Clostridium difficile associated disease – dramatic increase in the incidence among hospitalized patients

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Abstract

Many publications show an incidence increase of Clostridium difficile (CD) associated disease (CDAD), affecting both in- and outpatients being these recent infections more severe and difficult to treat. The aim of this retrospective study is to evaluate the incidence and clinical impact of CDAD in patients hospitalized from the 1st January 2004 to the 31st December 2009. Suggestive clinical manifestations and at least one of the following were the inclusion criteria: CDAD compatible colonoscopy or CD positive toxin. We identified 83 cases of CDAD (32M, 51W), in a total of 9581 patients (5198M, 4383W). Ages ranging from 47 to 94 years (average 79). Five patients had CDAD acquired in the community and 78 in hospital environment. The incidence of CDAD increased almost six fold between 2004 and 2009 (4.35/1000 vs. 21.63/1000), and 77.11% developed the disease during hospitalization. The disease was more frequent in women (11.64/1000 vs. 6.16/1000). All patients had undergone prior antibiotherapy. The comorbidities, number of antibiotics used, advanced age, duration of the antibiotherapy and the length of hospitalization did not seem to justify the increase in incidence and severity. In 96% the diagnosis was confirmed by the presence of Clostridium toxin and in 4% by colonoscopy. Seventy three patients (88%) were treated with metronidazole and 30% died (the department overall mortality was 13%). Probably, it was the advanced age related with the worst severity scenario which caused the high mortality in our cases.

Key words: Clostridium difficile, pseudomembranous colitis, nosocomial diarrhoea, metronidazole, vancomycin.

INTRODUCTION

Clostridium difficile (CD) is a gram-positive, anaerobic, spore-forming, toxin-producing bacillus that colonizes the colon of 3% of healthy adults, and around 50% of hospitalized patients, increasing with hospitalization time.[1,2] Its transmission occurs by the fecal-oral route, and it is responsible for a variable spectrum of clinical manifestations, from asymptomatic infection or self-limited diarrhea to sepsis, megacolon or death.[2]

For reasons that have not been fully explained, over the years, infections by CD have begun to be observed with greater frequently and greater severity, becoming refractory to the therapy instituted, and having a higher likelihood of recurrence.[3] In the United States of America, the incidence of CD associated disease (CDAD) increased, between 1990 and 2005, from 3 to 8.4 cases to every 10,000 patients hospitalized.[4] In Canada too, the incidence increased from 3.4 to 8.4 cases to every 1000 admissions between 1997 and 2005.[2] In Portugal it is known that CDAD is a frequent hospital infection, and that its incidence has been rising, including in social institutions and retirement homes, with an incidence of 3.71 cases being described for every 10,000 hospitalizations, a figure that increased in 8 years to 15 cases for every 10,000 hospitalizations in 2007.[5,6] Outbreaks associated with high morbidity and mortality have been reported.[6]

There are various explanations for the increased incidence, such as the existence of better detection methods, the increased prescription of antibiotics and immunosuppressants in the context of chemotherapy, hospital contamination with CD spores due to the greater frequency of the disease, increasing the likelihood of infection in susceptible patients.[7] Mutations that confer resistance to antibiotics, the growth of production of toxins, and the facilitation of transmission of spores have also increased the prevalence and virulence of this opportunistic organism.[4]

The main risk factor of CDAD is exposure to

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antibiotics, and it is responsible for 20%-30% of cases of diarrhea associated with antibiotherapy.[2] Nearly all antibiotics, whether administered orally or parenterally, are associated with CDAD, which may occur during or after the therapy. The most commonly used are clindamycin, cephalosporins and fluoroquinolones.[1] Besides the use of antibiotics, other risk factors include age over 65 years, female gender, existence of severe underlying disease and comorbidities, prolonged hospitalization (longer than 4 weeks), gastrointestinal manipulation/surgery and possibly, the use of proton pump inhibitors.[1,6] CDAD may, however, occur without any known risk factor.[4,8]

Currently, metronidazol is recommended as first line therapy for mild to moderate infections, at a dose of 500 mg, orally, for 10 to 14 days. In the case of severe infection, when there is no response, or the patient is intolerant to metronidazole, vancomycin is recommended, via oral, 125 mg every 6 hours, for 10 to 14 days.[4] Twenty to 25% of patients improve with suspension of the antibiotic.[4]

Careful selection of antibiotics, and avoiding its unnecessary prescription, are the basis of primary prevention.[4] It is also essential to use control measures of hospital infection, such as decontamination of the environment and minimizing cross infection through correct hygiene of the hands, barrier precautions, and effective measures for controlling infection.[4]

The objective of the present study was to evaluate the incidence and the clinical impact of CDAD in hospitalized patients, over a period of 6 years.

MATERIAL AND METHODS

A retrospective analysis was carried out of all the clinical processes of patients with CDAD admitted to two wards of the Internal Medicine Service of the Hospitais da Universidade de Coimbra from the 1st January 2004 to the 31st December 2009. Patients were included in the study who presented symptoms compatible with infection by CD (diarrhea with mucus) and the following minimal criteria: colonoscopy with pseudomembranes, and/or identification of toxin A and B in the feces by a rapid and qualitative enzyme immunoassay (ImmunoCard@ Toxins A & B).

The patients were distributed into two groups: Community-acquired CDAD (patients not admitted to hospital in the previous year[8]) and nosocomial CDAD.

The following variables were evaluated: demographic data (age, gender) epidemiological data (total number of cases of CDAD in one year, total number of hospitalizations per year, original – patient's home, retirement home, continuing care unit – and distribution by month of the year) and clinical data (associated co-morbidities, antibiotherapy and previous hospitalizations, complementary diagnostic methods, prescribed therapy, and clinical evolution). Statistical analysis of the data was carried out using the program SPSS Inc., Chicago, IL, USA, and a level of significance of 95% was defined ($p<0.05$).

The values of the continual variables were expressed as mean ± standard deviation, and the Student t, Kruskal-Wallis and Mann-Whitney U tests were used to compare the means.

RESULTS

Of the 9581 patients (5198 men and 4383 women) admitted between 1 January 2004 and 31 December 2009, 83 cases of CDAD were identified (0.87%). It was more frequent among females (51 cases – 61.4%) than males (32 cases – 38.6%) (*Table I*). The patient's ages ranged from 47 to 94 years, with a mean age of 79.17 ± 9.28 years (*Fig. 1*).

Seventy-eight patients (94%) were over 65 years. Ninety-four percent (46 women and 32 men) and nosocomial CDAD and 6% (5 women) had community-acquired infection. An increased incidence of CDAD was observed between 2005 and 2009, the higher number of cases being due to nosocomial infection (*Table I*).

It was observed that the number of antibiotics used and the average number of days from the start of antibiotics to the appearance of the disease, was higher in men; 3.25 vs 2.33 and 25.91 vs 18.61, respectively.

The following comorbidities were identified: bed-ridden, bedsores, malnutrition, ankylosing spondilytis, fibromyalgia, hepatitis B, liver cirrhosis, tuberculosis, depression, sequelae of stroke, dementia, epilepsy, Parkinson's disease, diabetes mellitus type 2, hypothyroidism, heart failure, high blood pressure, myocardiopathy, auricular fibrillation, ischemic heart disease, chronic obstructive pulmonary disease, pulmonary fibrosis, chronic kidney failure, monoclonal gammopathy, leukemia, beta-thalassemia minor, lymphoma, anemia, spinocellular carcinoma, bowel cancer, cancer of the rectum, prostate cancer, breast cancer, Paget's disease of bone, acoustic neurinoma *(Table II)*.

TABLE I

Incidence of *Clostridium difficile* Associated Disease (CDAD)

Year		2004	2005	2006	2007	2008	2009	TOTAL
Number of cases of community-acquired CDAD		2	0	2	1	0	0	5
Number of cases of nosocomial CDAD		6	5	5	10	14	38	78
Incidence of CDAD	Males	2,04/1000	4,00/1000	0	4,6/1000	6,92/1000	18,78/1000	6,16/1000
	Females	6,99/1000	3,34/1000	11,2/1000	9,26/1000	11,54/1000	24,65/1000	11,64/1000
	Overall	4,35/1000	3,71/1000	4,82/1000	6,76/1000	8,97/1000	21,63/1000	8,66/1000

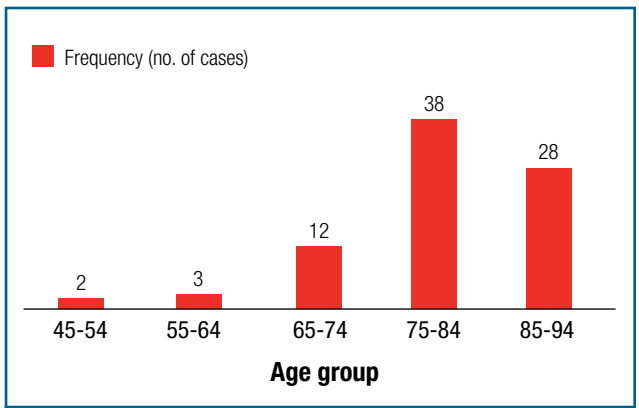
All the patients had received antibiotics before the appearance of the symptoms (*Figs. 2 and 3*). In patients with community-acquired CDAD, the mean number of days from the start of antibiotics to the appearance of diarrhea was 9 ± 4.42. In patients with nosocomial CDAD, the mean number of days from the start of antibiotics to the appearance of diarrhea was 21.6 ± 15.59.

Nineteen patients (22.89%) presented symptoms in the outpatient department, and were admitted for CDAD, 64 (77.11%) developed the disease during hospitalization, 46 (55.42%) had a history of hospitalization in the previous year, and of these, 29 had been discharged from hospital less than 1 month previously.

Comparing those who had been hospitalized in the previous year with those who had not, it was seen that the number of antibiotics used to develop CDAD was smaller (mean of 2.43 vs 3.09; p=0.030), there being no statistical difference in relation to age (p=0.643), hospitalization time (p=0.293) or the number of days from the start of antibiotics to the appearance of the disease (p=0.43).

In relation to gender, it was found that the mean number of antibiotics used was higher in men (3.25 vs 2.33; p=0.029), as was the number of days from the start of antibiotics to the appearance of the disease (25.91 vs 18.61; p=0.025). There were no differences in the number of comorbidities (p=0.176), hospitalization time (p=0.073) and mortality (p=0.924).

Comparing the patients coming from home (group 1) with those coming from a Retirement Home or Continuing Care Unit (group 2), it was seen that the mean number of comorbidities was higher in group 2 (0.75 vs 3.0; p=0.011), but there was no difference



Distribution by age group.

FIG. 1

in age (p=0.017), mean number of antibiotics used (p=0.17), number of days from the start of antibiotics to the appearance of disease (0.80) and hospitalization time (P=0.75).

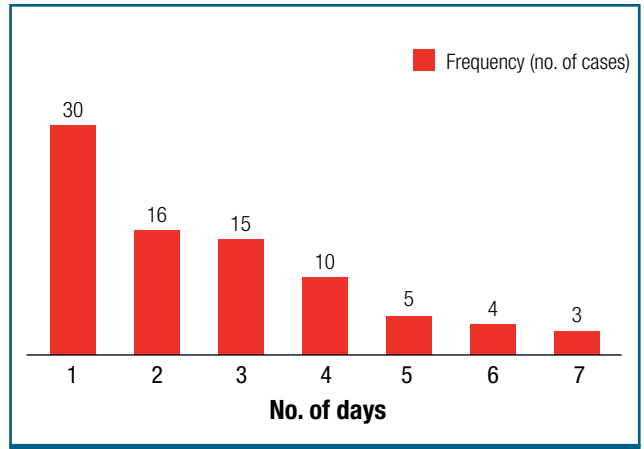
In an attempt to justify the increased incidence of nosocomial CDAD, these patients were distributed by year, and the different years were compared. There were no differences in age, number of comorbidities, number of antibiotics used, number of days from the start of antibiotics to the development of CDAD, total days of hospitalization, and place of origin (home, retirement home or continuing care unit), between 2004 and 2009.

In relation to diagnostic method, 80 patients (96%) had positive toxin tests for CD, 11 (13%) had positive toxin and suggestive colonoscopy, and 3 (4%) only had suggestive colonoscopy. In relation to treatment, 73 patients (88%) were medicated with metronidazol, 1 with vancomycin and 6 (7%) initially with metro-

TABLE II

Comorbidities

Type of comorbidity	Total patients
Bed-ridden	32
Bedsores	15
Malnutrition	7
Ankylosing spondylitis	1
Fibromyalgia	1
Hepatitis B	1
Liver cirrhosis	2
Tuberculosis	1
Depression	1
Sequelae of stroke	36
Dementia	21
Epilepsy	5
Parkinson's Disease	2
Diabetes Mellitus type 2	19
Hypothyroidism	2
Heart failure	23
High blood pressure	34
Myocardiopathy	1
Auricular fibrillation	6
Ischemic cardiopathy	3
Chronic obstructive pulmonary disease	4
Pulmonary fibrosis	1
Chronic kidney failure	13
Monoclonal gammapathy	2
Leukemia	1
Beta thalassemia minor	1
Lymphoma	1
Anaemia	3
Spinocellular carcinoma	1
Bowel cancer	1
Cancer of the rectum	2
Prostate cancer	2
Breast cancer	1
Paget's disease of bone	1
Acoustic neurinoma	1



Distribution by number of antibiotics used.

FIG. 2

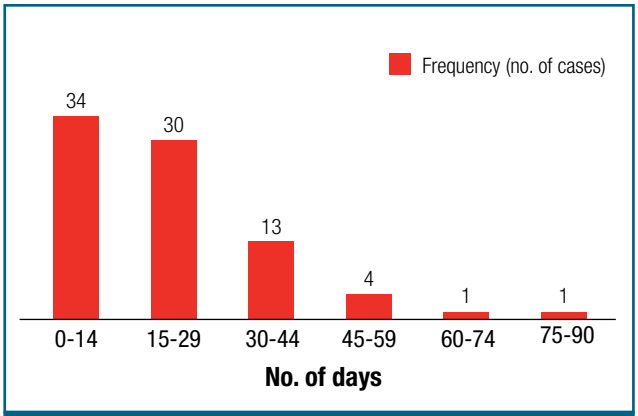
nidazol and then with vancomycin. The patients who were not medicated (3) died.

Twenty-five patients (30%), 12 men and 13 women), died (*Fig. 4*). In relation to mortality, there was no statistically significant difference between genders. The mean age of the patients who died was 79.52 ± 7.6 years. The overall of the patients hospitalized in the period studied (1267) was 13%.

DISCUSSION

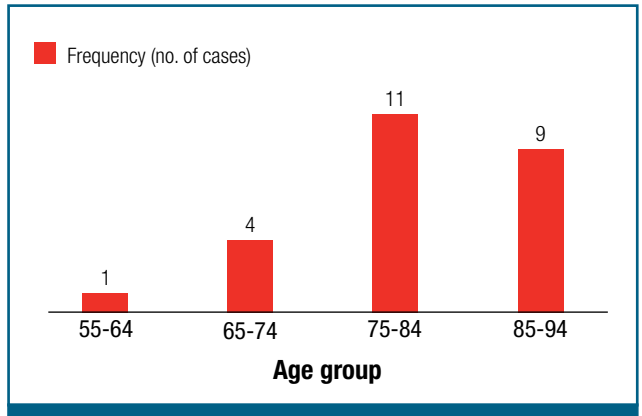
There was a mean annual incidence of CDAD of 8.55 out of 1000 hospitalizations, which is higher than that found in a Portuguese study (3.71 out of 10,000 hospitalizations).[6] It is also higher than that described in European epidemiological studies that describe annual incidences of 0.3 to 1.9 out of 10,000 hospitalizations.[9,10] However, 94% of patients were aged over 65 years, and incidences of 8.67 out of 1000 hospitalizations have been described in patients aged over 64 years, a figure that is close to that detected in our study.[4]

The incidence of CDAD increased from 2004 to 2009 (4.35/1000 vs 21.63/1000), particularly from 2008 to 2009 (8.97/1000 vs 21.63/1000), due to the higher number of cases of nosocomial infection (94% of cases). In various works, the percentage of nosocomial CDAD was 80%[9] and in a Portuguese study, the infection was acquired in the outpatients clinic in 45% of patients.[1] In our work, 22.89% of infections were acquired in the community, but the majority (77.1%) were developed during hospitalization.



Distribution by number of days from start of antibiotic to the appearance of diarrhea.

FIG. 3



Distribution of deaths by age group.

FIG. 4

This increase over the years has been described in various studies, but the cause is not yet known.[4,6] One possible explanation is the growing use of antibiotics.[2,7,11] Olson et al report that 96% of patients with symptomatic infection had received antibiotics in the 14 days prior to the appearance of diarrhea, and all had received antibiotics up to 3 months previously.[11] In the present study too, all the patients had received antibiotics up to 3 months prior to the appearance of diarrhea, 41% in the 14 days before, and 78% in the month before.

Multiple antibiotherapy and the length of time the antibiotherapy is administered, have been described as risk factors in the development of CDAD.[12] In the Portuguese article of Vieira et al., 33% of patients had been previously medicated with an antibiotic, 52% with more than one, and 26% with three or more.[6] In our study, 36% of patients had been previously medicated with an antibiotics, 64% with more than one antibiotic, and 45% with three or more antibiotics. However, there was no statistically significant difference in the number of antibiotics used, or in the number of days from the start of antibiotics to the development of CDAD, from 2004 to 2009. But it was seen that the number of antibiotics associated with the development of CDAD is smaller (mean of 2.43 vs 3.09), in patients who had been hospitalized in the previous year.

In females aged over 65 years, the number of comorbidities and the longer hospitalization time are other risk factors described.[4,6,13] In fact, it was more frequent among females than males (6.16/1000 vs 11.64/1000), the number of antibiotics used, the mean number of days from the start of antibiotics to the appearance of the disease being higher in men, which may partially explain the lower incidence. However, in our study, no statistically significant differences were found in relation to age, number of comorbidities, or total hospitalization days, between 2004 and 2009.

The prevention of infection by CD is an important point for minimizing transmission, and it is emphasized that the alcohol solution used to disinfect the hands is not effective in eradicating the CD spores. The hands should therefore be washed with water and a neutral soap.[14,15,16,17] In 2008, alcohol solution started to be used as a disinfection method in the wards where this study was carried out, coinciding with an exponential increase in the incidence of CDAD. Thus, it is admitted that decreasing the use of soap and water for washing the hands had some influence on the increased transmission within hospitals.

In relation to the diagnostic method, in 80 patients (96%), toxin tests for CD were positive. In fact, the standard test to establish the diagnosis is the assay to detect toxin A and toxin B, the most common being the immunoenzyme assay.[1] However, the sensitivity of this method is only 60% to 80%, and repeated tests are often necessary. When the clinical aspects are suggestive of disease, even with negative toxin tests, the patient should begin empirical treatment.[1]

The standard treatment consists of suspending

the antibiotic involved, where possible, instituting support care, and avoiding antiperistaltic agents. Patients with less severe infection generally respond to these measures.[1] In this work, 73 patients (88%) were medicated with metronidazol, 1 with vancomycin and 6 (7%) initially with metronidazol and then with vancomycin. Three patients who were not medicated died.

The mortality rate attributed to the disease is 16%, and the majority of lethal cases occur in patients aged over 65 years.1 In this study, 25 patients (30%) died, the mortality rate being higher than the overall hospitalization rate (30% vs. 13%). It was probably advanced age that was related to the greater severity, and consequently, the high mortality in our cases.

CONCLUSIONS

A mean annual incidence of CDAD of 8.66 out of 1000 hospitalizations was found, higher than that found in other studies,[6,9,10] but according to the description for the age range considered.[4]

The incidence of CDAD increased almost six-fold between 2004 and 2009, due to the higher number of cases of nosocomial infection (94% of cases). The majority of patients (77.11%) developed the disease during hospitalization. In the patients who were hospitalized in the previous year, the number of antibiotics used prior to the development of the disease was smaller than for those who were not hospitalized.

Although the disease was frequent among females, there was no difference in mortality between genders. In males, a higher number of antibiotics were used, and more days from the start of antibiotics to the appearance of the symptoms.

All the patients had received antibiotics previously. The number of comorbidities, antibiotics used, days from the start of antibiotherapy to the appearance of symptoms, days of hospitalization, and place of origin of the patients does not appear to explain the increased incidence and severity. The mortality was higher than the overall incidence of the Service (30% vs. 13%). It was probably advanced age that was related to the greater severity, and consequently, the high mortality in our cases.

Replacing the use of soap and water to wash the hands, with alcohol solutions for hospital disinfection may have contributed to the increased incidence from 2008 to 2009. ■

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