ORIGINAL ARTICLE

Risk factors associated with recurrent *Clostridium difficile* infection in a group of inpatients in Mexico

Nancy E. Aguilar-Olivos,* Brenda Balderas-Garcés,**
Cristina Gómez-Gutiérrez, Víctor Noffal-Nuno,*** Nahum Méndez-Sánchez******

RESUMEN

Antecedentes. La recurrencia de la infección por *Clostridium difficile* (CDI) se estima entre 5-50% y depende de diversos factores. **Objetivo.** Evaluar factores asociados con la recurrencia de CDI en grupo de población mexicana. **Material y métodos.** Se revisaron los expedientes clínicos de todos los pacientes hospitalizados en nuestra institución con diagnóstico de CDI del 1 de enero de 2012 al 30 de abril de 2015. Se detectaron los casos de recurrencia, considerados como una segunda pruebas positiva después de 15 días de la prueba inicial positiva. Se evaluaron los factores asociados a la recurrencia. **Resultados.** Se estudiaron 167 pacientes hospitalizados con CDI. El 8.4% de los pacientes presentaron recurrencia. Entre los pacientes con CDI recurrente, 54% estaba en tratamiento hospitalario con un antibiótico y presentaron mayor índice de Charlson. **Conclusión.** En la población estudiada la tasa de recurrencia de CDI fue de 8.4%. El uso de antibióticos y presencia de comorbilidades se asoció con la recurrencia.

Palabras clave. Enterocolitis. Pseudomembranosa. Basilos Gram-positivos formadores de endosporas. Infección.

ABSTRACT

Background. *Recurrence of Clostridium difficile infection (CDI) is estimated between 5-50% and depends on several factors.* ***Objective.*** *To assess factors associated with recurrent CDI in a Mexican population.* ***Material and methods.*** *We analyzed the clinical records of all inpatients in our institution with CDI from 1 January 2012 to 30 April 2015. Recurrence was considered as a second positive test after 15 days of the initial positive test. We evaluated the factors associated with recurrence.* ***Results.*** *One hundred and sixty-seven inpatients with CDI were studied. We found recurrence of 8.4%. Among patients with recurrent CDI, 54% were in hospital treatment with an antibiotic and had higher Charlson index.* ***Conclusion.*** *In the studied population, the CDI recurrence rate was 8.4%. Antibiotic use and presence of comorbidities were associated with recurrence.*

Key words. *Enterocolitis. Pseudomembranous. Gram-positive endospore-forming rods. Infection disease.*

INTRODUCTION

Clostridium difficile is a gram-positive anaerobic bacterium capable of producing spores and can cause potentially fatal diarrheal disease due to production toxinas.[1] *Clostridium difficile* infection (CDI) is the leading cause of death associated with gastroenteritis. In 2007 it was estimated that killed 14,000 inhabitants in the United States,[2] and today has become the most common cause of infections associated with health care. Approximately, 65.8% of the reported cases are associated with health care and 24.2% are developed in an inpatient setting. The crude incidence per 100,000 population ranges from 30 to 120 cases of community-acquired infections and 50 to 160 cases related to the care of health.[3] In cases of infections acquired in the community, it has been reported that the rate of first recurrence is 13.5% and the mortality rate at 30 days is 1.3%. The report of patients with infection

* Department of Gastrointestinal Endoscopy, ** Department of Digestive Diseases and Obesity,
*** Department of Clinical Pathology, **** Liver Research Unit.
Medica Sur Clinic & Foundation, Mexico City, Mexico.

Correspondence:

Prof. Nahúm Méndez-Sánchez, MD, MSc, PhD, FACG, AGAF.
Liver Research Unit. Medica Sur Clinic & Foundation.
Puente de Piedra, Núm. 150, Col. Toriello Guerra. Deleg. Tlalpan. C.P. 14050, Ciudad de México, México.
Tel.: (+52 55) 5424-7200. Ext. 4215. Fax: (+5255) 5666-4031
E-mail: nmendez@medicasur.org.mx

Manuscript received: March 03, 2016. Manuscript accepted: March 22, 2016.

related to health care indicates that the first recurrence rate is approximately 21%, and the rate of 30-day mortality is 9%.[3] It is reported that after the initial treatment, up to 20% of patients may experience a recurrence, so it is important to identify the factors associated with recurrent CDI to avoid them or get a close monitoring of patients with these factors. The aim of this study was to determine recurrence rate among inpatients and evaluate the associated factors.

MATERIAL AND METHODS

Patients

A cross-sectional study was conducted by reviewing medical records of all inpatients with a diagnosis of CDI at Medica Sur Clinic Foundation during the period from January 1st 2012 to April 30 2015. The CDI was defined by the presence of symptoms with a positive result of the immunoassay for detecting toxins A and / or B of *Clostridium difficile*. Recurrence was defined as the reappearance of symptoms with a second positive test for toxin A or B after 15 days from the first test.

The variables recorded were age, sex, Charlson comorbidity index, admission to intensive care unit, length of stay, use of antibiotics and proton-pump inhibitor during hospitalization and death during the inpatient stay. Ethics committee of our institution approved the study.

Statistic analysis

The variables were grouped according to the presence or absence of recurrence. The qualitative results were summarized as absolute frequencies and proportions, while quantitative variables were expressed as means or medians with standard deviation or minimum-maximum range. Qualitative data were analyzed using χ^2; meanwhile, analysis of quantitative data was done by *t*-test or Wilcoxon rank sum. A p value < 0.05 was considered statistically significant. The analysis was performed using STATA/SE 12.0, 2011 software.

RESULTS

One hundred and sixty-seven inpatients with diarrhea with at least one positive result for toxin A and/or B immunoassay of C. *difficile* were studied. The baseline characteristics of the groups showed no differences (Table 1).

Seventy percent (n = 107) were prescribed with metronidazole, 9% (n = 14) was treated with vancomycin and 21% (n = 32) received combined treatment with metronidazole and vancomycin. We did not find any significant differences between groups related to outcomes. We found a first CDI recurrence of 8.4% (n = 14) and, the second recurrence rate was 1.8%. Risk factors associated with CDI recurrence were inpatient antibiotic treatment different to metronidazole or vancomycin (p = 0.049) and the presence of a higher Charlson comorbidity index (p = 0.018). Other factors studied did not differ between groups (Table 2). The crude mortality in this study was 4.2% (7 of 167 patients).

DISCUSSION

The CDI recurrence rate was 8.4% between the inpatient Mexican group studied. Risk factors associated with CDI recurrence was administration of antibiotics others than those indicated for CDI and a high Charlson comorbidity score.

Other studies had been evaluated the risk factors associated with CDI recurrence and, highlighted the advan-

Table 1. Characteristics of patients with the presence of *Clostridium difficile* infection.

	Absence of CDI recurrence (n = 153)	Presence of CDI recurrence (n = 14)	p
Women, n (%)	90 (59)	10 (71)	0.357
Age in years, median (min-max)	58 (1-96)	61.5 (6.85)	0.341
Hemoglobin (g/dL), mean (SD)	11 (0.6)	10.9 (0.6)	0.966
Platelets, mean (SD)	278 (29)	210 (23)	0.119
Leucocytes, mean (SD)	12.9 (1.7)	12 (1.7)	0.736
Creatinine (mg/dL), mean (SD)	1.28 (2.3)	0.83 (0.3)	0.494
BUN (mg/dL), mean (SD)	20.9 (22.4)	16.07 (4.9)	0.448
Albumin (g/dL), mean (SD)	3.07 (0.9)	2.91 (0.7)	0.577
Previous antibiotic, n (%)	139 (91)	10 (77)	0.231

CDI: *Clostridium difficile* infection. min-max: minimum-maximum range. SD: standard deviation. BUN: blood urea nitrogen.

Table 2. Results of the factors evaluated according to the presence of the factors evaluated.

	Absence of CDI recurrence (n = 153)	Presence of CDI recurrence (n = 14)	p
Metronidazole,* n (%)	107 (70)	8 (54)	0.346
Vancomycin,* n (%)	14 (9)	3 (23)	0.231
Both,* n (%)	32 (21)	3 (23)	0.644
Other antibiotic,* n (%)	34 (22)	8 (54)	**0.049**
Probiotic,* n (%)	34 (22)	1 (8)	0.277
IBP,* n (%)	113 (74)	9 (62)	0.438
Charlson comorbidity index, median	0	3	**0.018**
Average length of inpatient stay in days, mean (SD)	1.43 (2.08)	3.9 (3.7)	0.468
UCI stay in days, mean (SD)	14 (9)	2 (15)	0.530
Death, n (%)	6 (4)	1 (8)	0.674

CDI: *Clostridium difficile* infection. IBP: proton pump inhibitor. ICU: intensive care unit. * Administration during the hospital stay.

ced age, the use of additional antibiotics and proton-pump inhibitor, and the presence of comorbilidades.[4] One study that included 2019 inpatients with CDI showed that recurrence within 90 days of the initial episode was 10.3%. Multivariate analysis showed that most recurrences occurred in patients with comorbidities and taking pump inhibitors protons.[5] The association between CDI and the use of proton-pump inhibitor is based on case and cohort studies, so it is difficult to accept a cause-effect relationship.[6] In accordance with previously conducted studies, we found that comorbidity index and additional antibiotic use are associated with CDI recurrence; however in our study, we could not evidence the association with pump inhibitors. We also analyzed the effect of admission to intensive care unit it has been reported that over 25% of all survivors of a critical illness complicated by CDI required readmission within 30 days,[7] we did not find this association probably due the small proportion of inpatients with CDI and admission to the ICU.

Studies carried out in Mexico had evaluated aspects of initial infection, reporting that risk factors for CDI include an average inpatient stay of 16.1 days prior to toxin detection, the use of antibiotics with a median of 3 antibiotics used and, reported the crude death rate at 30 days in 8.4%.[8] In our study the crude mortality was 4.2%.

Limitations of this study include its cross-sectional design that does not allow the assessment of the evolution of patients after being discharged. Another limitation is that the research was conducted at a single center so it is not possible to generalize the results the Mexican population.

In conclusion it was found that the CDI recurrence was 8.4% and presented association with the use of additional antibiotics and the presence of comorbidities. We believe that inpatients with CDI and these conditions require close monitoring by the higher probability of recurrence.

REFERENCES

1. Elliott B, Chang BJ, Golledge CL, Riley TV. Clostridium difficile associated diarrhoea. *Intern Med* 2007; 37: 561-8.
2. Hall AJ, Curns AT, McDonald LC, Parashar UD, Lopman BA. The roles of Clostridium difficile and norovirus among gastroenteritis-associated deaths in the United States, 1999-2007. *Clin Infect Dis* 2012; 55: 216-2
3. Banaei N, Anikst V, Schroeder LF. Burden of Clostridium difficile infection in the United States. *N Engl J Med* 2015; 372(24): 2368-9.
4. Deshpande A, Pasupuleti V, Thota P, Pant C, Rolston DD, Hernandez AV, Donskey CJ, et al. Risk factors for recurrent Clostridium difficile infection: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol* 2015; 36(4): 452-60.
5. Abdelfatah M, Nayfe R, Nijim A, Enriquez K, Ali E, Watkins RR, Kandil H. Factors predicting recurrence of Clostridium difficile infection (CDI) in hospitalized patients: Retrospective study of more than 2000 patients. *J Investig Med* 2015; 63(5): 747-51.
6. Tleyjeh IM, Bin Abdulhak AA, Riaz M, Alasmari FA, Garbati MA, AlGhamdi M, Khan AR, et al. Association between proton pump inhibitor therapy and clostridium difficile infection: a contemporary systematic review and meta-analysis. *PLoS One* 2012; 7(12): e50836.
7. Zilberberg MD, Shorr AF, Micek ST, Kollef MH. Clostridium difficile recurrence is a strong predictor of 30-day rehospitalization among patients in intensive care. *Infect Control Hosp Epidemiol* 2015; 36(3): 273-9. Doi: 10.1017/ice.2014.47.
8. Camacho-Ortiz A, López-Barrera D, Hernández-García R, Galván-De los Santos AM, Flores-Treviño SM, Llaca-Díaz JM, et al. First Report of Clostridium difficile NAP1/027 in a Mexican Hospital. *PLoS ONE* 2015; 10(4): e0122627.