



Review Paper

Diarrhea Caused by *Clostridium Difficile* in Hospitalized Patients of the Regional Hospital Lic. Adolfo Lopez Mateos. A Descriptive Study

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ABSTRACT

Diarrhoeas caused by *Clostridium difficile* comes out from different exogenous environmental transmission sources such as linens, bathrooms, fomites, medical devices or by health-care providers when patients are admitted. Diarrheic syndrome caused by *C. difficile* increased steadily over the last 10 years; however, there is a lack of studies in Latin-America focused on this problem. The objective of this study is to know the behaviour of nosocomial diarrhoea caused by *C. difficile* as well as the disease and patients characteristics. 220 cases of nosocomial diarrhoea were identified, 106 (48.2%) were positive for the *C. difficile* toxin A and/or B test. Incidence rate for the diarrheic syndrome for the study period was 5.78 cases/1000 discharge. All of the cases with positive test received at least one antimicrobial agent 41.4% as monotherapy and 58.6% two or more antimicrobial agents, during hospital stay and before presenting diarrheic syndrome. The follow up to the cases were performed in order to demonstrate the presence or absence of the endemic stain NAP-1/B1/027, define relapse or recurrence rates and establish rates on community disease. Not all of the patients colonized by *C. difficile* developed diarrhoea due to pathogenicity of the bacillus being directly related to the expression of virulence factors and the capacity of immune system. Another important factors for the infection and transition process are the capacity provided by spores to remain in hospitals for months. Diarrhoea is the cardinal symptom of the infection associated with *C. difficile*, however, diarrhoea indicates colonization but no toxin production. That is why it is possible to observe a spectrum of manifestations ranging from an asymptomatic carrier state to fulminant disease with toxic megacolon. Regarding asymptomatic carrier state, it is important to recognize that 20% of adult inpatients are carriers of *C. difficile* and constitute a source of infection.

Laura O. Estrada Hernández MC^{1*},
Edgar del Rey QFB¹, Adriana Martínez
QFB¹, Patricia Tomé Sandoval MC¹,
Juana Salazar Salinas QFB²

1. Lic. Adolfo López Mateos Regional
Hospital, ISSSTE

2. National Medical Center 20 de
Noviembre, ISSSTE.

*Corresponding author. E-mail:
aspirinamed@yahoo.com.mx

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INTRODUCTION

Clostridium difficile is an anaerobic, sporulating, Gram-positive bacillus responsible for most hospital-acquired diarrhoea in adult population. The spectrum of the disease ranges from mild diarrhoea to fulminant events associated with formation of pseudo-membranes and toxic mega colon. In recent years, there was an increase in infection

rates as well as morbidity and mortality associated with this infection in different regions such as Europe, Canada and The United States. However, information regarding this problem is insufficient in Mexico.

Diarrhoeas caused by this agent comes out from different exogenous environmental transmission sources such as

linens, bathrooms, fomites, medical devices or by health-care providers when patients are admitted. This bacillus colonizes the intestinal tract and causes diarrhea if the patient previously received antibiotic therapy. Such association between antibiotic therapy and *C. difficile* infection has been established to Clindamycin; nowadays, the importance of other agents as potential triggers, such as cephalosporines and fluoroquinolones are recognized. Large number of studies has found a clear association between *C. difficile* and antibiotic-associated diarrhea in one out of four cases, as well as all cases of colitis associated with the use of antibiotic therapy. The damage and inflammation in the colonic mucosa have been related with the direct effect of toxins A and B produced by the bacillus and whose detection in faeces is essential for diagnosis. Detection of toxin A by immunoassay (Beckton Dickinson) has been the technique used for identifying toxins; sensibility of this assay is 85% and specificity 93%. In Latin America, particularly in Chile, two studies focused on determining the epidemiological characteristics of the hospital populations affected by *C. difficile*. The first study in Mexico regarding this issue was conducted by The National Institute of Medical Sciences and Nutrition "Salvador Zubirán" with patients having positive test for toxin A during 2003 and 2007 (case-control study). Reported annual incidence rates of the disease associated with *C. difficile* during the period of the study was 5.04 cases /1000 discharge. It was found as significant related factors: use of H2 blockers, age under 65 years, hospitalization for 12 weeks prior diagnosis, previous use of cephalosporin and fluoroquinolones, stay in intensive care unit and prolonged hospital stay; all of these factors had significant statistical association, while odds ratio and confidence interval were significant.

JUSTIFICATION

Diarrheic syndrome caused by *C. difficile* increased steadily over the last 10 years; however, there is a lack of studies in Latin-America focused on this problem. Researches of INNSZ performed a review of databases of Latin-American countries and found just seven recent articles that describe the clinical features, risk factors and some outcomes of the disease in adult population in hospitals.

There was an outbreak of nosocomial diarrhoea in the Internal Medicine Service of the Regional Hospital Lic. Adolfo López Mateos, during early July, 2014. This outbreak involved 9 cases of nosocomial diarrhoea; patients were tested for toxins A and/or B, obtaining a positive result in 55.6%. Due to this issue and considering the current situation of the hospital, it was determined to test all patients with nosocomial diarrhoea after the outbreak in order to increase the knowledge about the occurrence of the disease on in-patients, addressing the diarrhoea caused by *C. difficile* as a health-care related problem.

Objectives

The general objective of this study is to know the behaviour of nosocomial diarrhoea caused by *C. difficile* as well as the disease and patients characteristics.

The specific objectives of this study are therefore:

- To describe the characteristics of the patients with nosocomial diarrhoea caused by *C. difficile* during the study period;
- To determine the incidence of nosocomial diarrhoea caused by *C. difficile*;
- To know the outcome of the infection caused by *C. difficile* and its characteristics.

Participating institutions

The participating institutions are:

- Lic. Adolfo López Mateos Hospital Regional, ISSSTE;
- Epidemiological Surveillance CMN 20 de noviembre ISSSTE (Epidemiological Surveillance, National Medical Centre "20 DE Noviembre" ISSSTE).

METHODOLOGY

From the identification of the outbreak of July, 2014, a longitudinal study was started from July 1st 2015 to April 30th 2016 (20 months), including all nosocomial diarrhea in the hospital from all clinical services identified by active epidemiological survey or inter-consultation. These cases were identified by the health-care associated diarrhea criteria as follows: watery stools for more than 3 or 12 days, after 24 h before hospitalization with or without vomiting or fever; or patient with acute diarrhea and history of antibiotic therapy.

Laboratory epidemiological surveillance of ISSSTE belonging to National Medical Centre "20 de Noviembre" tests all cases for the screening of toxins A and/or B. All patients presented with diarrhoea were treated with Metronidazole 500 mg orally every 6 h and/or Vancomycin 125 mg orally every 6 h for 14 days, regardless of the result of the test. Data on age, gender, previous antibiotic treatment and diagnosis were collected. Follow-up was performed for all patients until infection was resolved. Incidence rate was determined considering discharged patients of Internal Medicine, General Surgery and Intensive Care Unit, because the cases were obtained from these services.

RESULTS

Descriptive analysis of the cases involved during the study period was performed. 220 cases of nosocomial diarrhoea

was identified, 106 (48.2%) were positive for the *C. difficile* toxin A and/or B test, corresponding to Internal Medicine, General Surgery and Intensive Care Unit. Only one positive case on Paediatric Service was identified and that is why this case was not considered on incidence calculation. Incidence rate for the diarrheic syndrome for the study period was 5.78 cases/1000 discharge. Regarding the gender, 58 patients were females (54.7%) and 48 males (45.3%); average age was 60 years for both. Follow up was performed on 100 patients where 75 of them were discharged and 25 patients dead (lethality rate 25%). Internal Medicine was the service that had more cases (58, 54.7%) followed by General Surgery with 14 cases (13.2%) and Orthopaedic with 10 cases (10.6%). All of the cases with positive test received at least one antimicrobial agent 41.4% as monotherapy and 58.6% two or more antimicrobial agent, during hospital stay and before presenting diarrheic syndrome. The most frequent antibiotic used in monotherapy was Ceftriaxone (50%), followed by Meropenem (20.6%); there was a variety of combinations when combined. Patients discharged had an hospital stay ranging from 2 to 85 days (median 20 days) and for patients who died the hospital stay ranged from 5 to 112 days (median 24 days).

Recurrent disease

Risk factors include: patients older than 65 years, comorbidities and concomitant antibiotic therapy. Recurrent disease is due to the alteration on immune system and spore retention in the colon diverticula. It is important to distinguish between relapse and recurrence. Relapse is presented in 10 to 25% of patients and from 1 to 3 weeks after successful treatment of the infection the same symptomatology appears, while 65% occurs in the initial site of the infection.

Recurrence

Symptomatology is different than the initial and another stain involved. Some patients with recurrent diarrhoea, cramping and abdominal distention after treatment for *C. difficile* might have post-infection irritable bowel syndrome or another type of inflammatory colitis including microscopic colitis, concomitant ulcerative colitis and Crohn or celiac disease.

Histopathological findings

Pathological findings of the pseudo-membranous colitis were classified as follows:

Type 1: This is considered to be mild. It revealed inflammatory findings of the surface epithelium and

subjacent from the lamina propria. Typical pseudo membranes are observed and occasionally crypt abscesses.

Type 2: This has to do with more severe interruption of the glandules, mucine secretion and more intense inflammation of the basal lamina.

Type 3: This has to do with severe necrosis throughout the mucosa with confluent pseudo membrane.

DISCUSSION

Previously, it was thought that *C. difficile* might be a commensal, especially in the intestinal flora of newborn infants. Nowadays, *C. difficile* is recognized as a common nosocomial pathogenic bacillus; its reservoirs are patients, health care providers and hospital environment. The higher risk to develop diarrhea by *C. difficile* is the antibiotic therapy for 2 or 3 months before infection, which is exclusively a colon infection. It is important to clarify that not all colonized patients will develop the symptoms and only those colonized by a toxigenic stain develop the disease.

As earlier mentioned, antibiotic therapy increases the risk for an outbreak of 7 to 10 fold during the treatment and up to one month after the treatment increases the risk to 3 fold after 2 months once the treatment has finished.

Any antibiotic drug might result in the disease, however, some studies have shown that cephalosporin and fluoroquinolones are the agents with higher risk to develop 6 of the disease in the presence of the endemic stain BI/NAP1/027; those findings were related to the increase on the resistance of such stain to cephalosporin and fluoroquinolones.

The use of fluoroquinolones increased due to increase in the resistance to penicillin, β -lactams allergy, usually simple posology and broad spectrum.

In general, antibiotics that are closely related are the Clindamycin, with higher risk; ceftriaxone frequently associated by extended use; levofloxacin associated with more virulent and resistant stains. It is not necessary to have a large number of antibiotics to develop the disease, just one antibiotic is enough.

At the beginning, diarrhoea caused by *C. difficile* was considered in an isolated manner. Currently, this bacillus has been reported all over the world. In North America and Europe, cases have increased since 2000; by contrast in Latin America, there is not enough information regarding the cases. Camacho et al. (2008) published a case-control study with 113 cases of infection associated with *C. difficile*, all of which were hospitalized patients with average age being 52 years and mostly women with Clindamycin and Cefepime as the antibiotics were most related.

In 2005, the emergence of the endemic stain NAP-1/BI/027 was associated with increased infection

associated with *C. difficile*, not only among inpatients but in communities; its presence was documented in a large number of countries, such as: Canada, The United States, United Kingdom, France, Germany, Italy, Denmark, Finland, Ireland, The Netherlands, Austria, Poland, Switzerland, Norway, Belgium, Spain, Japan, Korea, Hong Kong and Australia. Until 2010, Latin America only has one publication that described isolation of this stain in a hospital of Costa Rica. Currently, there is a report of the stain in the Hospital Universitario Dr. José Eleuterio González, in Monterrey, Mexico. Other Mexican cities where this stain was found are Mexico City and Guadalajara. The lack on registered cases is due to tests for anaerobic bacteria diagnosis which are not a routine procedure in those countries; even when direct PCR for faeces is an extended test for the diagnosis of *C. difficile*. Due to its high sensibility, specificity, positive and negative predictive value, it is necessary to perform more accurate diagnosis. This is because we consider longitudinal study started on July, 2015 and ended April, 2016 (for publishing purposes) providing very similar information than the limited Mexican articles referred on this study regarding risk factors, variability on clinical manifestations, treatment opportunity, evidence of the indiscriminate use of antibiotics with therapeutic and/or prophylactic purposes and the necessity of multidisciplinary approach when patients are presented with severe disease. Importantly, H₂ blockers are used as an important risk factor (presented in more than 70% of the cases) and the use of Mesalazine and probiotics as treatment adjuvants 7. The follow up to the cases were performed in order to demonstrate the presence or absence of the endemic stain NAP-1/B1/027, define relapse or recurrence rates and establish rates on community disease and, if possible to establish a Transdisciplinary Clinic to treat specific patients through medical or surgical management and collaborate on the development of specific toxoid and faecal microbiota transplant.

CONCLUSIONS

Not all of the patients colonized by *C. difficile* developed diarrhea due to pathogenicity of the bacillus being directly related to the expression of virulence factors and the capacity of immune system. A large number of virulence factors for *C. difficile*, such as fimbriae, flagella, proteolytic enzymes and surface enzymes have been described; all of which contribute to the establishment of the disease through different stages of the infection.

Other contributing factors to the infection and transition process are the capacity provided by spores to remain in hospitals for months. The ability of sporulate increases when *C. difficile* stains are exposed to sub-inhibitory concentration of sodium hypochlorite.

Those virulence factor contribute to the pathogenesis of

the disease, although the main virulence factors are enterotoxin Tcd A and citotoxin TcdB; both are usually in patients faeces with antibiotic-related colitis, considering TcdB is 10-fold stronger to cause colonic mucosa damage. It is well known that healthy adult patients with balance intestinal flora are usually resistant to colonization by *C. difficile*, as the infection is prevented by the intestinal flora; regarding this, some studies revealed suppression of the intestinal flora since the beginning, at the end or during the treatment with antibiotics might facilitate colonization by *C. difficile*. Thus, once the antibiotic therapy is interrupted and the patient is exposed to *C. difficile* spores, these spore germinate and penetrate mucosa of the intestinal tract, then the bacillus adheres to the enterocytes as part of the first step of colonization.

Thus, the second step of the colonization is established when the bacteria starts producing toxins TcdA and TcdB that promote disorganization of cytoskeleton in the basal membrane, and the roundness and opening of GAP unions of the epithelium, damaging the integrity of the intestinal tract. These events provoke massive fluid secretion followed by diarrhea.

Diarrhoea is the cardinal symptom of the infection associated with *C. difficile*, however, diarrhoea indicates colonization but no toxin production. That is why it is possible to observe a spectrum of manifestations ranging from an asymptomatic carrier state to fulminant disease with toxic megacolon. Regarding asymptomatic carrier state, it is important to recognize that 20% of adult inpatients are carriers of *C. difficile* and constitute a source of infection.

Some unusual manifestations of the infection associated with *C. difficile* include protein losing enteropathy with ascithis and infection by *C. difficile* associated with chronic inflammatory intestinal disease and extra colonic compromise.

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