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Original

Clostridium difficile infections in a geriatric hospital in Costa Rica

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Abbreviations:
DACD, diarrhea associated with *Clostridium difficile*
Tox+/GDH+, positive *Clostridium difficile* test for toxins A/B and the GDH antigen
GDH+, *Clostridium difficile* test positive for glutamate dehydrogenase antigen only.

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Abstract

Aim: To describe the characteristics of older adult patients diagnosed with *Clostridium difficile* infections in a geriatric hospital in Costa Rica to contribute to improving their management and lead to a reduction in morbimortality and costs associated with their care.

Methods: A retrospective observational study was conducted with demographic and clinical information of 141 patients admitted to the Hospital Nacional de Geriatría y Gerontología Dr. Raúl Blanco Cervantes in Costa Rica from 2015 to 2018, who presented a positive immunochromatographic test for detection of *C. difficile* antigen and/or toxins in the diarrheal stool. Continuous variables were compared by ANOVA test, while categorical variables were compared by Fisher's exact test. Risk factors for each of the groups were evaluated by univariate analysis. Values of $p < 0.05$ were considered statistically significant at 95% confidence.

Results: 141 patients with *C. difficile-associated* diarrhea were studied. The patients had a mean age of 83 years and 57% were women. Thirty-five percent of the cases were of community origin and 27% were severe. Antimicrobial consumption was mainly cephalosporins and fluoroquinolones. The most used treatment was metronidazole (81%) and 30-day mortality related to *C. difficile* infection was 35%.

Conclusions: This is the first epidemiological report of *C. difficile* infection describing a group of hospitalized geriatric patients and their associated risk factors, highlighting an important percentage of community and severe cases, calling for establishing local guidelines and specific groups for the treatment and prevention of such infection.

Keywords: *Clostridioides difficile*, geriatric hospitals, diarrhea, Costa Rica.

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Clostridioides (Clostridium) difficile is an anaerobic sporulating Gram-positive bacillus, the main causative agent of in-hospital diarrhea whose route of transmission is fecal-oral or exposure to spore-contaminated environments. The prevalence of asymptomatic colonization by *C. difficile* in hospitalized patients is 3-26% and 5-7% in older adults hospitalized for long periods of time, while in asymptomatic adults without exposure to health systems, it is less than 2%.[1, 2]

The consumption of antimicrobials causes dysbiosis that allows *C. difficile* spores to germinate and colonize the colonic mucosa. There, this pathogen secretes its main virulence factors: enterotoxin A and cytotoxin B, which cause cytotoxic effects and alterations of the epithelial barrier that can lead to mild to severe diarrhea, fulminant colitis with toxic megacolon, and colonic perforations.[2, 3]

C. difficile is a globally distributed pathogen with reports of outbreaks since 2003[4] and an increase in the severity of clinical presentations attributed to emerging strains such as NAP1/RT027/ST01.[5] In Costa Rica, hospital outbreaks associated with this and another autochthonous strain, NPA_{CR1}/RT019[6,7] have occurred. The main risk factors for the development of *C. difficile-associated* diarrhea (CDAD) include advanced age, exposure to healthcare facilities, and the use of antibiotics and proton pump inhibitors.[8]

70-80% of *C. difficile* infections and more than 90% of associated deaths occur in adults aged 65 years or older.[9, 10] Because of its relevance, this study aims to describe the characteristics of *C. difficile* infections that occurred in a geriatric hospital in Costa Rica from 2015 to 2018 with the purpose of contributing to improving their management and leading to a reduction in morbidity and mortality and costs associated with their care.

Methods

This is an observational study with a retrospective data review. Demographic and clinical information was collected from 141 patients admitted to the Hospital Nacional de Geriatría y Gerontología, Dr. Raúl Blanco Cervantes (HNGG), of the Caja Costarricense de Seguro Social (CCSS), who presented a positive immunochromatographic test for detection of GDH antigen and/or *C. difficile* toxins in diarrheal stool, between August 2015 and December 2018 (41 months).

The data were collected through the medical records kept by the Epidemiological Surveillance Committee of that center. The study was authorized as protocol CCSS 13- 2019 by the Scientific Ethical Committee of the HNGG.

For clinical and demographic information, a descriptive analysis of the quantitative variables was carried out (range, mean and standard deviation) and qualitative (absolute value and/or percentage). The variables studied were: age, sex, days of hospitalization, reason for admission, origin of the case (in-hospital or community), body temperature, laboratory data (albumin, creatinine, and leukocytes), presentation of *shock*, admission to the ICU, consumption of antibiotics or antibiotic inhibitors, and the use of antibiotics or inhibitors of gastric secretion in the 8 weeks before infection, a treatment used for infection, and mortality related to *C. difficile* infection in the 30 days after infection. In addition, an analysis of the subgroup of cases with severe presentation was performed. Table 1 shows the definitions used for case description and classification.

Table 1. Definitions of the concepts used for the characterization of hospitalized Clostridium difficile-associated diarrhea cases, period August 2015 to December 2018, Hospital Nacional de Geriatría y Gerontología Dr. Raúl Blanco Cervantes, Caja Costarricense de Seguro Social, Costa Rica

Concept	Definition
Confirmed case of DACD	Patient with clinical suspicion and a positive test for toxin and/or GDH antigen in a stool sample (Techlab® *C.diff* Quik Chek complete®) and no previous positive test in the last 8 weeks.[6]
in-hospital case	A patient diagnosed with DACD more than 48 hours after admission or less than 4 weeks after discharge.[12]
Community case	A patient diagnosed with DACD within 48 hours of hospital admission and without hospitalization in the previous 12 weeks.[12]
Serious case [12, 13]	Patient with at least two points according to the following criteria: **Minor criteria (1 point each):** - Temperature ⩾38.5 °C - Leukocytes ⩾15,000 cells/µL - Creatinine >1.5 mg/dL - Albumin <2.5 mg/dL **Major Criteria (2 points each)** - Intensive Care Unit admission - Presence of Shock
Mortality due to *Clostridium difficile*-associated diarrhea.	Patient diagnosed with *Clostridium difficile*-associated diarrhea, whose death is recorded within 30 days of the first laboratory evidence.[6]

For statistical analysis, comparison of continuous variables was performed using a one-way ANOVA test followed by a Bonferroni correction or a Kruskal-Wallis analysis with a Mann-Whitney test, according to the assumptions of normality of the data. Categorical variables were compared with a Fisher exact test. Risk factors for each of the groups were evaluated by univariate analysis. Values of $p < 0.05$ were considered statistically significant at 95% confidence.

Results

The cases of 141 patients with positive laboratory tests for GDH antigen were studied and/or toxins, in 51% (n=72) toxins A/B and GDH antigen (Tox+/GDH+) were detected; in the others (n=69), only GDH antigen (GDH+) was detected. Patients ranged in age from 60-101 years, with a mean age of 83 years, and 57% (n=80) were women. These patients had a mean hospital length of stay of 16.2 ± 16.2 days, with a range of 3 to 91 days before the onset of diarrhea. The two main reasons for hospitalization were gastrointestinal pathologies (28.4%, n=40) and renal and/or urinary (21.3%, n=30) (Table 2).

Additionally, 83% (n=117) of the population reported antibiotic exposure in the 8 weeks prior to the onset of diarrhea. Of them, approximately half consumed more than one antimicrobial (n=82), 27% (n=36) consumed only one antimicrobial, and 17% (n=24) none (Figure 1). Cephalosporins (60%, n=84) were the most used antimicrobials prior to *C. difficile* detection, mainly cefotaxime, and ceftazidime. Fluoroquinolones, mainly ciprofloxacin, were the second most used in 26% of the cases (n=37). The aminoglycosides, mainly amikacin, were used in 19% of cases (n=27), followed by penicillins in 13% of patients in whom penicillins were used prior to detection of *C. difficile* (n=18) (Table 2).

In addition, 14% (n=19) of patients were administered at least one inhibitor drug. at least one gastric secretion inhibitor drug, including H2 antagonists and proton pump inhibitors. It was observed that a higher percentage of GDH+ patients consumed 2 antimicrobial agents, while Tox+/GDH+ patients consumed Tox+/GDH+ patients consumed only one antibiotic. In addition, in patients who had fluoroquinolones, the probability of being Tox+/GDH+ was Tox+/GDH+ was three times more likely than GDH+. GDH+ alone; the number of agents previously consumed was variable (Figure 1).According to the origin, it was determined that in 65% of the cases (n=88) the infection was acquired in the hospital, that the remaining percentage came from the community (n=47), and that 6 cases were imported from other health centers. No risk relationship was observed with respect to the hospital department in which the patient was (Table 2).

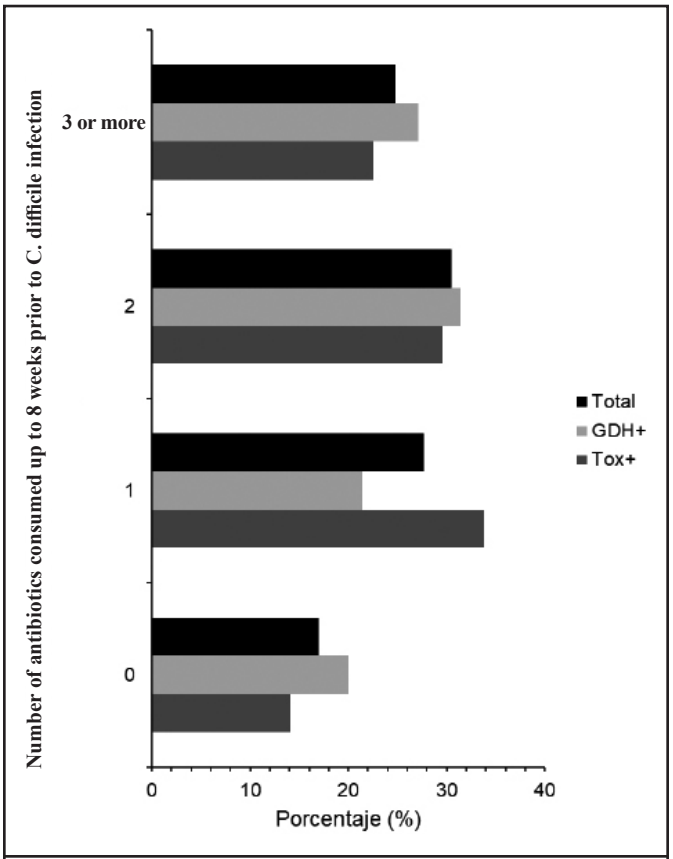

Figure 1. Relative distribution of patients (n=141) according to the amount of antibiotics consumed up to 8 weeks prior to C. difficile infection according to GDH+ (n=69) and Tox+/ GDH+ (n=72) profile, period from August 2015 to December 2018, Hospital Nacional de Geriatría y Gerontología, Caja Costarricense de Seguro Social, Costa Rica.

Table 2. Profile of the characteristics of the 141 patients hospitalized with C. difficile infection and univariate analysis of risk factors according to toxin or antigen detection groups, period August 2015 to December 2018, Hospital Nacional de Geriatría y Gerontología Dr. Raúl Blanco Cervantes, Caja Costarricense de Seguro Social, Costa Rica

	Proportion (%)			OR (95% CI)	P[a]
Parameter	Toxin detection n=72	Detection only GDH n=69	All N=141	Toxins A/B vs GDH	
Female	56	58	57	1,10 (0,5760-2,096)	0,865
Reason for admission					
Gastrointestinal	30,6	26,1	28,4	1,25 (0,6179-2,578)	0,580
Renal and/or urinary	28,8	21,7	21,3	0,95 (0,4343-2,067)	>0,999
Respiratory	9,7	10,1	09,9	0,95 (0,3472-2,622)	>0,999
Cardiovascular	9,7	10,1	9,9	0,95 (0,3472-2,622)	>0,999
Others[b]	29,1	31,9	30,5	0,88 (0,4400-1,851)	0,855
Drugs used up to 8 weeks before diarrhea					
Cephalosporin	60,6	58,6	60,6	1,01 (0,5278-1,940)	>0,999
Fluoroquinolone	33,8	18,3	26,2	2,29 (1,089-4,930)	0,038*
Aminoglycoside	18,3	20,0	19,1	0,86 (0,3643-2,014)	0,8315
Penicillin	12,7	12,7	12,8	---[c]	>0,999
Another	45,1	35,7	45,0	1,41 (0,7358-2,745)	0,391
Gastric secretion inhibitors	12,7	14,3	12,7	0,84 (0,3401-2,258)	0,808
Origin					
Inpatient	58,6	72,3	65,2	0,62(0,3070-1,207)	0,223
Community	41,4	27,7	34,8	1,91 (0,9385-3,832)	0,078
Treatment					
Metronidazole	83,1	77,9	80,6	1,370 (0,6235-3,164)	0,533
Metronidazole + Vancomycin	15,5	17,6	16,5	0,8566 (0,3561-2,006)	0,821
Vancomycin	0	1,5	0,7	---[c]	0,489
None	1,4	3	2,2	0,47 (0,03216-4,151)	0,614
Clinical features					
Mortality	29,2	40,6	34,8	0,75 (0,2230-2,524)	0,220
Gravity	30,5	23,18	27,0	1,46 (0,7076-3,163)	0,348

[a]P was calculated with Fisher's exact test.
[b]Other reasons were: CNS disorders, trauma, malignancy, metabolic diseases, diabetes, musculoskeletal pathologies, gynecological, and others.
[c] OR cannot be calculated because one of the portions was 0 or 100%.
*Statistically significant difference (P < 0.05).

Regarding laboratory parameters, an elevated leukocyte count (15006 ± 6547 cells/ µL) and low albumin values (2.5 ± 6547 cells/ µL) and 6547 cells/µL) and low albumin values (2.6 ± 0.6 mg/dL) were noted. Creatinine values were elevated in all in all cases; however, higher values with significant differences were observed in Tox+/GDH+ patients. Tox+/GDH+ versus GDH+ patients (1.8 ± 1.6 mg/ dL vs. 1.3 ± 1.5 mg/dL) (p < 0.05).

Metronidazole was the treatment mostly used against C. difficile, in 81% of cases (n=112), followed by combination therapy of metronidazole and vancomycin, in 16% of cases (n=23). In addition, vancomycin as sole therapy was used on one occasion in 2016 (0.7%) and 3 patients did not receive any antibiotic treatment (2%). In two cases, there was no record of the treatment used.

In terms of severity of infection, the population with a severe clinical picture was 27% (n=38) and this presentation over the years occurred in 23-33% of the population (Figure 3). This subgroup presented demographic data very similar to the general population. Of note, many patients with a severe clinical presentation were treated with metronidazole (84%, n=32) and the remainder with combination therapy of metronidazole and vancomycin. Regarding laboratory parameters, severe cases presented higher values of leukocytes (18181 ± 6455 cells/µL), lower in albumin (2.3 ± 0.5 mg/dL), but similar in creatinine (1.4 ± 0.8 mg/dL) ($p < 0.05$).

Finally, DACD-related mortality of 35% (n=49) was recorded within 30 days of detection in feces; this fluctuated over the years between 25-48% (Figure 2).

***Note:** This article has supplementary figures that can be seen in the digital version of the magazine.

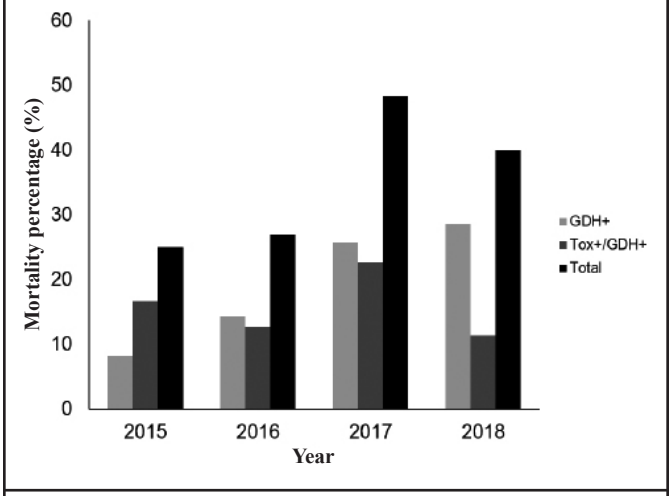

Figure 2. Relative distribution of patients (n=141) according to 30-day C. difficile infection-related mortality at 30-day follow-up and GDH+ (n=69), Tox+/GDH+ (n=72), and GDH+ (n=72) profile, period from August 2015 to December 2018, Hospital Nacional de Geriatría y Gerontología, Caja Costarricense de Seguro Social, Costa Rica.

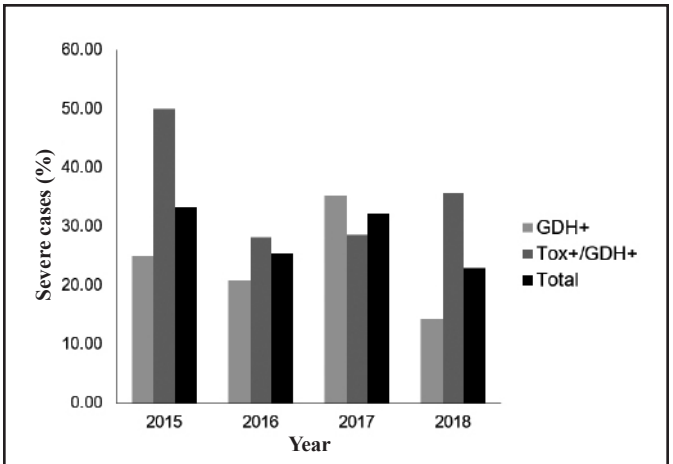

Figure 3. Relative distribution of patients (n=141) according to typing as *C. difficile* infection picture and GDH+ (n=69), GDH+/Tox+ (n=72) profile, period from August 2015 to December 2018, Hospital Nacional de Geriatría y Gerontología, Caja Costarricense de Seguro Social, Costa Rica.

Discussion

The study determined that half of the patients in whom DACD was suspected were considered as positive cases for the presence of toxins A/B and that the other half recorded a positive test only for GDH antigen in symptomatic patients with diarrheic stools. Characteristics such as the marked leukocytosis of these patients raise suspicions that they are cases of DACD that could not be confirmed by available laboratory tests.

According to the most recent guidelines,[1] the recommendation for the diagnosis of *C. difficile* is by means of a stool toxin test as part of a multistep algorithm that includes GDH antigen detection. Given that the patients had a clinical presentation suggestive of DACD, the relevance of the use of a molecular detection method in patients with negative immunochromatographic tests is evident, this being the main limitation of the medical center at the time the study was performed, which generated a bias in the case definition used and in turn, impacted the analysis of the results.

This was also demonstrated in a previous study conducted in patients with an average age of 62 years, diagnosed with *C. difficile* by FilmArray® molecular technique and immunological tests for toxin A/B detection, with which it was determined by the molecular technique that 95% of cases were positive and only 33% of them had a positive toxin detection test, with discordance of 68% between

both tests.[11] The difference in sensitivity and specificity between techniques can be considered one of the most important causes of variation, given that immunochromatography has 83-100% sensitivity and 82-95% specificity for GDH; 29-86% sensitivity, and 87-100% specificity for toxins A/B; while the sensitivity of molecular tests ranges from 77-100% and specificity from 87-98%.[12]

Although diarrhea may be caused by another pathogen not included in the study, in older adult populations such as the one studied, incidences of DACD have been observed 4 to 10 times higher than in the adult population, for reasons such as weakened immune system, and decreased gastric acid production, altered microbiota, and increased exposure to health care and antibiotics,[13] so it is likely that a carrier of *C. difficile* exposed to antibiotics will develop an infection.

Previous population-based studies have associated up to 41% of DACD cases with the community and have concluded that its incidence has almost doubled in the last decade.14 With a similar percentage, the report on the geriatric population in this study (35%) constitutes a first approach to the knowledge of the prevalence of DACD in this population who attended a hospital in Costa Rica.

Another previous study conducted during a hospital outbreak in Costa Rica in 2009-2010[6] found that 31% of *C. difficile* infections were of community origin and caused by strains other than NAP1 and NAP CR1, so the frequency seems to maintain a similar behavior a few years later; however, it is not the objective of this study to extrapolate the rate of community cases of CDAD in the general population due to the specificity of the population attended in the hospital.

Our study found a significant prevalence of severe CDAD over a 4-year period in 27% of patients. This is one of the first studies to evaluate the severity of *C. difficile* infections in older adults. In that sense, it provides a first picture of the presentation of severe cases in the geriatric population of Costa Rica outside periods of outbreaks. It also provides information on CDAD-related mortality in this population (35%), for which rates of 20% have been reported in population-based studies in other countries.[15]

Prolonged consumption of antimicrobials has been associated with increased risk of DACD,[16] given mainly, in descending order, by clindamycin, aztreonam, penicillin with beta-lactamase inhibitors, carbapenemics and cephalosporins.[17] According to data compiled by the Ministry of Health of Costa Rica in 2015 and 2016, the consumption of antimicrobial doses/1000 inhabitants/day was mainly given by amoxicillin, ciprofloxacin, cefalexin, and cefotaxime (Ministry of Health. National action plan for the fight against antimicrobial resistance 2018-2025. Costa Rica: Ministry of Health; 2018. [accessed 28-10-20]. Available at: https://www.ministeriodesalud.go.cr/ index.php/biblioteca-de-archivos-left/documentos- ministerio-de-salud/vigilancia-de-la-salud/normas- protocolos-guias-y-lineamientos/resistencia-a- los-antimicrobianos? limit=20&limitstart=0). This differs from the consumption presented in this geriatric population; however, it could be influenced by population characteristics, comorbidities, and access to different antimicrobials.

Vancomycin is the treatment of choice in patients with severe disease according to the most recent guidelines18, [19] however, only one patient received single therapy with vancomycin in the study period. A systematic review of 2012,[20] showed rates of significantly higher failure rates with metronidazole compared to vancomycin (22.4% vs. 14.2%; P = 0.002) and, in the case of severe infections, better cure rates have been observed with vancomycin compared to metronidazole (97% vs. 76%, P = 0.02).[21] However, it is possible that in the hospital center studied, metronidazole remains a viable and affordable option for treating CDAD, as this remains the treatment of choice in an initial mild-to-moderate episode.[18]

Among the limitations of this study are the impossibility of ruling out that GDH+ cases had diarrhea due to other infectious or non-infectious causes; the lack of confirmation of toxin expression in GDH+ cases with a more sensitive diagnostic method and the presence of variables that could have affected toxin detection (lack of maintenance of the cold chain in sample packaging and transport, inadequate processing and interpretation, presence of interferents, etc.). In addition, the loss of some laboratory data was used to assess the severity and the exclusion from the analysis of reinfections and relapses. Such weaknesses should be considered in future studies for a more complete description of *C. difficile* infections.

This is the first report in Central America that exposes the epidemiology of an older adult population treated in a geriatric hospital with a higher risk of CDAD and reveals a significant percentage of community cases of CDAD, so it should no longer be considered a strictly intrahospital infection. Likewise, it was determined that one-third of geriatric patients suffer from severe DACD, which is important for establishing specific treatment protocols for this population. Likewise, it is advisable to propose future studies to analyze therapeutic failures, considering the number of severe cases presented, as well as the establishment of management guidelines to reduce the risk of DACD in the vulnerable population of this geriatric hospital. The development of multicenter epidemiological studies could broaden the knowledge of *C. difficile* infections in Costa Rica and would allow comparisons and common improvements in the approach, management, and control of clinical cases.

Acknowledgments and collaborators

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