60 ANOS ARQUIVOS DE GASTROENTEROLOGIA

ORIGINAL ARTICLE

doi.org/10.1590/S0004-2803.230302023-36

Clinical outcome and severity of *Clostridioides (Clostridium) difficile* infection at a tertiary referral hospital in Brazil

Fernando Antônio Castro **CARVALHO**[1], Rodrigo Otávio Silveira **SILVA**[2], Bárbara Moreira Ribeiro Trindade dos **SANTOS**[1], Amanda Nádia **DINIZ**[2] and Eduardo Garcia **VILELA**[2]

[1] Hospital de Clínicas da Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brasil.
[2] Faculdade de Medicina da Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brasil.

HIGLIGHTS

- The outcomes of CDI were evaluated in 65 patients with CDI in a Brazilian tertiary hospital.
- Lack of clinical improvement after treatment and the severity score (ATLAS) increased the risk of death.
- The use of multiple antimicrobial agents was associated with longer hospital stays.
- Patients with high Charlson comorbidity index (>7) were more likely to recur.

Received: 28 February 2023
Accepted: 21 June 2023

Declared conflict of interest of all authors: none
Disclosure of funding: this work was supported by funds from Coordination for the Improvement of Higher Education Personnel (CAPES – Prêmio CAPES 2015 - 0774/2017), National Council for Scientific and Technological Development (CNPq - 406402/2018-3), Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG - APQ-00524-17) and Pró-Reitoria de Pesquisa da Universidade Federal de Minas Gerais (PRPq/UFMG).
Corresponding author: Fernando Antônio Castro Carvalho. E-mail: fernandoaccarvalho@hotmail.com

ABSTRACT – Background – *Clostridioides difficile* infection (CDI) is a potentially severe disease that can present with refractoriness, recurrence, and evolution to death. In Brazil, the epidemiology of CDI seems to differ from that of the United States and most European countries, with only one ribotype (RT) 027-related case and a high prevalence of RT106. **Objective** – The aim of this study was to evaluate the outcomes of CDI and its possible association with ribotypes at a university hospital in Brazil. **Methods** – A total of 65 patients with CDI were included and stool samples were submitted to A/B toxin detection and toxigenic culture, and toxigenic isolates (n=44) were also PCR ribotyped. **Results –** Patients' median age was 59 (20–87) years and there were 16 (24.6%) deaths. The median Charlson comorbidity index (CCI) was 4 (0–15) and 16.9% of the patients had CCI ≥8. The ATLAS score and non-improvement of diarrhea were related to higher mortality. A longer length of hospitalization was related to the enteral nutrition and use of multiple antibiotics. The period between CDI diagnosis and hospital discharge was longer in those who received new antibiotics after diagnosis, multiple antibiotics, and required intensive care treatment. Recurrence was associated with CCI >7. Twenty ribotypes were identified and RT106 was the most frequently detected strain (43.2%). No relationship was observed between the ribotypes and outcomes. CDI was present in patients with more comorbidities. **Conclusion** – Risk factors for higher mortality, longer hospital stay and recurrence were identified. A diversity of ribotypes was observed and *C. difficile* strains were not related to the outcomes.

Keywords – Pseudomembranous colitis; antibiotic associated diarrhea; ATLAS.

INTRODUCTION

Over the last few decades, *Clostridioides (Clostridium) difficile* infection (CDI) has been recognized as nosocomial pathogen of great epidemiological importance because it is the main bacteria causing diarrhea associated with antibiotic therapy, and is related to increasing morbidity and mortality in several countries since the 2000s[1]. The most relevant factor for altering the epidemiological behavior of the disease and evolutionary profile of the infection is the spread of hypervirulent strains, especially the ribotype (RT) 027 in North America and Europe[2,3]. However, recent epidemiological studies have found a reduction in the number of cases of RT027-related infections[4,5,6]. Meanwhile, an increase in cases related to RT014/20 and RT106 has been reported in several countries[7].

In Brazil, there are no robust data to assess the behavior of CDI in a more precise way[8]. Little is known about the severity profile of the infection, including complications such as the need for colectomy, clinical refractoriness to treatment, recurrence, and mortality. Only in 2018, Pires et al. first detected RT027, after which, no more reports were registered[9]. Thus, the present study aimed to describe the presentation and clinical evolution of CDI and evaluate the possible associations between these outcomes and the main circulating ribotypes at a university hospital in Brazil.

METHODS

Patients and study design

The study was conducted at the Clinical Hospital of the Federal University of Minas Gerais, a 400-bed quaternary care hospital in Belo Horizonte, Brazil, between November 2011 and December 2015, and between November 2017 and December 2019. Sixty-five patients of both sexes, aged >18 years, with diarrhea (three or more bowel movements with unformed stools per day) in the previous 48 h, after 72 h of hospitalization, were included retrospectively by medical records and after signing an informed consent term (FIGURE 1).

All patients were confirmed with CDI as recommended by the Infectious Diseases Society of America (IDSA), Society for Healthcare Epidemiology of America (SHEA), and European Society of Clinical Microbiology and Infectious Diseases (ESCMID)[10,11]. Stool samples were subjected to enzyme-linked immunosorbent assay (ELISA) analyses for detecting A/B toxins (*C. difficile* Tox A/B II - Techlab Inc., USA) and toxigenic culture protocol described previously[12]. Toxigenic *C. difficile* strains were submitted to PCR ribotyping as described by Janezic & Rupnik[13]. The study was approved by the Institutional Ethics Committee of the Federal University of Minas Gerais (CAAE: 13552719.3.0000.5149).

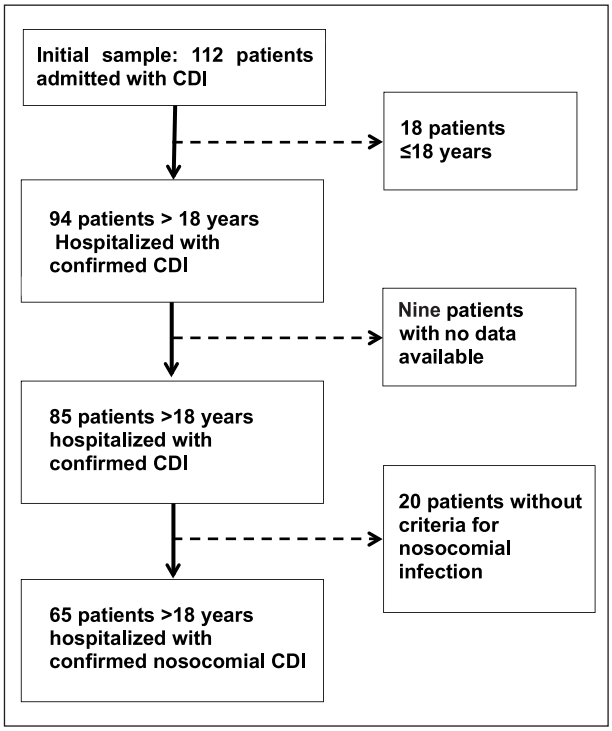

FIGURE 1. Diagram showing the sample universe, exclusions, losses and final number of participants for analysis.

Definitions

"Recurrence" was defined as a new diarrhea episode in a patient who presented with a new laboratorial confirmation of CDI, or a new episode of diarrhea in a patient who responded to specific treatment, even without laboratory confirmation, within 2–8 weeks after laboratory-based confirmation of CDI index case[10,14]. "Refractoriness" was defined as exchange of the initial treatment due to lack of clinical response, as assessed by the assisting team; while "response to treatment" was defined as improvement in stool consistency and reduction in diarrheal fre-

quency (<3 episodes in 24 h)[15]. "Death related to CDI" was defined as patients who died in the presence of active CDI and under treatment[10,14,15].

Demographics, clinical, and laboratory variables

We included data related to demographics (age and sex); clinical and laboratory variables that may be associated with severity, recurrence, and death; risk factors for infection; and variables related to treatment. The following clinical variables were included: date of onset of diarrhea, date of stool collection, body mass index (BMI), vital signs (mean arterial pressure, heart rate, and body temperature), date of diagnosis, reason for admission, comorbidities (diabetes mellitus, human immunodeficiency virus [HIV], inflammatory bowel disease [IBD], chronic kidney disease, cirrhosis, heart failure, coronary artery disease, previous stroke, and peripheral arterial disease), Charlson comorbidity index (CCI), organ transplant history, antibiotic use, classes and period of antibiotic use during hospitalization and in the 3 months prior to diagnosis, length of stay in the intensive care unit (ICU) and surgery during hospitalization, use of immunosuppressants or chemotherapy in the previous 3 months, use of corticosteroids during hospitalization, use of proton pump inhibitors (PPI) or histamine H2 receptor inhibitors during hospitalization, need for nutritional support via the enteral or parenteral route, date of discharge or death and cause of death, ATLAS severity score, and IDSA/SHEA severity criteria[10,16,17]. The following laboratory variables were included: C-reactive protein, total leukocytes, serum albumin, and creatinine at diagnosis. The following treatment-related variables were included: type of treatment administered (oral metronidazole, oral vancomycin, oral vancomycin plus intravenous metronidazole, and oral metronidazole followed by oral vancomycin), duration and response to treatment, duration in days for diarrhea to resolve, and need for a second treatment. Outcomes were defined as death during hospitalization, length of hospital stay (in patients who did not progress to death), recurrence, improvement of diarrhea within 5 days and need for a second treatment due to refractoriness. To reduce the interference of other factors related to this condition, the length of hospital stay was also evaluated after CDI diagnosis.

Statistical analysis

Categorical variables are presented as absolute and percentage values. Numerical variables were assessed for normality (Kolmogorov-Smirnov test) for data presentation. Continuous variables were analyzed using independent Student's *t*-test or Mann-Whitney U test according to the data distribution. The chi-square test or Fisher's exact test, when appropriate, was used to compare the categorical variables. Univariate analysis was performed to determine the factors associated with CDI outcomes. Variables with $P<0.2$ and biological plausibility, obtained using univariate analysis, were included in the logistic regression analysis. The adjustment of the logistic regression model was verified using the Hosmer-Lemeshow test. The Cox regression model was used to assess the length of hospital stay. The level of significance was set at 5%. The sensitivity, specificity, and accuracy of ATLAS scores were calculated for mortality. Data were analyzed using SPSS statistical software (version 23.0; SPSS Inc., Chicago, IL, USA).

RESULTS

The median age of the patients was 59 (20–87) years, and 32.3% were aged ≥65 years. The median length of hospital stay was 44 (10–150) days. Antibiotic (ATB) in the last 3 months was used in 64 (98.5%) patients. Only one patient did not receive antibiotic before CDI diagnosis, hospitalized for chemotherapy treatment for acute leukemia. Multiple courses of ATB (two or more) were used in 48 (73,8%) of patients and 44 were receiving ATB concomitant on CDI diagnosis. The most used classes of antibiotics were carbapenems (72,3%), cephalosporins (61,5%), glycopeptides (53,8%) and penicilins (46,2%). The main reasons for using antibiotics were pneumoniae (21,5%) and febrile neutropenia (20%). New ATB after CDI diagnosis were prescribed to 27 (41.5%) patients. The CCI, adjusted for age, was calculated for each patient and presented as a median of four (0–15). Eleven patients had CCI ≥8.

A total of 29 patients (44.6%) were diagnosed with cancer and 14 (21.5%) underwent transplantation. Most malignancies are onco-hematological diseases (FIGURE 2). Thirty-three (50.8%) patients have been receiving chemotherapy or immunosup-

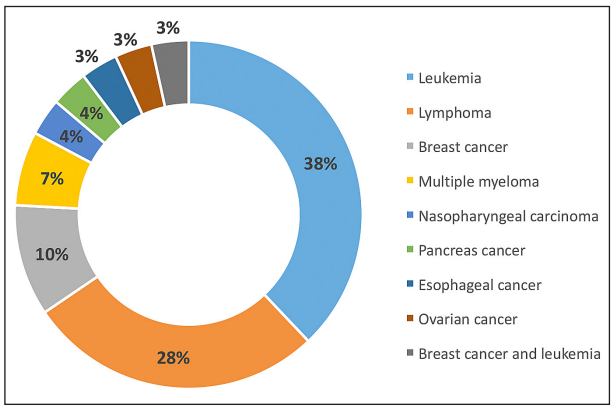

FIGURE 2. Distribution of malignancies types.

pressants in the last 3 months. Hospitalizations in the previous three months were reported in 25 out of 56 patients in whom this parameter could be evaluated (44.5%), and nutritional support was needed in 32 (49.2%) patients. More than 60% of the patients required intensive care center support (TABLE 1). Sixteen (24.6%) deaths occurred during hospitalization, of which, three (18.7%) had concomitant active CDI.

TABLE 1. Patients' profile with *Clostridioides (Clostridium) difficile* infection at a tertiary referral hospital in Brazil.

Patients' profile	n (%)
ATB in the last 3 months	64 (98.46)
Multiple courses of ATB* (two or more)	48 (73.8)
ATB concomitant on CDI* diagnosis	44 (67.7)
Hospitalization in ICU*	42 (64.6)
Chemotherapy or immunosuppressants in the last 3 months	33 (50.8)
Enteral nutritional support	32 (49.2)
Cancer patients	29 (44.6)
New ATB after CDI* diagnosis	27 (41.5)
Hospitalization in the last 3 months	25 (38.4)
Transplant patients	14 (21.5)
CCI* ≥8	11 (16.9)
Paralytic ileus	1 (0.01)

*ATB: antibiotic; CCI: Charlson comorbidity index; CDI: *Clostridioides difficile* infection; ICU: intensive care unit; n: number of patients.

Forty-two patients tested positive for A/B toxins and 59 were positive for toxigenic culture. Eight isolates (12.3%) were positive for the binary-toxin-encoding gene (*cdtB*). Forty-four isolates were ribotyped, and RT106 and RT014/020 were the most frequent strains, identified in 19 (43.2%) and 4 (9.1%) cases, respectively. High diversity of ribotypes were detected (FIGURE 3). Ribotypes 027 and 078 were not identified in the cohort. Of the seven patients who recurred, ribotyping was performed in four cases—two RT106 (one after the first infection by RT106 and the other by 104), one RT104, and one RT012.

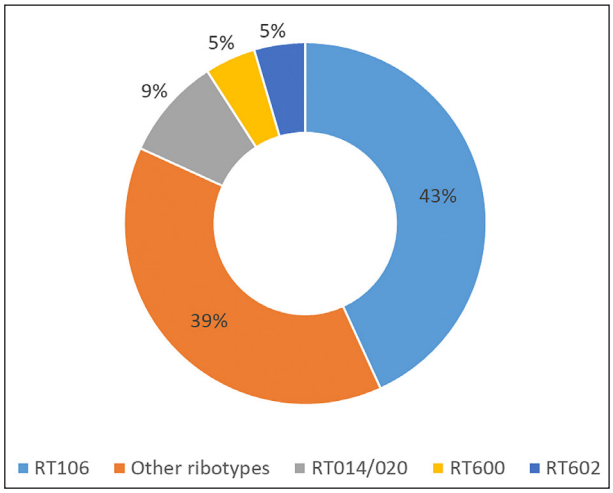

FIGURE 3. Distribution of ribotypes identified in patients with *Clostridioides difficile* infection between 2011 and 2019 at the Clinical Hospital of the Federal University of Minas Gerais.

Based on the IDSA/SHEA criteria, CDI was considered severe in 18 (28.1%) patients and fulminant in 4 (6.3%) patients, of which one had paralytic ileus. There was no difference between the medians of age between the non-severe group and the severe and fulminant group (TABLE 2). When the ATLAS score was applied, the median value was 4 (0–7). The median ATLAS score for patients who died was five and for those who survived was three. The receiver operating characteristic (ROC) curve analysis was performed to assess its accuracy in relation to the outcome of death; analysis pointed to a value of 0.678 for a score ≥5 and associated to a sensitivity and specificity of 45% and 81.9%, respectively. No relationship was observed between the clinical severity measured by the ATLAS classification and IDSA/SHEA score and the detection of A/B toxins or isolation of *cdtB*-positive strains.

TABLE 2. Relationship between severity by IDSA/SHEA criteria and age over 65 years.

	Non severe	Severe and fulminant	
<65 anos	31	12*	43
≥65 anos	11	10*	21
	42	22	64

**P*=0.101.

The clinical response rate to treatment was 84,6% (44/52). More than one-third of the sample (25 patients) received oral metronidazole, 12 (18.5%) received oral vancomycin, 10 (15.4%) received oral vancomycin plus intravenous metronidazole, and 5 (7%) received oral metronidazole followed by oral vancomycin. In 13 (20%) patients any antimicrobials were not administered for treatment and presented a self-limiting course after the discontinuation of the antimicrobial agents. Among the untreated group, two were not conducted as CDI due to the non-access of the assistant team to toxigenic culture result and the isolated ribotypes were three RT106, two RT014/020, one RT32 and one RT9. A total of 44 (84.6%) of the 52 treated patients showed a clinical response to treatment. There was no need for colectomy.

Multivariate analysis was performed to assess death outcome, length of hospital stay in patients who survived, length of hospital stay after diagnosis of CDI in patients who survived, recurrence, improvement of diarrhea within 5 days and need for a second treatment due to refractoriness. The results were summarized in TABLE 3. Death was related to the ATLAS score (*P*=0.021; OD: 1.76, CI: 1.08–2.86) and non-improvement of diarrhea (*P*=0.002; OD: 1.08, CI: 1.008–1.747). The increase in hospital stay was related to enteral nutrition (*P*=0.001; OD: 1.66, CI: 1.36–1.82) and multiple courses of antibiotics (*P*=0.003; OD: 1.64; CI: 1.29–1.82); and, during the period after diagnosis, new antibiotics administered after diagnosis (*P*=0.001; OD 1.75. CI: 1.48–1.88), multiple courses of antibiotics (*P*=0.02; OD: 1.58, CI: 1.13–1.80), and admission to the ICU (*P*=0.01; OD: 1.57, CI: 1.18–1.78) were associated to lengthy of hospital stay. Recurrence increased in patients with a CCI >7 (*P*=0.02; OD: 24.52; CI: 1.67–360.22). No variable was present in the final multivariate model for improvement of diarrhea within 5 days and refractoriness to initial treatment.

DISCUSSION

C. difficile is the most frequent cause of antibiotic-associated diarrhea and a nosocomial pathogen of great importance worldwide[1]. Studies in Brazil have indicated that the epidemiology of the disease differs from that in most of the other countries, with a high diversity of circulating ribotypes and a marked absence of cases caused by classic epidemic ribotypes, including RT027 and RT078[8,18,19]. However, the degree of severity is not known. There are very few studies on the outcomes of CDI in Brazilian hospitals.

The clinical-epidemiological data obtained in the present study revealed that a majority of the patients were severely ill; a majority needed intensive care support, approximately 50% had cancer, and >40% were previously hospitalized. This finding corroborates the fact that CDI occurs more frequently in patients with more severe and complex comorbidities, who require longer hospital stays, and who are more exposed to antimicrobial agents[10,20]. Previous studies also suggest that patients with hematological cancer have a high incidence of CDI, ranging from 6% to 33%[21,22]. In the present study, in the group of patients with cancer, 75.8% (22 patients) had hematological cancers.

TABLE 3. Results of the final models of logistic regression analysis and Cox regression of the clinical outcome of patietns with *Clostridioides (Clostridium) difficile* infection at a tertiary referral hospital in Brazil.

Outcomes	Variable	*P* value	Odds ratio	Confidence interval 95%
Death during hospitalization	ATLAS score*	0.021	1.76	1.08–2.86
	Non improvement of diarrhea	0.002	1.08	1.008–1.747
Length of hospital stay in patients who survived	Multiple courses of ATB*	0.003	1.64	1.29–1.82
	Enteral nutrition	0.001	1.66	1.36–1.82
Length of hospital stay after the diagnosis of ICD in patients who survived	Multiple courses of ATB	0.02	1.58	1.13–1.80
	New ATB after diagnosis	0.001	1.75	1.48–1.88
	Admission to ICU*	0.01	1.57	1.18–1.78
Recurrence	CCI* >7	0.02	24.52	1.67–360.22

*ATLAS: severity score of *C. difficile* infection based on age, treatment with systemic antibiotics, temperature, total leucocyte count, serum albumin and serum creatinine. ATB: antibiotic; ICU: intensive care unit; CCI: Charlson's comorbidity index.

Interestingly, almost one-third of the patients were characterized as having severe colitis, according to the IDSA/SHEA criteria, however it is important to emphasize that these criteria do not perform well in patients with underlying hematological malignancies or renal insufficiency, since it takes account total leukocytes count and creatinine level[23,24]. In the present study, 15 (23.1%) patients had chronic kidney disease and 22 (33.8%) had onco-hematological diseases (TABLE 4).

The number of deaths related to CDI (18.8% of total deaths) was also significant. CDI has been associated with increased mortality in hospitalized patients, particularly in the first 30 days after infection[25]. A prospective study conducted in Austria suggested that hospitalized patients with CDI had a 2.74-times higher risk of death during hospitalization than other patients, regardless of age or severity of comorbidities[26]. Moreover, in the present study, the risk factors related to death were the ATLAS score and lack of clinical improvement in colitis (diarrhea) caused by *C. difficile*. Notably, the risk of death increased by 76% for each extra point in the ATLAS severity score in the present study. Both variables (ATLAS score and lack of clinical improvement in colitis) are intrinsically related to the severity of CDI and reinforces the concept of this condition as an important hospital complication, with implications for patient prognosis.

The median ATLAS score of patients who died was five, and those who survived was three. Interestingly, once the roc curve has been performed, the sensitivity of ATLAS with a score ≥5 for mortality was low (45%), but it had a specificity of 81.9%, leading to an accuracy of 0.678. A previous cohort study that assessed the ability of the ATLAS score to predict mortality indicated that patients with a median 6 score had a higher mortality rate than patients with a median 5[16]. Another prospective study suggested that patients with ATLAS scores between 5 and 7 had a higher probability of colectomy and those with score ≥8 had higher probability of death[27]. The present study, together with previously published literature, suggests that the ATLAS score can be a useful and practical tool to predict outcome in CDI. On the other hand, the median ATLAS score in patients was four, and predicted a clinical response rate of 84.6%, similar to 81.1% predicted in earlier study[17].

Moreover, no improvement in diarrhea was associated with an 8% increase in mortality in the present study. A previous study of 207 patients treated for *C. difficile* colitis demonstrated a mortality rate of 33% in patients who failed to respond to therapy and 21% in those who were cured ($P<0.05$), corroborating with the results of the present study[28]. The detection of A/B toxins in fecal samples was not associated with a negative outcome or increased occurrence of complications; this result is in contrast to those of previous studies, including that of a recent study at another Brazilian hospital[29,30,31].

The use of multiple antibiotic courses and the need for enteral nutrition increased the length of the hospital stay by 64% and 66%, respectively. When considering the length of hospital stay after the diagnosis of CDI, the use of new antimicrobial agents for other infectious foci after diagnosis of CDI, use of multiple antibiotic courses, and need for intensive care increased the length of hospital stay by 75%, 58% and 57%. Notably, the independent variables associated with a longer hospital stay were events present in patients with more severe clinical evolution and those with more infectious complications due to other causes during hospitalization. The use of antimicrobial agents appears to be the main predisposing factor for CDI; and, multiple courses of antibiotics during hospitalization are related to a longer hospital stay in these patients, that reinforces the need for rational use of antibiotics and the

TABLE 4. Relatioship between comorbidities and severity by IDSA/SHEA criteria and mortality.

	Non severity	Severity and fulminant		Death	
CKD*	2	13	$P<0.001$	6	$P=0.11$
Cardiovascular and pulmonary disease	14	12	$P=0.085$	7	$P=0.53$
DM*	8	5	$P=0.48$	3	$P=0.60$
Mieloproliferative disease	16	5	$P=0.17$	6	$P=0.47$

*CKD: chronic kidney disease; DM: diabetes mellitus.

importance of control and prevention of nosocomial infections, as suggested previously[6,32-34]. A recent meta-analysis suggested that reducing the duration of antimicrobial use led to decrease in hospital stay by 1.12 days without increasing the mortality rates[35]. Considering the pathophysiological rationale for the deleterious effects of antimicrobial agents on the intestinal microbiota, combined with the evidence of longer hospital stays and their associated complications and costs, the introduction of new antimicrobial agents must be accurate for this population[32,35-37].

The 84.6% (44/52) clinical response rate to treatment was similar to 85% cure rate reported by a recent Brazilian study[38]. Interestingly, treatment with oral metronidazole-alone was administered in 74% of the cases in this study; whereas, it was administered in only 56.8% (25/44) of the patients in the present study. A total of 7 (14%) cases of recurrence were identified, similar to those in two previous Brazilian studies[29,38], and in previous studies from other countries[39,40]. It is important to remember that recurrence is also associated with an increased mortality[41]. In the present study, the only risk factor related to recurrence identified through logistic regression was CCI >7 that failed to reflect the presence of more severe comorbidities and was not related to higher mortality in the context of CDI, as opposed to that identified in a previous study[42]. CCI >7 increased the chance of recurrence by 23.52-times. In a previous study conducted at the same center, CCI >7 was associated with a risk of CDI in patients with nosocomial diarrhea associated with antibiotics by 4.74-times[43].

There were no associations between ribotypes and outcomes in the present study. The high frequency of the ribotypes 106 and 014/020 corroborates with previous studies on humans and animals in Brazil and in several other countries[8,19,44,45]. Approximately half of the ribotypes were characterized as RT106, but a great diversity of strains was observed in the sample, similar to that reported recently by Girão et al. at five Brazilian hospitals[19]. This high diversity differs from what happens at most European hospitals and reinforces the importance of surveillance of *C. difficile* strain in the environment to better understand the epidemiology of CDI in Brazil. In terms of clinical severity, previous studies indicated a lower occurrence of severe cases and lower mortality in patients infected with RT106 than in those infected with RT027[46,47,48].

CONCLUSION

CDI was present in patients with more severe diseases. A lack of clinical improvement after CDI treatment and the ATLAS score were related to a higher risk of death, and demonstrated the direct impact of this condition on the prognosis of patients during hospitalization. The need for enteral nutrition and the use of multiple antimicrobial agents were associated with longer hospital stays in patients who did not succumb. In the analysis of the length of hospital stay after diagnosis of CDI, the use of a new antibiotic for another purpose, the use of multiple courses of antimicrobial agents and admission to intensive care were related to increase in the period of hospitalization. The severity of comorbidities, characterized by CCI >7, was related to higher recurrence. No association between ribotypes, binary-toxin positive strains, or presence of A/B toxins and progression to severe forms of infection was detected.

ACKNOWLEDGMENTS

We thank CAPES, CNPq, FAPEMIG and PRPq/UFMG for all the financial support. ROSS has a fellowship from CNPq (Brazil).

Authors' contribution

All authors contributed to the study conception and design. Material preparation and samples collection were performed by Carvalho FAC, Silva ROS, Santos BMRT, Diniz AN, Vilela EG. Laboratory analysis were performed by Silva ROS and Diniz AN. The first draft of the manuscript was written by Carvalho FAC. All authors read and approved the final manuscript.

Orcid

Fernando AC Carvalho: 0000-0001-7006-7292.
Rodrigo O Silveira Silva: 0000-0003-0074-2488.
Bárbara MRT dos Santos: 0000-0002-7792-5920.
Amanda Nádia Diniz: 0000-0002-5287-5779.
Eduardo Garcia Vilela: 0000-0002-5443-7553.

Carvalho FAC, Silva ROS, Santos BMRT, Diniz AN, Vilela EG. Desfechos clínicos e gravidade da infecção pelo *Clostridioides (Clostridium) difficile* em um hospital terciário de referência no Brasil. Arq Gastroenterol. 2023;60(3):330-8.

RESUMO – Contexto – A infecção pelo *Clostridioides difficile* (ICD) é uma doença potencialmente grave que pode se apresentar com refratariedade, recidiva e evoluir para óbito. No Brasil, a epidemiologia da ICD parece diferir da dos Estados Unidos e da maioria dos países europeus, com apenas um caso relacionado ao ribotipo (RT) 027 e alta prevalência do RT106. **Objetivo –** Avaliar os desfechos da ICD e sua possível associação com ribotipos em um hospital universitário do Brasil. **Métodos –** Um total de 65 pacientes com ICD foram incluídos e amostras de fezes foram submetidas à detecção de toxina A/B e cultura toxigênica e as cepas toxigênicas isoladas (n=44) também foram ribotipadas por PCR. **Resultados** – A idade mediana dos pacientes foi de 59 (20–87) anos e houve 16 (24,6%) óbitos. A mediana do índice de comorbidade de Charlson (ICC) foi de 4 (0–15) e 16,9% dos pacientes apresentaram ICC ≥8. O escore ATLAS e a não melhora da diarreia foram relacionados a maior mortalidade. Maior tempo de internação esteve relacionado à nutrição enteral e ao uso de múltiplos antibióticos. O período entre o diagnóstico de ICD e a alta hospitalar foi maior naqueles que receberam novos antibióticos após o diagnóstico, múltiplos antibióticos e necessitaram de tratamento intensivo. A recorrência foi associada com ICC >7. Vinte ribotipos foram identificados e o RT106 foi a cepa mais frequentemente detectada (43,2%). Não foi observada relação entre os ribotipos e os desfechos. ICD esteve presente em pacientes com mais comorbidades. **Conclusão** – Foram identificados fatores de risco para maior mortalidade, maior tempo de internação e recorrência. Uma diversidade de ribotipos foi observada e cepas de *C. difficile* não foram relacionadas aos desfechos.

Palavras-chave – Colite pseudomembranosa; diarreia associada a antibioticoterapia; ATLAS.

REFERENCES

1. Bartlett JG. Clinical practice. Antibiotic-associated diarrhea. N Engl J Med. 2002;346:334-9.
2. Warny M, Pepin J, Fang A, Killgore G, Thompson A, Brazier J, et al. Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America and Europe. Lancet. 2005;366:1079-84.
3. McDonald LC, Killgore GE, Thompson A, Owens RC, Kazakova SV, Sambol SP, et al. An epidemic, toxin gene-variant strain of Clostridium difficile. N Engl J Med. 2005;353:2433-41.
4. Snydman DR, McDermott LA, Jenkins SG, Goldstein EJC, Patel R, Forbes BA, et al. Epidemiologic trends in Clostridioides difficile isolate ribotypes in United States from 2011 to 2016. Anaerobe. 2020;63:102185.
5. Wilcox MH, Shetty N, Fawley WN, Shemko M, Coen P, Birtles A, et al. Changing epidemiology of Clostridium difficile infection following the introduction of a national ribotyping-based surveillance scheme in England. Clin Infect Dis. 2012;55:1056-63.
6. Dingle KE, Didelot X, Quan TP, Eyre DW, Stoesser N, Golubchik T, et al. Effects of control interventions on Clostridium difficile infection in England: an observational study. Lancet Infect Dis. 2017;17:411-21.
7. Cheknis A, Johnson S, Chesnel L, Petrella L, Sambol S, Dale SE, et al. Molecular epidemiology of Clostridioides (Clostridium) difficile strains recovered from clinical trials in the US, Canada and Europe from 2006-2009 to 2012-2015. Anaerobe. 2018;53:38-42.
8. Trindade CNR, Domingues RMCP, Ferreira EO. The epidemiology of Clostridioides difficile infection in Brazil: A systematic review covering thirty years. Anaerobe. 2019;58:13-21.
9. Pires RN, Monteiro AA, Saldanha GZ, Falci DR, Caurio CFB, Sukiennik TCT, et al. Hypervirulent Clostridium difficile Strain Has Arrived in Brazil. Infect Control Hosp Epidemiol. 2018;3:371-3.
10. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66:987-94.
11. Crobach MJ, Planche T, Eckert C, Barbut F, Terveer EM, Dekkers OM, et al. European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for Clostridium difficile infection. Clin Microbiol Infect. 2016;22 (Suppl 4):S63-81.
12. Silva RO, Ribeiro MG, Palhares MS, Borges AS, Maranhão RP, Silva MX, et al. Detection of A/B toxin and isolation of Clostridium difficile and Clostridium perfringens from foals. Equine Vet J. 2013;45:671-5.
13. Janezic S, Rupnik M. Molecular typing methods for Clostridium difficile: pulsed-field gel electrophoresis and PCR ribotyping. Methods Mol Biol. 2010;646:55-65.
14. Prevention CfDCa. Multidrug-resistant organism and Clostridium difficile infections. 2020.
15. Debast SB, Bauer MP, Kuijper EJ, Diseases ESoCMaI. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect. 2014;20 (Suppl 2):1-26.
16. Chopra T, Miller M, Severson R, Marchaim D, Kate KS, Alangaden G. ATLAS - A bedside scoring system predicting mortality due to Clostridium difficile infection (CDI) in elderly hospitalised patients. 48th Annual meeting of the Infectious Diseases Society of America (IDSA). Vancouver, BC2010. p. 21-4.
17. Miller MA, Louie T, Mullane K, Weiss K, Lentnek A, Golan Y, et al. Derivation and validation of a simple clinical bedside score (ATLAS) for Clostridium difficile infection which predicts response to therapy. BMC Infect Dis. 2013;13:148.
18. Silva RO, Rupnik M, Diniz AN, Vilela EG, Lobato FC. Clostridium difficile ribotypes in humans and animals in Brazil. Mem Inst Oswaldo Cruz. 2015;110:1062-5.
19. Girão ES, de Melo Tavares B, Alves Dos Santos S, Gamarra GL, Rizek C, Martins RC, et al. Prevalence of Clostridioides difficile associated diarrhea in hospitalized patients in five Brazilian centers: A multicenter, prospective study. Anaerobe. 2020;66:102267.
20. Loo VG, Bourgault AM, Poirier L, Lamothe F, Michaud S, Turgeon N, et al. Host and pathogen factors for Clostridium difficile infection and colonization. N Engl J Med. 2011;365:1693-703.

21. Revolinski SL, Munoz-Price LS. Clostridium difficile in Immunocompromised Hosts: A Review of Epidemiology, Risk Factors, Treatment, and Prevention. Clin Infect Dis. 2019;68:2144-53.
22. Schuster MG, Cleveland AA, Dubberke ER, Kauffman CA, Avery RK, Husain S, et al. Infections in Hematopoietic Cell Transplant Recipients: Results From the Organ Transplant Infection Project, a Multicenter, Prospective, Cohort Study. Open Forum Infect Dis. 2017;4:ofx050.
23. Wang MS, Evans CT, Rodriguez T, Gerding DN, Johnson S. Clostridium difficile infection and limitations of markers for severity in patients with hematologic malignancy. Infect Control Hosp Epidemiol. 2013;34:127-32.
24. Shah DN, Bhatt NS, Welch JK, Koo HL, Garey KW. Defining acute renal dysfunction as a criterion for the severity of Clostridium difficile infection in patients with community-onset vs hospital-onset infection. J Hosp Infect. 2013;83:294-9.
25. Gao T, He B, Pan Y, Deng Q, Sun H, Liu X, et al. Association of Clostridium difficile infection in hospital mortality: A systematic review and meta-analysis. Am J Infect Control. 2015;43:1316-20.
26. Wenisch JM, Schmid D, Tucek G, Kuo HW, Allerberger F, Michl V, et al. A prospective cohort study on hospital mortality due to Clostridium difficile infection. Infection. 2012;40:479-84.
27. Hernández-García R, Garza-González E, Miller M, Arteaga-Muller G, Galván-de los Santos AM, Camacho-Ortiz A. Application of the ATLAS score for evaluating the severity of Clostridium difficile infection in teaching hospitals in Mexico. Braz J Infect Dis. 2015;19:399-402.
28. Musher DM, Aslam S, Logan N, Nallacheru S, Bhaila I, Borchert F, et al. Relatively poor outcome after treatment of Clostridium difficile colitis with metronidazole. Clin Infect Dis. 2005;40:1586-90.
29. Maestri AC, Raboni SM, Morales HMP, Ferrari LF, Tuon FFB, Losso A, et al. Multicenter study of the epidemiology of Clostridioides difficile infection and recurrence in southern Brazil. Anaerobe. 2020;64:102238.
30. Planche TD, Davies KA, Coen PG, Finney JM, Monahan IM, Morris KA, et al. Differences in outcome according to Clostridium difficile testing method: a prospective multicentre diagnostic validation study of C difficile infection. Lancet Infect Dis. 2013;13:936-45.
31. Longtin Y, Trottier S, Brochu G, Paquet-Bolduc B, Garenc C, Loungnarath V, et al. Impact of the type of diagnostic assay on Clostridium difficile infection and complication rates in a mandatory reporting program. Clin Infect Dis. 2013;56:67-73.
32. Campbell R, Dean B, Nathanson B, Haidar T, Strauss M, Thomas S. Length of stay and hospital costs among high-risk patients with hospital-origin Clostridium difficile-associated diarrhea. J Med Econ. 2013;16:440-8.
33. Brown KA, Fisman DN, Moineddin R, Daneman N. The magnitude and duration of Clostridium difficile infection risk associated with antibiotic therapy: a hospital cohort study. Plos One. 2014;9:e105454.
34. Leffler DA, Lamont JT. Clostridium difficile infection. N Engl J Med. 2015;372:1539-48.
35. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017;2:CD003543.
36. Vaughn VM, Flanders SA, Snyder A, Conlon A, Rogers MAM, Malani AN, et al. Excess Antibiotic Treatment Duration and Adverse Events in Patients Hospitalized With Pneumonia: A Multihospital Cohort Study. Ann Intern Med. 2019;171:153-63.
37. Theriot CM, Young VB. Microbial and metabolic interactions between the gastrointestinal tract and Clostridium difficile infection. Gut Microbes. 2014;5:86-95.
38. Girão ES, de Melo Tavares B, Dos Santos SA, Gamarra GL, Rizek C, Martins RC, et al. Predictive factors, outcomes, and molecular epidemiology of Clostridioides difficile diarrhea in Brazilian hospitals. Eur J Clin Microbiol Infect Dis. 2021;40:1821-32.
39. Fekety R, McFarland LV, Surawicz CM, Greenberg RN, Elmer GW, Mulligan ME. Recurrent Clostridium difficile diarrhea: characteristics of and risk factors for patients enrolled in a prospective, randomized, double-blinded trial. Clin Infect Dis. 1997;24:324-33.
40. McFarland LV, Surawicz CM, Rubin M, Fekety R, Elmer GW, Greenberg RN. Recurrent Clostridium difficile disease: epidemiology and clinical characteristics. Infect Control Hosp Epidemiol. 1999;20:43-50.
41. Olsen MA, Yan Y, Reske KA, Zilberberg MD, Dubberke ER. Recurrent Clostridium difficile infection is associated with increased mortality. Clin Microbiol Infect. 2015;21:164-70.
42. Baiomi AM, Abbas HM, Pirzada UM, Zaidi BM, Saturno DM, Nayudu SKM. Charlson Comorbidity index (CCI): An independent predictor of outcomes in Clostridium difficile infection. AJG. 2018;13:S1525.
43. Lopes Cançado GG, Silveira Silva RO, Rupnik M, Nader AP, Starling de Carvalho J, Miana de Mattos Paixão G, et al. Clinical epidemiology of Clostridium difficile infection among hospitalized patients with antibiotic-associated diarrhea in a university hospital of Brazil. Anaerobe. 2018;54:65-71.
44. Carlson TJ, Blasingame D, Gonzales-Luna AJ, Alnezary F, Garey KW. Clostridioides difficile ribotype 106: A systematic review of the antimicrobial susceptibility, genetics, and clinical outcomes of this common worldwide strain. Anaerobe. 2020;62:102142.
45. Davies KA, Ashwin H, Longshaw CM, Burns DA, Davis GL, Wilcox MH, et al. Diversity of Clostridium difficile PCR ribotypes in Europe: results from the European, multicentre, prospective, biannual, point-prevalence study of Clostridium difficile infection in hospitalised patients with diarrhoea (EUCLID), 2012 and 2013. Euro Surveill. 2016;21(29).
46. Sundram F, Guyot A, Carboo I, Green S, Lilaonitkul M, Scourfield A. Clostridium difficile ribotypes 027 and 106: clinical outcomes and risk factors. J Hosp Infect. 2009;72:111-8.
47. Kelly CP, LaMont JT. Clostridium difficile--more difficult than ever. N Engl J Med. 2008;359:1932-40.
48. Walker AS, Eyre DW, Wyllie DH, Dingle KE, Griffiths D, Shine B, et al. Relationship between bacterial strain type, host biomarkers, and mortality in Clostridium difficile infection. Clin Infect Dis. 2013;56:1589-600.