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Original

Epidemiologic, clinical, and microbiologic description of an outbreak of *Clostridium difficile* associated diarrhea in Costa Rica

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Abstract

Background: *Clostridium difficile* associated diarrhea (CDAD) is the main cause of nosocomial diarrhea in the world.

Recently there was an outbreak of CDAD in the San Juan de Dios Hospital, San José - Costa Rica; a tertiary care center with 700 beds. This study analyses the epidemiological, clinical and microbiological characteristics of the inpatients with CDAD treated from November 2008 to June 2009.

Population and methods: A CDAD case was defined as a patient with diarrhea and with positive ELISA for *C. difficile* A toxin in feces. An analysis of the annual incidence of CDAD from 2004 to 2008, and the monthly incidence in 2009 at HSJD was made, as well as a retrospective and observational study of 112 medical records for patients diagnosed with CDAD treated at this hospital, from November 15, 2008 to June 15, 2009. The analysis of the data was made using descriptive statistics and measures of association.

Results: The incidence of CDAD increased significantly since the end of 2008 and reached its maximum peak in April 2009, when sanitary measures were implemented. They reduced by 75% the number of patients with CDAD in 8 months. Of the 112 medical records reviewed, 63 (56%) were men. The mean age was 65.33 years, 103 (92%) patients developed the disease while hospitalized; the mean period of hospitalization was 18.6 days. Only 9% did not suffer from any comorbidity.

The most frequent comorbidities were: hypertension and type 2 diabetes, with 57.5% and 39.8%, respectively, and neuropsychiatric disease with 29.2%. A 96% (107 patients) had received three or more antibiotics before the onset of diarrhea. The mean duration of antibiotic therapy was 32 days per patient. In average, the duration of diarrhea was 10.2 days (1-90 days). Most patients were treated with metronidazole or vancomycin. The mortality directly associated to CDAD was 7%.

Discussion: An outbreak of CDAD in a national hospital with 700 beds is described. It was observed more frequently in elderly (>65 years) with long hospital stays, with multiple comorbidities and who had received multiple antibiotics for prolonged periods; mainly cefotaxime, fluoroquinolones or clindamycin. After sanitary and medical measures were implemented, the impact was reduced in 75% over 8 months.

Key words: Diarrhea, *Clostridium difficile*, outbreak, nosocomial infection.

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Clostridium difficile-associated diarrhea (CDAD) is in the medical spotlight around the world, due to the constant outbreaks reported in the medical literature, with health, economic and scientific consequences. [1-3]

C. difficileis an anaerobic Gram-positive bacillus, that forms spores and produces cytotoxic toxins.It is present in feces of less than 5% of the healthy adult population, and 20-30% of hospitalized patients are colonized by this bacterium during the first week.[1]Due to its ability to form thermostable spores, it is not easily eradicated from the hospital environment. Despite its discovery in1935, it was not until 1977 when it was linked to a medical condition, pseudo-membranous colitis associated with the use of antibiotics, at that moment, with clindamycin.[4]

C. difficile is the most frequent cause of acquired diarrhea in the hospital, estimating tens of thousands of cases per year around the world, with costs that surpass one billion dollars.[5]In the last decades there has been observed an important rise in the number of patients, due to improved diagnostic methods, an increased use of antibiotics and chemotherapeutic agents, as well as a rise in the number of sick persons, which increases the chance of contamination by spores in health centers, with a higher probability of infection in susceptible patients.[6]

The gravity of the outbreak in Canada between 2003 and 2005 should be noted, when several hospitals had to be shut down in order to stop the epidemic. A strain of C. difficile was identified, the one denominated hypervirulent, with some particular characteristics that were not observed before, as an increased production of A and B toxins, resistance to fluorochinolones, ability to hypersporulate and production of a binary toxin. This strain had been identified in 1982 and was denominated BI, based on the analysis of the restriction-endonuclease, but it is now known as NAP1/027 (North American Pulsed Field type 1 and ribotype 027, usingpolymerase chain reaction).[5]

At the San Juan de Dios Hospital (SJDH), in Costa Rica, an outbreak of CDAD occurred towards the end of 2008 and in the first semester of 2009. This study describes the epidemiologic, clinical and microbiological characteristics of that episode.

Materials and methods

The case definition of CDAD was performed based on the presence of diarrhea and a positive result for C. difficiletoxin A in feces, detected by an ELISA assay. An analysis was performed of annual incidence of CDAD in San Juan de Dios Hospital, for adult patients, with approximately 700 beds since 2004, and in 2009 it was analyzed monthly. Records of 112 patients evaluated with a diagnosisof CDAD were studied, in the period between November 15, 2008 and June 15, 2009. It is an observational, retrospective, descriptive and transversal study; the Bioethics Committee of the medical center approved it.

The following epidemiologic information of each patient was analyzed: age; gender; address (province, canton and district); date of admittance to SJDH; date of diarrhea onset. Associated comorbidities and infections in all patients were registered and the hospital department where the diarrhea originated was consigned, as well as the type of antibiotic used and how long was it used before the diarrhea started. The following clinical variables were collected: record of daily stools, presence of abdominal pain, fever (it is the highest temperature value during the course of the disease), use of laxatives, use of drugs that modify gastric acidity, use of nasogastric tube and history of recent surgery (in the last 3 months), leukocytosis, bands percentage and serum albumin.

Initial treatment for diarrhea was obtained: oral metrodinazole, parenteral metronidazole, oral vancomycin 125 mg o 500 mg every 6 hours, probiotic agents, prebiotic agents, colestyramin and immunoglobulin; and last, the suspension of "aggressor antibiotics"; and the duration of these was indicated. Diarrhea complications were also documented: recurrence of the episode, toxic megacolon, bacteremia, hydroelectric disorder, acute renal insufficiency, intestinal perforation, digestive bleeding, septic shock and other.

Regarding recurrence of the episode, latency time was identified between the first and second episode; it was not registered if there were more than 2 episodes. Finally, it was recorded if death occurred and its relation with diarrhea.

Microbiologic analysis was published previously.[8]

Data was entered using Microsoft Office Excel software, and for the statistical analysis, descriptive tests were used.

Results

Incidence of CDAD increased since November 2008 and reached its peak in April 2009. An excess of 216 cases more was expected with respect of what was expected in 2009. With the measures taken in the Hospital, the number of new cases was reduced by 75% in the course of 8 months, with a monthly incidence below of that observed in previous years (Figs. 1 and 2).

Out of 112 patients analyzed (Table 1), 63 were men (56%). The mean age was of 65,33 years (SD=16,63) and the age range varied from 16 to 93 years.

Ten patients developed the disease before their admittance, or during the first day of this. The rest 112 patients (93%) were diagnosed during their hospitalization, and the average time of onset of the disease was of 18,6 days, with a median of 14 and a mode of 5 days.

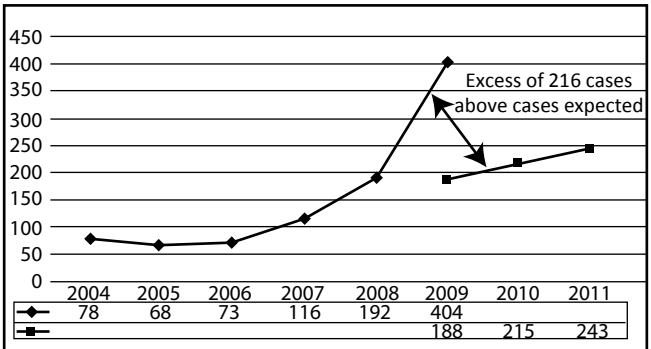

Fig. 1 Annual incidence of diarrhea associated to C. difficile SJDH 2004-2011

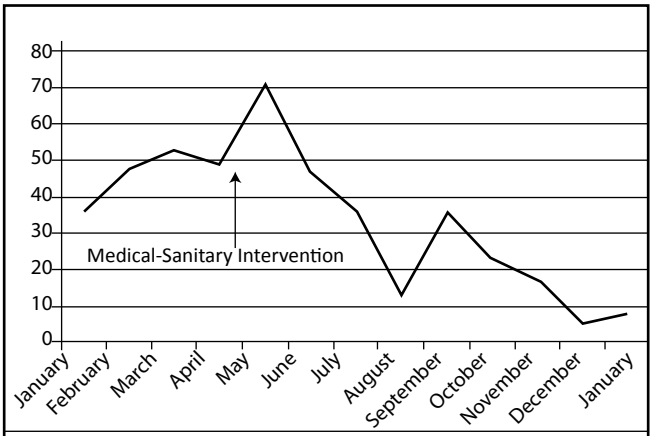

Fig. 2 Incidence of diarrhea cases associated to C. difficile SJDH 2009-2010

Table 1. *Clostridium difficile* associated diarrhea disease. (CDAD) Clinical characteristics (N= 112 patients)

Sex	63 (56%) male
Age	65.3 years average, (16-93 years)
Average time for onset of diarrhea	18,6 days
Average duration of diarrhea	10,2 days (1-90 days)
Comorbidities	102 (91%)
AHT	64 (57,5%)
Type 2 DM	43 (38,5%)
Neuropsychiatric diseases	33 (29,2%)
Nephropathies	17 (15%)
Cancer	12 (10%)
Concomitant infections	105 (93%)
Prior use of antibiotics (3 or more) (cefotaxime,fluorochinolones,clindamycin)	107 (96%)
Duration of antibiotic therapy	32 days average (SD 25.4)
Fever>38.5 ° C	81 (72%)
Abdominal pain	61 (50%)
Leukocytes/mm3	19.803 (300-93000)
Average bands	9%
Use of H2 inhibitors	76 (68%)
Use of proton bomb inhibitors	52 (47%)
Use of nasogastric probe	26 (23%)
Complications	44 (39%)
Acute renal insufficiency	20 (18%)
Hydroelectric disorder	11 (10%)
Recurrence	6 (5%)
Septic shock	6 (5%)
Severe digestive bleeding	2 (2%)
Toxic megacolon	
Total lethality	18 (16%)
Directly associated lethality	7 (6%)

On average, the duration of CDAD was of 10,2 days (1-90 days).

71% of patients were admitted to Internal Medicine Department, 28% to the Surgery Department and 1% stayed in Emergency Room.

Only 9% of patients did not present any known comorbidity at the time of diagnosis. Themost common comorbidities were: HBP (high blood pressure) and Type 2 DM, with 57,5% and 39,8% respectively. 29,2% of patients associated a neuropsychiatric disease, among the 4 most relevant: cerebrovascular event (10%), epilepsy (6%), depression (3%) and dementia (3%); other associated conditions were nephropathy with or without dialysis (15%) and cancer (10%).

Concomitant infections were present in 105 patients (93%) and were: 42% urinary tract infections (UTI), 34% bronchopneumonia (BN), 25% skin and bland tissue infection (ISBT), 16% bacteremia, 6% infection of the superior respiratory tract (ISRT) and 1% infection of the central nervous system.

Only 5 persons (4%) had not received any antibiotic at the moment of diagnosis; the rest (107,96%) used at least 3 different antibiotics before presenting the disease (two patients received 9 antibiotics and one received 11 different antibiotics).

The average duration of antibiotic use was of 32 days (1-96 days).

The three most used antibiotics were: third generation cephalosporin, ciprofloxacin, and clindamycin, in this order.

Fever was present in 72% of patients. Abdominal pain was present in 50% of those ill. The average leukocytosis was of 19.803/mm3 (300-93000 cells/mm3). The average for immature forms, particularly bands, was of 9%. Near 60% presented hypoalbuminemia. Moreover, 28% had a recent surgery history.

A 12,4% of patients had received a laxative before the symptoms began; 46,9% had received proton bomb inhibitors (PBI) as antacid, and 68%, H2 receptor inhibitors. Only in 23% of the patients a nasogastric tube(NGT) was used.

The treatment for the first episode was, in average, of 13 days per patient.

An 87,5% of patients received oral metronidazole at a given time; 16% parenteral metronidazole; 25% oral vancomycin 125 mg every 6 hours, and 5,3% received oral vancomycin 500 mg every 6 hours. 58% of patients received only one drug for the first episode of CDAD. As alternative treatments, probiotics were used in 6,25%, colestyramin in 10%, immunoglobulin in 3% and colectomy was performed in 1%.

Regarding complications, they were present in 93 patients (83%), and the most frequent ones were: acute renal failure (ARF) (39%), hydroelectric disorders (18%), sepsis (10%) or hypovolemic shock(5%), severe gastrointestinal bleeding(SGB) (5%), bacteremia (3%), toxic megacolon (2%) and one patient suffered colon perforation.

Eighteen patients (16%) died and only 7 (6%) of those cases by a direct effect of the CDAD; in 6 patients the diarrhea was considered a contributing cause of death and in 5 patients it did not have causal relation.

Bacteriological analysis was performed in 37 bacterial isolates; all showed in vitro resistance to clindamycin and fluorochinolones, and sensitivity to vancomycin and metronidazole; 54% was of NAP1 type, positive for genes that codify for toxins A and B (tdcA, tdcB) and for binary toxin and with deletion of tcdC gene, which regulates the transcription of toxins.

Discussion

By the end of the 90s, hospitals in different parts of the world have been challenged with a new epidemic: the CDAD, which has caused great economic and health costs, even the closure of several clinics in Canada, a developed country with high health indicators.[1,2,7]

In the study, the information of the Local Committee for Prevention and Control of Infections of the SJDH allowed the detection of an unusual increment in the number of patients between November 2008 and April 2009. Between May and June of 2009, emergency health measures were taken, comprising, among other: development of protocols for patient care; strictisolation of affected patients in a special unit; promotion of hand-washing in health personnel; reduction in visits to patients; disinfection of hospital rooms, materials and equipment with chlorinated solutions; rationalization antibiotic use, as well as analysis of the isolated bacteria in a specialized laboratory.[9]

A significant reduction in the number of patients was achieved with these measures in a short time, and the complications and lethality were similar and in some cases lower to those reported in other countries.[10,11] For the first time in Latin America the strain of C. difficile NAP1 was identified, responsible for this and other outbreaks in the world.[3,8]

Data obtained through the study clearly evidences the disproportionate affectation in the elderly, the average age is 65,33 years, and the median age 67 years. The disease has a tendency to affect preferentially persons older than 65 years, as described in the literature.[2, 12-14] The CDAD is more aggressive in the elderly, with a higher relapse frequency, and they also present a lower response to treatment, the disease causes a prolonged hospitalization and, it also is associated to a higher mortality.[14] The elderly population has several risk factors that make it particularly susceptible to C. difficile, like multidrug use with an extended use of antacids, antibiotics and laxatives, immunosenescence and comorbidities, [12-14] not considering the continuous ethical dilemmas that some of these patients represent.

Comorbidities of the patients are another risk factor and they describe this population accurately from a clinical - biological point of view, since 91% of the sick patients presented some associated pathology.

The HBP and type 2 DM, were the most prevalent pathologies, probably because the elderly predominate in

the population, among whom the incidence is high; in fact, in many of the published studies, these two affectations occupy the first place in comorbidities of the patients.[16-18] It draw the attention the fact that neuropsychiatric pathology as comorbidity is not mentioned in the literature, with some emphasis, as a comorbidity in CDAD; in this study it showed, as important pathologies, cerebrovascular disease, epilepsy, depression and dementia syndromes.

CDAD is closely related with abuse in the use of antibiotics.[1,2,18-22] Among the undesirable effects of these drugs is the emergence of resistant bacteria, as well as the disturbance of normal bacterial flora, in these cases, intestinal flora´s delicate equilibrium is altered by the indiscriminate use of antibiotics and there is elimination of fundamental bacteria for intestinal homeostasis; so it generates destruction of bacterial flora, that is proven with fecal tests where a decrease is found in these patients. This destruction allows the proliferation of pathogenic bacteria, as *C. difficile*. Most of the patients (91%) had received 3 or more antibiotics, among which were included third generation cephalosporins, fluorochinolones and clindamycin, that have been related with this pathology.[21-22] A study showed that the new fluorochinolones induced, in a model of a human intestine, the sporulation and an increase in the production of cytokinin in C. difficile, despite the resistance to these antibiotics,[23] and epidemiologically they have been directly related with the outbreaks of this new strain.Pépin et al [22] evidenced in the outbreak analyzed in Canada, that the probability of developing CDAD was from 3 to 7 times greater if fluorochinolones were used, and from 1 to 3 times, if third generation cephalosporins were used. Similar relations were obtained with antibiotic therapy of a longer than five days duration. In the present study, the prolonged lapse of the antimicrobial therapy previous to the beginning of CDAD should call for reflection.

Data from the Pharmacy Department of the SJDH showed that from 2007 to 2008 there was an increment of 49% in the use of cefotaxime, and of 23,5% in levofloxacin, with similar projections for 2009. An inadequate use of antibiotics was documented in this analysis, in quantity as well as in duration of treatment. Even though, the indiscriminate and irrational use of antibiotics is not the only risk factor for developing CDAD, it is one of the most important ones.

Prolonged hospitalizations are also a risk factor for CDAD, because patients have a higher risk of infection with this bacteria, they have a higher risk of exposure to antibiotics and other treatments; as those used to lower gastric acidity, which have already been associated with the pathology,[18] as it is observed in this study. Again, it should be pointed out that most patients received antibiotics for very prolonged times while they were hospitalized.

Among clinical manifestations, fever and abdominal pain were the most frequent. Regarding fever, data should be analyzed with precaution, since it could be related with a concomitant infection.

Leukocytosis is a common finding reported in the medical literature and it has been related with the severity of the infection, as well as hypoalbuminemia, which was present in more than 60% of the patients.[1,11,18] This last data can be associated with the loss of proteins due to the diarrhea, because it behaves as a protein-losing enteropathy.[24]

Of all the patients, 31 (28%) had a history of recent surgery in the past three months prior to the diarrheic episode, these information reveals something very similar to what occurred in other outbreaks, like the one in Canada.[16-24]

Before the emergence of this new strain, the treatment for CDAD was relatively simple, where the suspension of the antibiotic therapy, the use of probiotics and the use of oral metronidazole for 5-7 days cured, practically 90% of the patients, and the complications were less common and moderately severe.[1-4]

Since NAP1 has been related with this pathology, the treatment is more complex, and the complications are more frequent and more serious,[10,17,21] even when some authors doubt that the severity is exclusive to this strain. [11,18,19]

In our experience and according to the reports of literature around the world,[25,26] a consensus exists that in outbreaks where the hypervirulent strain is involved, patients must be treated aggressively from the onset, by using oral vancomycin for 2-3 weeks; these will lower the duration of the diarrhea as well as the complications associated with it. In some cases, intravenous metronidazole should be associated, since its bioavailability by oral administration in the intestine, is not high enough. With this study, it is not possible to elucidate which was the best therapeutic scheme, since it was a retrospective study.

The importance of alternative treatments has been discussed, for example probiotics, immunoglobulin, fecal bacteriotherapy, etc, however, only the use of immunoglobulin showed effectiveness, where an immunodeficiency is demonstrated in some patients with multiple recurrences.[27,28] During the outbreak, this therapy was used in three patients with satisfactory results.

Regarding the complications, they were similar to those reported in the literature,[2,5-7] and it is noticeable the there is a low recurrence and lethality associated directly to this pathology, contrary to the popular perception externalized by the local media at the time of the incident.

Bacteriological studies during this outbreak[8] demonstrated for the first time in Latin America, the presence of the hypervirulent strain of C. difficile NAP1, associated to epidemic outbreaks in several parts of the world.

In conclusion, in 2008 and 2009, an outbreak of CDAD occurred in the SJDH, a hospital of 700 beds for adults, and the NAP1 strain was identified, for the first time in Latin America, as the responsible agent in a group of patients. Thanks to the measures implemented, the emergency was controlled in a satisfactory way, as compared to outbreaks in other latitudes, where even hospitals had to be shut down.

The occurrence of such a multifactorial and complex outbreak, as the one described in the present study, should evidence the reality regarding the quality of the medical service offered to all the patients, and it should allow the identification of weak points in our everyday attention. Events like this one test the response capacity of a hospital and its human resource.

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