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ORIGINAL ARTICLE

Antibiotic-associated diarrhea: Clinical characteristics and the presence of *Clostridium difficile*☆

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KEYWORDS
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Abstract
Introduction and aims: Evidence in Colombia and Latin America has been insufficient for establishing the clinical characteristics of patients with antibiotic-associated diarrhea (AAD). The present study attempts to describe the clinical characteristics of patients with AAD and to determine the presence of *Clostridium difficile*, utilizing the polymerase chain reaction (PCR) technique.
Materials and methods: Forty-three patients with AAD, managed at the *Hospital Universitario San Ignacio* in Bogotá, Colombia, were evaluated. Prospective patient information was collected, with respect to demographic characteristics, profile of the antibiotic management received, clinical manifestations, risk factors, and paraclinical reports. In addition, the real-time PCR test for *Clostridium difficile* (Cepheid Xpert®) was performed.
Results: Patient mean age was 58 years (19.31 SD). The majority of the patients received 2 or more antibiotics (62.9%) and the beta-lactams were the most frequently used. Hospital stay ranged from 2 to 104 days with a median of 10 days. The most frequent clinical manifestations were abdominal pain and bloating, followed by fever and tachycardia. At the time of diagnosis, 23 patients had noninflammatory results in the stool sample analyses and 18 had kidney failure. The mean level of albumin was 2.4 mg/dl (0.7 SD). The presence of *Clostridium difficile* was documented through PCR in 6 patients (13.95% of the cases).

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Conclusions: AAD patients were characterized by a high frequency of severe comorbidities and prolonged hospital stay. The presence of *Clostridium difficile* in only 13.9% of the cases suggests that other causes of diarrhea in the hospitalized patient should be considered.

PALABRAS CLAVE
Diarrea;
Antibióticos;
Clostridium difficile;
Reacción en cadena de la polimerasa

Diarrea asociada a antibióticos: características clínicas y presencia de *Clostridium difficile*

Resumen
Introducción y objetivos: Hasta ahora existe información insuficiente en Colombia y Latinoamérica que permita establecer las características clínicas de los pacientes con diarrea asociada a antibióticos (DAA). El presente estudio busca describir las características clínicas y determinar la presencia de *Clostridium difficile* (CD) utilizando PCR en pacientes con DAA.
Materiales y métodos: Se evaluó a 43 pacientes con DAA manejados en el Hospital Universitario San Ignacio, Bogotá (Colombia). Se recolectó información de forma prospectiva con respecto a las características demográficas, el perfil de uso del manejo antibiótico recibido, las manifestaciones clínicas, los factores de riesgo y los reportes de paraclínicos. Adicionalmente se realizó prueba de PCR en tiempo real (Xpert® de Cepheid, Sunnyvale, CA, United States) para CD.
Resultados: La edad media fue 58 años (DE 19.31). La mayoría de los pacientes recibieron 2 o más antibióticos (62.9%), siendo los betalactámicos los más frecuentemente utilizados. El rango de días de hospitalización estuvo entre 2 y 104, con mediana de 10 días. Las manifestaciones clínicas más frecuentes fueron dolor y distensión abdominal, seguidas de fiebre y taquicardia; 23 pacientes tuvieron análisis coproscópico no inflamatorio y 18 falla renal en el momento del diagnóstico. El nivel promedio de albúmina fue 2.4 mg/dl (DE 0.7). En 6 pacientes (13.95% de los casos) se documentó la presencia de CD mediante PCR.
Conclusiones: Los pacientes con DAA se caracterizan por tener una alta frecuencia de comorbilidades severas y estancias hospitalarias prolongadas. La presencia de CD en solo el 13.9% de los casos nos sugiere que deben considerarse otras causas de diarrea en el paciente hospitalizado.

Introduction and aims

Diarrhea is a frequent adverse event during antibiotic treatments and a relatively common condition among hospitalized patients. The majority of antibiotic-associated diarrhea (AAD) cases are secondary to the alteration of the physiologic intestinal microbiota and to pathogenic microorganism overgrowth. This alteration results in a reduction in carbohydrate and biliary acid metabolism on the part of the microbiota, with the consequent osmotic or secretory diarrhea.[1] Allergies, toxins, and direct effects on the intestinal motility of some medications and antibiotics have also been described. The incidence of AAD varies from 5-25%, depending on the antibiotic utilized,[2,3] and has been reported in up to 30% of patients that have received antibiotics.[4]

Clostridium difficile (CD) infection is the cause of approximately 20% of AAD cases and of practically all cases of pseudomembranous colitis, which is the most severe manifestation of AAD.[5–7] Elseviers et al.[8] recently reported a 5.63% incidence of confirmed CD infection.

There are numerous methods for diagnosing CD infection. Polymerase chain reaction (PCR) is a highly sensitive technique that utilizes DNA initiators to amplify two specific genes, different from the CD toxigenic strains: *tcdB* that encodes the B toxin and *tcdC* that encodes a regulatory pathway of the toxin. Advantages of this test are its high sensitivity and specificity, but it does not enable active infection to be differentiated from asymptomatic carriers.[9] Its use was once restricted in Latin America due to its high costs, but in recent years that is no longer an impediment.

At present, there is little information in Colombia and the rest of Latin America on the clinical characteristics of AAD, and it is limited to those cases with CD infection.[10] The aim of the present study was to describe the clinical characteristics of patients with AAD, as well as the first Latin American experience utilizing the PCR technique for determining the presence of CD in that group of patients.

Materials and methods

A prospective, observational case series was conducted that included hospitalized patients at the *Hospital Universitario San Ignacio* (Bogotá, Colombia) diagnosed with AAD within the time frame of February 2014 and August 2015. The inclusion criteria were loose stools more than 3 times a day for at least 48 h[3] and antibiotic use for at least 48 h within 90 days prior to the onset of diarrhea. Patients diagnosed with inflammatory bowel disease, amoebiasis, or human immunodeficiency virus infection, and patients that used laxatives or enteral nutrition 48 h prior to the onset of diarrhea were all excluded from the study.

Information was collected through direct interview and case record review, in relation to age, sex, antibiotic management and duration, number of bowel movements, presence of mucus or blood in the stools, days of hospital stay, clinical manifestations, and evaluation of paraclinical tests carried out at diagnosis that included hemogram, stool sample, creatinine, and albumin. The risk factors of immunosuppressant use, active neoplasia, recent hospitalization or gastrointestinal surgery, residence in chronic care institutions or homes for the elderly, and intensive care unit (ICU) stay were also evaluated.

The PCR test for CD was carried out on all the patients through the Xpert® real-time PCR technique from the Cepheid laboratory (Sunnyvale, CA, USA). The samples were collected in sterile recipients. To guarantee sample quality, they were frozen within the first half hour of their collection. The test results were available to the attending physicians.

The results were analyzed using the STATA 11 statistics program. The continuous variables were presented as means and standard deviations when the assumption of normal distribution was met, and as medians and interquartile ranges when it was not. The categorical variable data were expressed as proportions.

Results

Forty-three patients diagnosed with AAD were included in the study. Table 1 shows the demographic characteristics of the study population. The days of hospitalization ranged from 2 to 104 days, with a median of 10 days. The majority of the patients received 2 or more antibiotics (62.9%) and the beta-lactams were the most frequently used.

Tables 2 and 3 describe the clinical manifestations at the time of diagnosis and the identified risk factors, respectively. Immunosuppressant use was documented in 27.9% of the patients, and the most frequent were chemotherapy for cancer management (18.6%) and corticosteroids (13.9%).

Regarding the diarrheic characteristics, there were a mean 4.8 (2.1 SD) bowel movements per day, with a median 4-day duration of the diarrhea at the time of diagnosis. The diarrhea was resolved in all the patients after antibiotic suspension. Total duration of the diarrhea ranged from 2 to 21 days. Of the 43 patients, 23 had noninflammatory results in the stool sample analysis. The mean albumin level was 2.4 mg/dl (0.7 SD). Eighteen of the 43 patients presented with kidney failure defined as a creatinine level above 1.3 mg/dl. The mean leukocyte count in the hemogram was 10,674 cell/ml (6,676 SD). None of the patients died during follow-up.

CD was documented through the PCR technique in 6 patients (13.95% of the cases). The higher frequency of CD cases in patients that had been hospitalized in the ICU (4 out of 11) than in those that did not have that risk factor (2 out of 32) was striking. Likewise, CD was more frequent in patients with a recent prior hospitalization (5 out of 22 vs 1 out of 21) and in those that had undergone recent gastrointestinal surgery (3 out of 5 vs 3 out of 38). A similar trend associated with immunosuppressant use or the presence of active neoplasias was not observed. In addition, no relation

Table 1 Demographic characteristics of the patients and profile of antibiotic use.

Variables	N = 43
Age, mean (SD), years	58 (19.31)
Sex, men/women	13/30
Hospital stay, median (IQR), days	10 (6-20)
Antibiotic treatment duration, median (IQR), days	7 (5-15)
Number of antibiotics, n (%)	
1	16 (37.2)
2	18(41.9)
3	7(16.3)
4	2(4.7)
Antibiotics used, n (%)	
Penicillins	32 (74.4)
Cephalosporin	10 (23.3)
Metronidazole	2 (4.7)
Aminoglycoside	1 (2.3)
Clindamycin	5 (11.6)
Vancomycin	15 (34.9)
Quinolones	2 (4.7)
Macrolide	5 (11.6)
Other	8 (18.6)

IQR: Interquartile range; SD: Standard deviation.

Table 2 Clinical manifestations at the time of diagnosis and clinical characteristics of diarrhea.

Variables	N = 43
Fever, n (%)	15 (34.9)
Abdominal pain, n (%)	24 (55.8)
Abdominal distension, n (%)	15 (34.9)
Hypotension, n (%)	10 (23.3)
Tachycardia, n (%)	28 (65.1)
Desaturation, n (%)	10 (23.3)
Number of stools per day, n (SD)	4.8 (2.1)
Duration of the diarrhea (days)	4

Desaturation: Arterial oxygen saturation under 90%, registering the lowest value in the 48 h prior to diagnosis. Fever: Temperature higher than 38° C during the days the antibiotic-associated diarrheic episode presented. Hypotension: Systolic blood pressure < 90 mmHg, diastolic blood pressure < 60 mmHg, or mean blood pressure < 65 mmHg, registering the lowest value in the previous 48 h. Tachycardia: HR above 100 at the time of diagnosis.

Table 3 Risk factors.

Variables	N = 43
Active cancer, n (%)	14(32.6)
Prior hospitalization, n (%)	22(51.2)
Gastrointestinal surgery, n (%)	7(16.3)
Management in the ICU, n (%)	11(25.6)
Residence in a home for the elderly, n (%)	2(4.7)
Immunosuppressant use, n (%)	12(27.9)
PPI use, n (%)	29(67.4)

Active cancer: active neoplasia diagnosed through imaging study or histology. Prior hospitalization: a minimum 48-h hospitalization within the previous 90 days. Gastrointestinal surgery: GI surgery within the previous 90 days. Management in the ICU: ICU management for at least 24 h during the hospitalization in which the diarrhea was detected. PPI: proton pump inhibitor.

between the type or number of antibiotics received and the presence of CD was found. Of the 6 cases in which the PCR test was positive for CD, 4 had noninflammatory results in the stool sample analysis. All the patients with CD infection were treated with oral vancomycin in accordance with the institutional protocol and their clinical progression was favorable after management.

Discussion

The present study is the first conducted on a Colombian population that describes the demographic characteristics, antibiotic management profiles, clinical manifestations, risk factors, and paraclinical reports in patients with AAD. It is also the first study evaluating the frequency of CD identified through PCR in Latin America.

Upon assessing the demographic and clinical characteristics of the patients with AAD, the high frequency of simultaneous, multiple antibiotic use was noteworthy. An important percentage of patients were identified with hypoalbuminemia and acute renal failure, possibly associated with the severity of the underlying pathologies and chronic diseases. It should be mentioned that stool sample testing did not provide characteristic AAD findings, given that approximately 50% of the results were for noninflammatory diarrhea.

Compared with the results of other authors,[8] we found several differences among populations. Our patients were younger (58 vs 71.9 years of age), the majority were women (69.7 vs 46.5%), antibiotic treatment duration was shorter in our hospital (4.9 vs 7 days), and the number of patients with AAD that received more than one antibiotic was higher (62.9 vs 31%). This is probably associated with the fact that our hospital is a quaternary care center, which sees highly complex patients, most of whom have multiple comorbidities and require a greater number of antibiotics.

The risk factors we found to be most frequently associated with AAD were previous hospitalization within the last 90 days (51.2%), active cancer (32.6%), the use of immunosuppressants, such as chemotherapy and steroids (27.9%), and prior stay in the ICU (25.6%). We also found that penicillins were the most frequently used antibiotics (74.4 vs 64.8%), which was similar to that reported in previous studies.

CD infection was confirmed by PCR in 6 of the 43 cases (13.9%), close to the 15% reported in a larger case series by Kyne et al.,[11] and the 15-25% of CD infection described by other authors.[12,13] Our findings are similar to those reported in the literature, with respect to greater frequency of CD infection in patients with prior hospitalization, those with ICU stay, and patients with recent gastrointestinal surgery.

The biggest limitations of our study were its descriptive, observational design that did not let us establish causality, its small sample size, and the fact that it was conducted at a single hospital. Even so, the prospective data collection turned out to be a strength in limiting the possibility of bias associated with the incomplete report of information in the medical histories. Another strength was the processing of the PCR samples under strict quality parameters.

Our data enabled us to know the clinical and demographic factors of AAD in Colombia, an important starting point for defining therapeutic and prevention strategies in our environment, given the scant amount of information on this entity in Latin America. The high incidence of hypoalbuminemia and kidney failure in AAD, as well as the presence of risk factors, such as immunosuppression and recent hospitalization, call for an integrated approach to these patients, in which the importance of the simultaneous management of the multiple comorbidities is understood. In addition, the data invite us to re-evaluate the simultaneous use of numerous antibiotics and to leave that therapeutic alternative only for those patients in whom it is absolutely necessary.

Finally, it is worth emphasizing that only 15% of the patients with AAD were positive for CD infection in the PCR test, making it very important to consider other causes of diarrhea in the hospitalized patient.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of interest

The authors declare that there is no conflict of interest.

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