Epidemiology of Clostridium difficile–Associated Diarrhea in a Peruvian Tertiary Care Hospital

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Abstract. The prevalence, incidence, and epidemiologic factors of Clostridium difficile–associated diarrhea (CDAD) in a Peruvian hospital were studied. We conducted a cross-sectional study in patients > 14 years of age from medical/surgical wards of the Cayetano Heredia National Hospital (Lima, Peru) from September 2005 to May 2006. CDAD was defined in a case of nosocomial diarrhea when C. difficile toxin A and/or toxin B was detected by enzyme immune assay (EIA) in stools. A total of 4,264 patients were admitted, with 156 (3.7%) developing nosocomial diarrhea. Fifty-five of 156 (35.2%) cases of nosocomial diarrhea were diagnosed as CDAD. The overall incidence per 1,000 admissions was 12.9. Multivariate analysis showed that use of diapers (OR, 3.54; 95% CI, 1.71–7.34; P = 0.001) and presence of another patient with CDAD housed in the same room (OR, 2.97; 95% CI, 1.14–7.76; P = 0.026) were significantly associated with CDAD. Hospital transmission of C. difficile commonly occurred, supporting infection-appropriate measures directed toward the reduction of CDAD in low-resource settings.

INTRODUCTION

Nosocomial diarrhea is an important recognized cause of morbidity, mortality, and cost for hospitals in the industrialized world. 1–3 Clostridium difficile, an anaerobic, spore-forming, gram-positive rod, is the major cause of infectious diarrhea developing in patients after hospitalization in these regions. 4–5 Recent studies in hospitals from North America and Europe have reported an increase in the incidence rates of C. difficile–associated diarrhea (CDAD), with much of the increase being caused by a more virulent strain of C. difficile. 6–10

Despite the large number of studies that address the prevalence and morbidity of CDAD in the developed world, information on the prevalence of CDAD in hospitalized patients in developing countries is limited. The diagnosis of CDAD cases are based on clinical aspects and/or endoscopic findings because laboratory diagnostic methods for C. difficile are not routinely available in many areas.

Studies that have evaluated the presence of C. difficile toxin in stools from children of different ages in Latin America using diverse methodology found a prevalence of 6–8%. 11–13 Prevalence of CDAD in adult inpatients from India, Iran, Chile, and Argentina have ranged from 6% to 17%. 14–17 C. difficile was identified as a major cause of diarrhea among AIDS patients in a Peruvian hospital. 18

Most hospitals in developed countries have programs for infection control. On the contrary, in developing regions, 90% of hospitals lack personnel or structures for health care control of infection. The lack of measures to deal with infections in the hospitals may contribute to a high incidence of nosocomial infections in these regions.

The objective of our study was to examine the importance of and risk factors for CDAD in a Peruvian tertiary care hospital.

MATERIALS AND METHODS

Study subjects and site. All inpatients > 14 years old admitted to four medical and four surgical wards of Cayetano Heredia National Hospital were eligible. The facility is a tertiary care teaching hospital with 420 beds located in a poor urban area of Lima, Peru. No infection control program has been developed in the hospital.

Study design. A prospective, observational, cross-sectional study using active surveillance of nosocomial diarrhea was performed from September 2005 through May 2006. Nosocomial diarrhea was defined if the onset of the enteric illness occurred ≥ 72 hours after admission of the patient to the hospital. Using active surveillance, all patients were followed from the time of admission until discharge to look for the occurrence of nosocomial diarrhea. If a patient developed nosocomial diarrhea, he/she was invited to participate in this study and was asked to provide a stool sample. The following data were obtained from medical records: date of admission, age, sex, comorbid condition, antibiotics received during hospitalization, enteral feeding, date of the onset of diarrhea episode, presence of other gastrointestinal symptoms (abdominal pain, vomiting), use of diapers, altered mental status, type of ward (medical or surgical), and room number. Detection of C. difficile toxins A and B was performed using an ELISA kit (Remel, Lenexa, KS) following the manufacturer’s instructions. This study was approved by the Cayetano Heredia Peruvian University Ethics Committee.

Statistical analysis. The incidence per 1,000 admissions was measured by the number of CDAD cases among the total number of patients admitted during the same period per 1,000. The study variables were compared between the patients who developed CDAD and the remaining patients who developed nosocomial diarrhea but were negative for fecal C. difficile toxins. Student t test and χ² test were performed to compare continuous and categorical variables, respectively. Univariate and multivariate logistic analysis regression were done using STATA program version 9.0. P < 0.05 was defined as significant.

RESULTS

Among the total of 4,264 patients admitted to the hospital over the 9-month study time period, 156 (3.7%) developed nosocomial diarrhea. The median age of patients with nosocomial diarrhea was 57.5 years, and 76 (48.7%) were men.
The incidence per 1,000 admissions of nosocomial diarrhea was 36.9. The highest rate of nosocomial diarrhea per 1,000 admissions was found in Medicine Ward A (103.9; Figure 1). Of the 156 patients developing nosocomial diarrhea, 55 (35.3%) were diagnosed as having CDAD with *C. difficile* toxin–positive stools. The overall CDAD incidence per 1,000 admissions was 12.9. Medicine Ward A also had the highest incidence per 1,000 admissions of CDAD (35.3; Figure 1).

There was no significant difference with respect to age, sex, and concomitant disease between the patients who developed CDAD and those who did not (Table 1). Compared with controls, patients who developed CDAD had a significantly prolonged (> 7 days) hospitalization stay before the onset of diarrhea (*P* = 0.007), more often received clindamycin (*P* = 0.022), used diapers (*P* < 0.001), or were housed in the same room with another patient with CDAD (*P* = 0.010; Table 1).

In univariate analysis of risk factors, hospitalization stay > 7 days before the onset of diarrhea was significantly associated with the development of CDAD (*P* = 0.027). The use of clindamycin (*P* = 0.024), use of diapers (*P* < 0.001), and being housed in the same room with another patient with CDAD (*P* = 0.0013) were also significantly associated with the development of CDAD (Table 2). In the multivariate model assessing factors associated with CDAD, use of diapers (*P* = 0.001) and being hospitalized in the same room with another patient with CDAD (*P* = 0.026) remained significant risk factors (Table 3).

**DISCUSSION**

In our study carried out in a tertiary care university hospital, *C. difficile* was identified in more than one third of the

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**Figure 1.** Incidence of nosocomial diarrhea and CDAD on medical and surgical wards, Cayetano Heredia National Hospital, Lima, Peru, September 2005 to May 2006. ICU, intensive care unit; S-ICU, surgical intensive care unit.

**Table 1**

Epidemiologic characteristics of patients with nosocomial diarrhea, Cayetano Heredia National Hospital, Lima, Peru, September 2005 to May 2006

<table>
<thead>
<tr>
<th>Epidemiologic variable</th>
<th>Patients with nosocomial diarrhea</th>
<th>Total</th>
<th><em>C. difficile</em> toxin positive</th>
<th><em>C. difficile</em> toxin negative</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients—no. (%)</td>
<td>156 (100)</td>
<td>55 (35.3)</td>
<td>101 (64.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Age—yr
  Median (Interquartile range) | 57.5 (43–74.5) | 61 (47–79) | 51 (39–66) | 0.068 |
| Male sex—no. (%)       | 80 (51.3)                         | 34 (61.8) | 46 (45.5) | 0.052 |
| Concomitant disease—no. (%) | 37 (23.7) | 10 (18.2) | 27 (26.7) | 0.230 |
| Hospitalization period before onset of diarrhea > 7 days—no. (%) | 103 (66.0) | 44 (80.0) | 59 (58.4) | 0.007 |
| Number of antibiotics during hospitalization
  Median (Interquartile range) | 2 (2–4) | 2 (2–4) | 2 (2–3) | 0.441 |
| Use of clindamycin—no. (%) | 100 (64.1) | 42 (76.4) | 58 (57.4) | 0.022 |
| Use of proton pump inhibitors and/or H2 receptor blockers—no. (%) | 96 (61.5) | 33 (60.0) | 63 (62.4) | 0.771 |
| Enteral feeding—no. (%) | 40 (25.6) | 17 (30.9) | 23 (22.7) | 0.081 |
| Altered mental status—no. (%) | 54 (34.6) | 24 (43.6) | 30 (29.7) | 0.081 |
| Use of diapers—no. (%) | 81 (51.9) | 40 (72.7) | 41 (40.6) | < 0.001 |
| Other patient with CDAD in the same room—no. (%) | 24 (15.4) | 14 (25.5) | 10 (9.9) | 0.010 |
patients who developed nosocomial diarrhea. The overall CDAD incidence per 1,000 admissions was 12.9, but two medical floors had rates higher than 25/1,000 admissions. These frequencies are higher than seen in other studies in industrialized countries where CDAD incidence per 1,000 admissions is between 1 and 20.\textsuperscript{19–23} CDAD incidence found in our two medical floors was even higher than epidemic rates described recently in Quebec, Canada. During this outbreak, a study that evaluated 12 Canadian hospitals found an overall incidence per 1,000 admissions of 22.5.\textsuperscript{8}

The high incidence of CDAD in this hospital is probably related to a number of factors including inappropriate use of antibiotics and implementation of an active surveillance system. Also, in this hospital, all rooms have multiple beds (two to six) with shared toilets, and patients are assigned to the rooms only by bed availability, facilitating infection transmission within the hospital.

An association between length of hospital stay and development of CDAD has been described repeatedly. The risk of colonization of \textit{C. difficile}–negative patients who are admitted to hospitals has been shown to be directly proportional to length of hospitalization stay, with an acquisition rate of 13\% between the first and second week and 50\% after the fourth week.\textsuperscript{22} The hospital environment is known to be an important setting for CDAD acquisition, where the organisms have been recovered from beds, room furniture, and bathrooms. Moreover, \textit{C. difficile} has been isolated from hands of health care workers who attend to patients with CDAD.\textsuperscript{23,24} In our study, on the two medical wards with the highest incidence, inpatients tended to be older with prolonged lengths of stay. Nursing homes are not available for families with low resources in Peru, and many persons remain in hospitals longer than needed for social reasons and medical issues.

The most important factor associated with CDAD is antibiotic exposure, particularly penicillin, cephalosporin, and clindamycin.\textsuperscript{25} Recently, outbreaks in the United States and Canada have been strongly related to the use of fluoroquinolones.\textsuperscript{8} Clindamycin was the most common antibiotic used in patients with nosocomial diarrhea in this study but was used even more frequently in patients who developed CDAD. The use of clindamycin is frequent in this institution because of its relative low cost and activity against both gram-positive infections and anaerobes. A prospective study published in 1974 showed that 20\% of patients who received clindamycin developed diarrhea.\textsuperscript{26} The precise mechanism is unknown, but the most accepted hypothesis is that antibiotics alter the resident flora of the colon, leading the colonization of \textit{C. difficile} with production of its toxins.

The most important factor related to the development of CDAD in this study was fecal incontinence and the use of diapers. This factor has not been described in other adult settings. A previous study showed an increased incidence of nosocomial diarrhea in a pediatric ward among diapered children and when multiple patients were housed together in the same room.\textsuperscript{27} Presence of multiple diapered patients in a common room is undoubtedly a favorable environment for cross-infection.

Our finding of an association between being housed with another patient with CDAD in the same room and risk of developing CDAD fits with a previously published report where patients who share the room with other patients with \textit{C. difficile} acquired the infection more frequently and earlier than those patients who were housed with \textit{C. difficile}–negative patients.\textsuperscript{28} Also, our findings support the notion that transmission of CDAD occurs within the hospital through direct contact by hands of health care personnel and/or the contamination of surfaces with \textit{C. difficile} spores.\textsuperscript{23}

Our study has a number of limitations. We did not assess the presence of and severity of underlying co-morbidity. Underlying co-morbidity and severity of underlying disease have been shown to be an important predictor of the development of CDAD.\textsuperscript{29} Also, we used an ELISA test for screening that has a high specificity (99–100\%) but a low sensitivity (75–85\%) to detect \textit{C. difficile} toxins A and B.\textsuperscript{30,31} Thus, we likely have an underestimation of the number of CDAD cases in our hospital. Finally, molecular typing of \textit{C. difficile} strains was not performed to determine the presence of a limited number or multiple strains in the environment.

In conclusion, our study provides evidence that CDAD is an important but unrecognized problem in developing regions with low resources. Analysis of epidemiologic risk factors suggests that there is ongoing transmission within the hospital, particularly on the medical wards. Active infection control measures should be pursued in hospitals in developing regions. Identification of patients with CDAD is advisable in hospitals in developing countries along with cohorting of infected patients with confinement in designated areas with dedicated personnel for their care. Strict handwashing and enteric isolation should be aggressively pursued for patients with fecal incontinence, including diapered patients.

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### Table 2

Results of univariate analysis of risk factors for development of CDAD, Cayetano Heredia National Hospital, Lima, Peru, September 2005 to May 2006

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.01 (0.99–1.03)</td>
<td>0.058</td>
</tr>
<tr>
<td>Sex</td>
<td>1.94 (0.99–3.78)</td>
<td>0.053</td>
</tr>
<tr>
<td>Hospitalization period before onset of diarrhea &gt; 7 days—no. (%)</td>
<td>2.21 (1.99–4.45)</td>
<td>0.027</td>
</tr>
<tr>
<td>Use of clindamycin</td>
<td>2.34 (1.12–4.89)</td>
<td>0.024</td>
</tr>
<tr>
<td>Use of diapers</td>
<td>3.90 (1.91–7.97)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Another patient with CDAD in the same room</td>
<td>3.11 (1.27–7.58)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

### Table 3

Results of multivariate analysis of risk factors for development of CDAD, Cayetano Heredia National Hospital, Lima, Peru, September 2005 to May 2006

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Another patient with CDAD in the same room</td>
<td>2.74 (1.08–6.97)</td>
<td>0.035</td>
</tr>
<tr>
<td>Use of diapers</td>
<td>3.69 (1.79–7.61)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Disclosure: The authors state that there are no conflicts with the study.

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