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Short Communication

# Incidence of healthcare-associated *Clostridioides difficile* infection in a quaternary referral university hospital in Brazil

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ABSTRACT

*Clostridioides difficile* infection (CDI) is an important cause of diarrhea in hospitals worldwide. The incidence of CDI in Latin America has not yet been standardized. To fill this gap, the present study performed a daily active surveillance, for three months, between April to July of 2021, at a quaternary referral university hospital in Brazil. The incidence density was 9.2 cases per 10,000 patient-days. Cases were associated mostly with ribotypes 014 and 106 (44% and 22%, respectively). Ribotype 027 was not identified. The findings strongly reinforce the need for broad epidemiological studies on the incidence of CDI in Brazilian hospitals to increase the understanding, prevention, and treatment of this infection.



*Clostridioides difficile* infection (CDI) is the leading cause of bacterial infectious diarrhea in healthcare. CDIs is responsible for significant morbidity and mortality, as well as high treatment-related costs worldwide [1]. In Europe, the incidence density of healthcare-associated CDI in tertiary hospitals in 2016 was 5.8 cases/10,000 patient-days [2]. In the United States, a systematic review followed by a meta-analysis of data from 2000 to 2019 estimated an incidence of 8.3 cases/10,000 patient-days [3]. In Canada, the rate evaluated between 2009 and 2015 peaked in 2011 at 6.7 cases/10,000 patient-days [4]. In most Latin American countries, including Brazil, there are no standardized data on the incidence of CDI(5-7). The few studies that have reported occurrence measures of CDI were not based on an active surveillance of cases during the minimal recommended interval [8,9], which is strongly recommended by guidelines [10–12].

To fill this knowledge gap, we performed a prospective and observational study at Hospital das Clínicas of the Federal University of Minas Gerais in Belo Horizonte, Brazil. It is a public university hospital and reference for medium- and high-complexity cases, with approximately 300 occupied beds for adult patients. During a three-month period between April and July 2021, daily active surveillance identified adult patients (>18 years) with acute diarrhea in order to test for CDI diagnosis. This study was based on a previously reported protocol [12] in order to identify incidence density of healthcare-associated CDI (HA-CDI) and the profile of patients with CDI. Incidence density was adopted as a specific measure of incidence, as it represents the instantaneous rate of the disease per unit of time. It considers in the denominator only patients at risk of becoming infected, that is, it excludes patients who are already infected.

Suspected cases were defined as adult patients who had at least three loose stools per day, starting on the third day of admission, or earlier if they were hospitalized for up to four weeks before the new admission [11,12]. CDI was defined according to the United States Centers for Disease Control and Prevention criteria, which include a

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**Table 1**
Demographic, clinical and laboratory variables of the patients with healthcare-associated *Clostridioides difficile* infection in a quaternary referral Brazilian university hospital.

| Variable | Total | Variable | Total |
|---|---|---|---|
| Gender | | Creatinine at diagnosis (mg/dL) | |
| Male – *n* (%) | 12 (57,1%) | Median [Min.–Máx.] | 0,8 [0,2–6,27] |
| **Age (years)** | | **Albumin (g/dL)**[a] | |
| Median [Mín.–Máx.] | 63 [19–80] | Median [Min.–Máx.] | 2,5 [1,9–3,9] |
| **Length of hospitalization (days)** | | **CRP (mg/L)**[b] | |
| Median [Min.–Max.] | 37 [4–214] | Median [Min.–Max.] | 101,7[6,5–405] |
| **Death** | | **GDH** | |
| Yes – *n* (%) | 3 (14,3%) | Positive – *n* (%) | 19 (90,5%) |
| **The Charlson Comorbidity Index** | | **Toxin (immunochromatography)** | |
| Mean (SD) | 4,1 (2,48) | Positive – *n* (%) | 15 (71,4%) |
| **Enteral or Parenteral Diet** | | **Toxigenic Culture**[c] | |
| Yes – *n* (%) | 8 (38,1%) | Positive – *n* (%) | 9 (52,9%) |
| **Shock** | | **Treatment** | |
| Yes – *n* (%) | 1 (4,8%) | No antibiotic – *n* (%) | 2 (9,5%) |
| **ICU in the last month** | | Metronidazole – *n* (%) | 2 (9,5%) |
| Yes – *n* (%) | 13 (61,9%) | Vancomycin – *n* (%) | 14 (66,7%) |
| **Using PPI** | | Both – *n* (%) | 3 (14,3%) |
| Yes – *n* (%) | 15 (71,4%) | Treatment duration (days) | |
| **Antibiotic in the last 3 months** | | Median [Min.–Max.] | 10 [0–20] |
| Yes – *n* (%) | 17 (81%) | **Need for second drug** | |
| **Number of antibiotics in the last 3 months** | | Yes – *n* (%) | 2 (9,5%) |
| Mean (SD) | 3,29 (2,72) | **Treatment Response** | |
| **Leukocytes ($10^3$ cells/$mm^3$)** | | ≤5 days – *n* (%) | 11 (52,4%) |
| Median [Min.–Max.] | 9,75 [0,54–30,86] | **Recurrence** | |
| | | Yes – *n* (%) | 4 (19%) |

[a] Albumin (g/dL): n = 19; Reference Value (RV): 3,5-5,0 g/dL.
[b] CPR (mg/L): n = 20; RV: < 5 mg/L.
[c] ELISA and toxigenic culture: n = 17.

positive test for A/B toxins and/or the presence of toxigenic *C. difficile* in unformed feces [11]. After obtaining informed consent from patients with diarrhea, stool samples were subjected to a rapid test to investigate glutamate dehydrogenase (GDH) (ECO Diagnóstica, Brazil) and *C. difficile* A/B toxins (R-Biopharm, Germany). In samples positive for GDH but negative for A/B toxins, diagnostic confirmation was made using toxigenic culture [13]. Toxigenic isolates (positive for toxin A-and/or toxin B-encoding genes) were subjected to PCR ribotyping [14].

During three months, 104 suspected cases of diarrhea were identified. CDI was confirmed in 21 patients (20.2%). The incidence density was 9.2 cases per 10,000 patient-days. A total of nine isolates were ribotyped: 002 (1 case), 014 (2 cases), 087 (1 case), 105 (1 case), and 106 (4 cases). The median age of patients with CDI was 63 years (range, 19–80) (Table 1). Over half (57.1%) were male. The mean Charlson Comorbidity Index was 4.10 (±2.49). The majority of patients (81%) used antimicrobials in the 3 months preceding the infection. The mean number of antimicrobials used was 3.29 (±2.72). Meropenem was the most frequently administered antimicrobial (47.6% of the cases). CDI was considered severe in 11 patients (52.4%) based on the criteria of the Infectious Disease Society of America [1]. Vancomycin was the initial treatment option in the majority of patients (66.7%). In one patient, metronidazole was replaced by vancomycin after treatment failure. In another patient, vancomycin was added to metronidazole due to a lack of satisfactory response on the fifth day of treatment. Metronidazole monotherapy was used in five cases. A response by the fifth day was observed in 11 patients (52.4%). Four patients (19%) experienced recurrence of infection. Three deaths occurred during hospitalization (14.3%). The deaths were not directly related to CDI.

This is the first study to evaluate the incidence density of HA-CDI in a Brazilian hospital using proper methodology to allow direct comparisons with reports from other countries. The incidence density was higher than that reported in most studies in Europe, United States, and Canada [2–4]. It was also higher than that in previous reports in Brazil [5,7–9] and in other Latin countries [6]. However, it is important to note that these previous studies did not report active surveillance of cases, which possibly led to underestimations of the incidence.

The patients with CDI in the present study were characterized by multiple comorbidities and recent use of several antimicrobials, similar to that previously reported in another study in the same institution [15]. The recurrence rate observed in the present study (14%) is close to that observed previous studies, including in Brazil [16–18]. Notably, five ribotypes were identified. This finding corroborates previous studies reporting a high diversity of toxigenic *C. difficile* in the same institution [13,15,19]. Interestingly, epidemic strains, including ribotypes 027 and 078, were not detected, which also corroborates other reports in Brazil. Ribotypes 106 and 014/020 that were both isolated in the present study appear to be the most frequent strains throughout the country [5,19,20].

The high incidence revealed in this study strongly reinforces the need for broad epidemiological studies on the incidence of CDI in Brazilian hospitals to better understand the whole picture. A description of the infection scenario can encourage the qualification of professionals involved in care, aiming for an assertive and rapid diagnosis, as well as adequate intervention, with the objective of effective infection control in the hospital environment. The present findings are also expected to become a tool for managers, given their eminently epidemiological character, despite being obtained in a single center.

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## Declaration of competing interest

There are no potential conflicts of interest involving the authors.

## Data availability

Data will be made available on request.

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