

# *Clostridium difficile* colitis in an Internal Medicine Ward

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### Abstract

*Clostridium difficile* colitis is increasingly affecting morbidity and mortality in hospitalized patients. Epidemiological and clinical features of all *Clostridium difficile* colitis cases diagnosed in an Internal Medicine ward, over a certain period of time, were studied retrospectively, as a contribution to improving the treatment of this infection in Portugal.

The incidence of this disease is now close to its lowest known levels since the beginning of this century. The widespread use of broad-spectrum antibiotics appears to be a decisive risk

factor, among others. Despite several outbreaks worldwide caused by antibiotic-resistant strains, the results of treatment with metronidazole and/or vancomycin seem favorable, though the initial choice of treatment could. The level of complications and recurrences found in this study were close to those recently reported in the literature.

Key words: *Clostridium difficile* colitis; antibiotics; toxins; pseudomembranous colitis; metronidazole; vancomycin.

### INTRODUCTION

Infection by *Clostridium difficile* is the leading cause of antibiotic-associated colitis, and is currently one of the most common hospital-acquired infections, with significant morbidity and mortality, particularly among elderly hospitalized patients.<sup>1</sup>

In the last decade, with the emergence of more virulent strains, a higher incidence, greater severity, greater refractoriness to the therapy, and higher likelihood of recurrence of *Clostridium difficile* colitis (CDC) have been recorded worldwide.<sup>2</sup>

The incidence in hospitals increased from 3-12 per 1000 hospitalized patients in the period from 1991 to 2002, to 25-43 per 1000 hospitalized patients in 2004.<sup>3</sup> Its incidence in the community has also increased, currently corresponding to up to 36% of all cases.<sup>4</sup>

The main risk factor for CDC is the recent use of antibiotics, particularly clindamycin, fluoroquinolones, penicillins, and broad-spectrum cephalosporins.<sup>5,6</sup> Other risk factors are recent hospitalization or institutionalization, age over 65 years, and serious comorbidities.<sup>2</sup> The role of gastric acid-suppressive drugs is still not clear.<sup>6,7</sup>

The diagnosis of *Clostridium difficile* infection can be confirmed by the detection of bacterial toxins in the stools, most often through the enzyme-linked immunosorbent assay (ELISA), the identification of the microorganism in the stools, even through anaerobic culture, or endoscopic visualization of lesions suggestive of pseudomembranous colitis.<sup>8</sup>

Patients with clinical manifestations suggestive of CDC and confirmed laboratory and/or endoscopic diagnosis should begin antibiotic treatment. Currently, oral or intravenous metronidazole and/or oral vancomycin are indicated, depending on the severity of the disease.<sup>9</sup> Empirical therapy is valid when there is a strong clinical suspicion, but asymptomatic individuals should not be treated.<sup>1</sup>

Patients with CDC should receive precautionary contact measures. Their carers and visitors should also adopt hygiene measures, such as washing the hands with soap and water, in order to contain the spread of bacterial spores and prevent infecting other people.<sup>10</sup>

The complications of CDC can be fatal. Fulminant colitis occurs in approximately 3% of cases.<sup>11</sup> Patients with signs of systemic toxicity (e.g.: leukocytosis above 20000 cells/ $\mu$ L, serum lactic acid from 2.2 to 4.9 mmol/L, increasing serum creatinine) and ileus associated with colonic dilation above 7cm at its widest point (toxic megacolon), or manifestations of perforation of hollow viscus, should be evaluated by the surgical team, who will consider colectomy.<sup>8,12</sup>

Recurrence of the disease has increased, and it has

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been observed in 10% to 25% of cases.<sup>13,14</sup> Risk factors include the disease with criteria of severity, prolonged hospitalization, prolonged antibiotic treatment, age over 65 years, serious comorbidities and diverticular disease of the colon.<sup>15</sup> Thus, new therapies such as bacterial antitoxins and monoclonal antibodies have been tested, apparently with favorable results.<sup>16</sup>

The present study documents the epidemiological and clinical characteristics of cases of CDC that occurred in a ward of an Internal Medicine department during a particular period, as a contribution to the implementation of more efficient strategies for mitigating the disease in our country, in accordance with the guidelines of international reference entities.

## METHODOLOGY

A retrospective study was conducted including all the patients diagnosed with CDC at the ward over a total period of 22 months between the 1<sup>st</sup> January 2008 and the 31<sup>st</sup> October 2009.

Data were collected using the patients' medical records, which were submitted to statistical analysis using the computer program SPSS®.

## RESULTS

Eighteen cases of CDC were accounted for; information was obtained for only 14 of these cases, out of a total of 5093 patients discharged from the ward over the period analyzed. The incidence of the disease was about 4 cases per 1000 hospitalized patients.

More than half (10) of the patients were female. The average age was 73 years (minimum 52 and maximum 91 years), but 29% (4) of the patients were aged under 65 years.

At the time of admission, 86% (12) of the patients had a diagnosis of chronic disease involving two or more organs or systems, with two cases of immunosuppression, both associated with carcinoma.

64% (9) of the patients had been hospitalized in the last month. On admission, 29% (4) of the patients were living in a nursing home.

Three months prior to admission, 79% (11) of the patients had received at least one antibiotic; 64% (7) had received broad-spectrum penicillins; 36% (4) had received broad-spectrum cephalosporins; and 27% (3) had received fluoroquinolones.

21% (3) of the patients were from the community, had not been hospitalized in the previous month, and had not received antibiotic treatment in the previous

three months.

The average hospitalization time was 41 days (minimum of 6 days and maximum of 119 days). During this period, at least one non-gastrointestinal infection was observed in 93% (13) of the patients. In addition to the antibiotics indicated for the treatment of CDC, 71% (10) of the patients were treated with other antibiotics - on average, two additional antibiotics for each patient.

*Clostridium difficile* was identified as the etiological agent of diarrhoea in half (7) of the cases, by bacterial toxins alone in 43% (3), by endoscopy alone in 28.5% (2), and by a combination of bacterial toxins and endoscopy in 28.5% (2). None of the culture analyses isolated the bacteria.

All the patients were treated with metronidazole and/or vancomycin: 43% (6) with combined therapy, 36% (5) with metronidazole alone and 21% (3) with vancomycin alone. The average duration of the antibiotic treatment was 14 days (minimum of 3 and maximum of 28 days).

During hospitalization, 79% (11) of the patients received gastric acid-suppression therapy.

Leukocytosis analysis was performed in 64% (9) of the patients when the targeted therapy for CDC began; the values were above 20000 cells/ $\mu$ L for three of the patients. A case of complicated colitis was observed in a patient aged over 65 who had multiple serious comorbidities. This patient was hospitalized for less than a month and was then treated with broad-spectrum penicillin. The patient was dehydrated and hypotensive, but improved with aminergic support, had prerenal oliguric acute renal failure which reversed after haemodialysis, and high anion gap metabolic acidosis requiring bicarbonate; the patient, however, had no leukocytosis.

Three patients died for causes that were not attributable to *Clostridium difficile* (two patients had septic shock to methicillin-resistant *Staphylococcus aureus*, the third patient had septic shock to non-isolated agent).

The patient with complicated colitis was re-admitted one month after discharge, due to continued diarrhoea and positive bacterial toxins; endoscopy revealed pseudomembranous colitis lesions, corresponding to a possible case of recurrence of the disease.

## DISCUSSION

The incidence of CDC observed is consistent with

the lowest rates reported in various studies from the beginning of this century, even before several outbreaks of the disease occurred in various parts of the world, attributable to the emergence of new, more virulent strains, such as ribotype 027, which led to a significant increase in the incidence of this disease.<sup>3</sup>

Almost three quarters of the patients were elderly, and most of them had comorbidities affecting various organs or systems, known risk factors for the disease.<sup>2</sup>

Most patients had a history of hospitalization in the previous month and treatment with antibiotics in the previous three months, two of the most relevant risk factors for CDC.<sup>2</sup> The most commonly used classes of antibiotics were among those most commonly associated with the disease.<sup>5,6</sup>

More than a quarter of the patients lived in nursing homes, a condition also associated with CDC.<sup>2</sup> But about one fifth of the patients lived in the community, and had no history of recent hospitalization or antibiotic therapy, a fact that is supported by several studies that demonstrate an increase in community-acquired incidence of *Clostridium difficile* infection.<sup>4</sup>

The average hospitalization time for patients with CDC was longer than the hospitalization time for all causes (11 days), probably due to the characteristics of the predominant age group, and in particular, to the comorbidities associated with this age group.

Most of the patients had some other non-gastrointestinal infection during hospitalization, and were treated with two antibiotics, on average, that were not metronidazole or vancomycin. This may suggest some weakness in the criteria for antibiotic prescription, even in a hospital environment. This fact, and the prolonged average hospitalization time, may be affecting the current incidence and severity of CDC.<sup>5,6,15</sup>

More than three quarters of the patients were treated with gastric acid-suppressant drugs, a risk factor for the disease that still remains controversial.<sup>6,7</sup>

A confirmed diagnosis of CDC was only possible in half of the cases, especially by the ELISA and endoscopy methods, which have greater specificity than anaerobic culture.<sup>12</sup> The introduction of new, more specific methods of diagnosis is still to be considered, such as cytotoxicity assay or polymerase chain reaction.<sup>8</sup>

Treatment of the initial episode of CDC with metronidazole or, alternatively, with vancomycin is recommended.<sup>1,9</sup> Nevertheless, combined therapy with metronidazole and vancomycin was the most widely

used therapeutic option, although only one case of complicated colitis had occurred.<sup>12</sup> In one quarter of the cases, monotherapy with vancomycin was the first therapeutic option, and is increasingly recommended for severe or refractory disease.<sup>1,9</sup>

The average duration of treatment was about 14 days, as suggested by the literature.<sup>1,9</sup>

Only one case of complicated colitis was observed, in a patient with multiple risk factors for CDC.<sup>2,5,6</sup> In this patient, the disease apparently recurred, although up to half of the cases of recurrence correspond, in fact, to cases of re-infection.<sup>14,15</sup> The recurrence of the disease observed is similar to the lowest rates reported in various studies.<sup>13,14</sup>

The main limitations of this trial were the small number of cases analyzed, and the lack of similar series published in our country, which will prevent, in the short term, a better characterization of the national reality of CDC and hospital-acquired infections.

## CONCLUSION

The incidence of CDC has increased within and outside hospitals and nursing homes. The indiscriminate use of antibiotics, especially broad-spectrum antibiotics, is a decisive risk factor for the disease.

A confirmed diagnosis of CDC is not always possible, but this should not delay the start of empirical therapy when there is strong clinical suspicion. Although it is reported in the literature that bacterial strains already resistant to certain antibiotics, such as ribotype 027, are responsible for several outbreaks of the disease, the results of therapy with metronidazole and/or vancomycin still appear to be favorable.

Complicated CDC, though rare, should be diagnosed in a timely manner, and treatment should take into account the indications for surgical intervention.

The precautionary contact measures adopted for each patient are essential to prevent further transmission of the *Clostridium difficile* infection.

Increasing attention should be drawn to the recurrence of the disease, focusing on the limitation of the risk factors associated with it, and optimization of the therapy, including the most recent drugs. ■

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