbreak guidelines were implemented solely in wards with positive cases (11). Initial strategies included a hand-hygiene enforcement campaign for medical staff and patients, mandatory use of personal protective equipment by facility employees in contact with patients suspected of being infected, strict isolation measures, a deep disinfection protocol, and restriction of the use of antibiotics associated with CDAD. A strict isolation area was set up for patients with confirmed cases of *C. difficile*. Deep disinfection was performed on surfaces in patients' rooms and on equipment used through a procedure of double cleaning, with 45 minutes between each cleaning. The solutions used were a 1:10 hypochlorite solution in the medical wards and 1:10 quaternary ammonium for medical equipment.

The restricted antibiotics were those previously recommended in the literature, which include fluoroquinolones, clindamycin, and third-generation cephalosporins and carbapenems.

The initial control measures had been implemented in affected areas of the hospital in December 2009 and were intensified in January 2010. Four weeks later, the initial trend of the epidemiologic curve was interrupted. However, in April 2010 another increase in the incidence rate from the same wards was observed, but it was found in patients who had been referred from other wards. At this point, the described measures were applied to all areas of the hospital. After expanded implementation of these control measures, the outbreak was declared controlled in July 2010.

The control measures were maintained until the first semester of 2011 as part of routine prevention of further *C. difficile* nosocomial outbreaks and proved effective in reestablishing the usual incidence pattern of CDAD (Figure 1).

TABLE 1. General features of *Clostridium difficile*–associated diarrhea cases and controls, Costa Rican general hospital, 2010

Variable	Controls (n = 552)		Cases (n = 84)	
	No.	%	No.	%
Sex				
Male	270	48.9	36	42.9
Female	282	51.1	48	57.1
Medical history				
Diabetes	78	14.1	32	38.1
Cancer	0	0.0	14	16.7
Ulcerative colitis	0	0.0	0	0.0
Chronic renal failure	5	0.9	4	4.8
Immunosuppression	0	0.0	8	9.5

Associated factors

General patient features are described in Table 1. Females experienced a greater

frequency of CDAD in both the case and the control groups. The average age was 55.3 years [standard deviation (SD) 18.8 years] for the control group and 62.3 years (SD 21.8 years) for the case group. The difference in the average age between the two groups was significant ($P = 0.02$).

Underlying medical conditions such as diabetes, cancer, chronic renal failure, and immunosuppression were more frequent in case subjects than in control subjects (Table 1).

The most frequent clinical presentation associated with diarrheal disease was abdominal pain, which was present in 23.8% of patients, in addition to fever and leukocytosis, which together were present in 21.4% of patients.

The average length of hospitalization was 11.5 days (SD 14.0 days) for cases and 7.8 days (SD 7.7 days) for controls. The most frequently prescribed antibiotics were cefotaxime, clindamycin, and oxacillin for patients in the case group; clindamycin, gentamicin, and ciprofloxacin were prescribed more often in the control group.

According to the nonadjusted ORs of each group, subjects older than 59 years with a hospitalization stay longer than 7 days, diabetes, and chronic renal failure were the conditions most significantly associated with risk of CDAD. The evaluation of drug exposures revealed an association with antibiotics, in particular ceftazidime, cefotaxime, meropenem, and levofloxacin.

The adjusted OR demonstrated that CDAD was associated with underlying medical conditions of diabetes [OR 3.4, 95% confidence interval (CI) 1.5–7.7, $P = 0.04$] and chronic renal failure (OR 9.0, 95% CI 1.5–53.0, $P = 0.02$). Other conditions that maintained association in the adjusted model were administration of cephalosporins, including ceftazidime (OR 33.3, 95% CI 2.9–385.5, $P < 0.01$) and cefotaxime (OR 20.4, 95% CI 6.9–60.3, $P < 0.01$), before the onset of symptoms (Table 2).

Table 2. Factors associated with *Clostridium difficile* infection, Costa Rican general hospital, 2010

Variable	Controls ($n = 552$)	Cases ($n = 84$)	OR	95% CI	*P*	Adjusted OR	95% CI	*P*
Sex								
Male	270	36	1.0					
Female	282	48	1.3	0.7–2.1	0.30	1.3	0.6–2.9	0.47
Age, years								
< 60	440	53	1.0					
≥ 60	112	31	2.3	1.3–3.8	< 0.001	1.4	0.6–3.2	0.37
Location								
Medical ward	178	45	2.4	1.4–3.9	< 0.001	0.9	0.4–2.0	0.87
Surgical ward	374	39	1.0					
Length of hospitalization, days								
≤ 7	437	55	1.0					
> 7	115	29	2.0	1.1–3.4	< 0.001	1.0	1.0–1.1	0.07
Medical history								
Diabetes	78	32	3.7	1.8–7.6	< 0.001	3.4	1.5–7.7	0.04
Cancer	0	14	NC					
Ulcerative colitis	0	0	NC					
Chronic renal failure	5	4	5.5	0.5–34.5	0.02	9.0	1.5–53.0	0.02
Immunosuppression	0	8	NC					
Cephalosporins								
Cefotaxime	28	8	34.0	11.9–100.1	< 0.001	20.4	6.9–60.3	< 0.01
Cefalotin	10	38	1.8	0.5–1.0	0.21[a]			
Cefalexin	2	49	0.2	0.0–1.5	0.24[a]			
Ceftazidime	10	1	74.4	7.7–3526.5	< 0.001[a]	33.3	2.9–85.5	< 0.01
Penicillins								
Amoxicillin	0	25	NC					
Penicillin	0	2	NC					
Oxacillin	14	85	1.1	0.4–2.6	0.82			
Quinolones								
Ciprofloxacin	12	90	0.8	0.3–2.1	0.73			
Levofloxacin	12	19	4.7	1.4–13.1	< 0.001	0.9	0.2–4.1	0.94
Macrolides								
Clarithromycin	8	43	1.2	0.3–3.7	0.56[a]			
Aminoglycosides								
Gentamicin	10	120	0.5	0.1–1.3	0.16			
Amikacin	6	25	1.6	0.3–5.7	0.44			
Carbapenems								
Meropenem	8	8	7.2	1.5–27.9	< 0.01	2.4	0.4–14.7	0.35
Tetracyclines								
Doxycycline	2	17	0.8	0.0–5.2	1.0			
Sulfonamide								
Trimethoprim-sulfamethoxazole	6	72	0.5	0.1–1.7	0.27			
Lincosamide								
Clindamycin	16	120	0.8	0.3–1.9	0.68			
5-Aminosalicylic acid derivative								
Sulfasalazine	0	2	NC					
Gastric acid								
Esomeprazole	2	1	13.4	0.2–1 056.6	0.14[a]	2.0	0.5–77.7	0.71

Notes: OR: odds ratio, CI: confidence interval, NC: not calculable.
[a] Fisher's exact test.

DISCUSSION

The results demonstrate that the incidence rate observed in *C. difficile* outbreaks can rise dramatically within a matter of weeks, a phenomenon that can be explained by a mechanism of bacterial transmission in which hospital surfaces are contaminated with spores. The incidence rate of 2.4 cases per 10 000 patient-days in this Costa Rican hospital was lower than what has been reported in previous studies in the United States of America and Canada (12), a condition that could be related to factors such as the *C. difficile* reported strain, the different hospital sizes, and the complex level. Nonetheless, the high transmissibility of *C. difficile* infection emphasizes the importance of rapid implementation of the comprehensive infection control measures to prevent further cases.

The current outbreak was controlled by implementation of guidelines established by the CCSS in 2009, which included strategies that have proven to be successful in achieving outbreak control in other documented cases (13–15), although the efficacy of each individual intervention in this case is not known. The prescription of high-risk antibiotics as the most important factor associated with CDAD supports enforcement of the restriction of antimicrobial use as part of recommended

control measures, which was appropriately implemented in this case to achieve outbreak control. Several described *C. difficile* outbreaks have considered antibiotic restriction as an effective control strategy, especially with regard to fluoroquinolones and cephalosporins (14, 16). The use of fluoroquinolones has been reported to be one of the most important factors associated with CDAD (14). The study did not find an association with fluoroquinolones, which could be explained by the concomitant prescription of this medication with other antibiotics associated with CDAD that resulted in larger differences between case and control exposures than the exposures between those groups and fluoroquinolones.

Increased age has been associated with increased susceptibility to CDAD (17), a condition that was shown to be relevant during the outbreak with a significantly higher mean age in the case group than in the control group.

The underlying medical conditions associated with CDAD in this outbreak have been described as risk factors mainly in patients who had undergone surgery (18, 19). However, association of these underlying medical conditions with CDAD during this outbreak was independent of a history of surgical procedures. The described association thus could more likely have resulted from increased susceptibility due to antibiotic use than from the surgical procedures.

The main limitation of the study was the diagnostic test used to determine infection status. This assay is based on the presence of *C. difficile* toxin, which is not the most sensitive method of establishing the presence of this toxigenic bacterium. To limit the possibility of false negatives in the control group, all patients with previous diarrheal disease were excluded. During the time of the outbreak, this test was the only one being used to determine CDAD in the affected hospital.

This study evaluated the infection control measures implemented during a hospital outbreak and established various factors associated with a *C. difficile* outbreak in a Latin American country. Few studies of such outbreaks have been published in this region, where the availability of resources and health conditions experienced are very different from those in other parts of the world.

In this case, the initial incidence rate of the outbreak experienced a significant reduction during the weeks after implementation of infection control measures, which were shown to effectively achieve outbreak control. This result is consistent with reports of similar outbreaks in which such interventions were enforced in conjunction with early detection of infection (2, 20).

A large body of evidence related to *C. difficile* as a nosocomial agent has been documented and the investigation of this Costa Rican *C. difficile* outbreak has confirmed that the findings are consistent with previously described risk factors for development of CDAD (18). This study also confirms the importance of rapid implementation of such interventions (20) to reduce transmission of the disease and the impact of the outbreak.

As part of the development of effective strategies for preventing and controlling *C. difficile* outbreaks, it is important that the design of such protocols in each hospital follow evidence-based guidelines (9, 20). These guidelines include environmental strategies, hand-hygiene enforcement campaigns, disinfection of surfaces, and restrictive use of high-risk antibiotics.

The nosocomial surveillance system must improve the sensitivity of *C. difficile* testing methods to ensure timely detection of future outbreaks and implementation of control measures to prevent the incidence of further cases and transmission to other hospital wards.

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RESUMEN

Brote de infección por *Clostridium difficile* en Costa Rica: medidas de control y factores asociados

Objetivo. Describir las intervenciones ejecutadas durante un brote intrahospitalario de infección por *Clostridium difficile* en un hospital general de Costa Rica desde diciembre del 2009 hasta abril del 2010 para lograr el control del brote y de los factores asociados a la infección por *C. difficile*.

Métodos. Se analizaron los casos de infección por *C. difficile* que se habían confirmado mediante pruebas de laboratorio a fin de describir las características del brote y las medidas que se tomaron. Se seleccionaron los casos y se incluyeron en un estudio de casos y testigos; se seleccionaron los testigos en los mismos servicios y el mismo periodo que los casos. Las exposiciones evaluadas incluían las afecciones médicas subyacentes y los tratamientos administrados antes de que comenzaran los síntomas.

Resultados. La media de la edad en los grupos de los casos y de los testigos fue de 62,3 años y 55,3 años, respectivamente. Las medidas de control incluyeron una campaña de promoción de la higiene de las manos, la desinfección a fondo de las superficies hospitalarias, el aislamiento estricto de los casos, el uso de equipo de protección personal y la restricción del uso de antibióticos. Los riesgos atribuibles ajustados que se asociaron al brote fueron la diabetes (razón de posibilidades [OR]: 3,4; intervalo de confianza [IC] de 95%: 1,5-7,7), la insuficiencia renal crónica (OR: 9,0; IC de 95%: 1,5-53,0) y el uso de ceftazidima (OR: 33,3; IC de 95%: 2,9-385,5) y cefotaxima (OR: 20,4; IC de 95%: 6,9-60,3).

Conclusiones. La aplicación oportuna de medidas de control redujo la transmisión de la infección y permitió controlar satisfactoriamente el brote. Las afecciones y los factores que se asociaron a la infección por *C. difficile* fueron similares a los que se encontraron en brotes de esta infección descritos anteriormente.

Palabras clave *Clostridium difficile*; enterocolitis; Costa Rica.