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Brief report

Epidemiology and risk factors for *Clostridium difficile* infection in critically ill patients in Spain: The PROCRID study

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ABSTRACT

Introduction: Our objectives were to describe the incidence, clinical characteristics, and risk factors for *Clostridium difficile* infection (CDI) in critically ill patients and to determine *C. difficile* PCR-ribotypes.
Methods: Prospective, observational study in 26 Spanish ICUs. Patients with diarrhea meeting ESCMID criteria for CDI were included. Molecular characterization of isolates was performed using PCR ribotyping.
Results: Of 4258 patients admitted to the ICUs, 190 (4.5%) developed diarrhea. Only 16 patients (8.4%) were diagnosed with CDI. Ribotype 078/126 (25.0%) was the most frequently identified. The mortality rate was similar in patients with ICD compared to patients with diarrhea not caused by *C. difficile* ($p = 0.115$). Chronic renal insufficiency was identified as the only factor independently associated with the development of CDI (OR 5.87, 95% CI 1.24–27.83; $p = 0.026$).
Conclusions: The incidence of CDI in Spanish ICUs is low. Only chronic renal insufficiency was observed to be a risk factor for CDI development.

Epidemiología y factores de riesgo para la infección por *Clostridium difficile* en pacientes críticos en España: Estudio PROCRID

Palabras clave:
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RESUMEN

Introducción: Pretendemos describir la incidencia, las características clínicas y los factores de riesgo de la infección por *Clostridium difficile* (ICD) en pacientes ingresados en unidades de cuidados intensivos, así como los ribotipos identificados.
Métodos: Estudio observacional, prospectivo, realizado en 26 unidades de cuidados intensivos de España. Se incluyeron pacientes con diarrea y criterios clínicos de la ESCMID por sospecha de ICD. La caracterización molecular se realizó mediante PCR.

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Resultados: De 4.258 pacientes ingresados, 190 (4,5%) presentaron diarrea; en 16 causada por ICD. El ribotipo más frecuentemente aislado fue 078/126 (25%). La tasa de mortalidad cruda fue similar en pacientes con ICD y en pacientes con diarrea no causada por *Clostridium difficile* (p = 0,115). La insuficiencia renal crónica fue identificada como factor independientemente asociado a desarrollo de ICD (OR: 5,87; IC 95%: 1,24-27,83; p = 0,026).
Conclusiones: La incidencia de ICD en las unidades de cuidados intensivos españolas es baja. La insuficiencia renal crónica es el único factor identificado para desarrollo de ICD.

Introduction

Clostridium difficile is a Gram-positive, spore-forming anaerobic bacillus and, the leading cause of healthcare-associated diarrhea.[1] *Clostridium difficile* infection (CDI) is a major public health concern in developed countries.[1] Some patients remain asymptomatic after exposure to *C. difficile*, while in others, disease symptoms can vary from mild diarrhea to fulminant colitis.[2] Clinicians sometimes fail to suspect CDI in patients with diarrhea, and many microbiology laboratories apply suboptimal diagnostic techniques.[3]

Another problem is the emergence of the "hypervirulent" 027 ribotype strain of *C. difficile* that may cause fulminant cases with high mortality rates.[4] To date, *C. difficile* 027 ribotype has only been identified in a limited number of episodes in Spain.[5] The vast majority of our knowledge about CDI in the critical care setting is derived from retrospective studies without a predefined diagnostic workup or from studies carried out during outbreaks.[6] The main objective of the study was to assess the incidence of CDI in critically ill patients with diarrhea fulfilling European Society of Clinical Microbiology and Infectious Diseases (ESCMID) clinical criteria for CDI suspicion.[7] Secondary objectives were to describe clinical presentation, risk factors for development of CDI and the most prevalent *C. difficile* ribotypes in Spanish intensive care units (ICUs).

Methods

This multicenter, prospective, observational, non-interventional admitted to 26 ICUs in Spain between February 3 and April 3, 2014. The Institutional Review Board of the Virgen del Rocío Hospital (Seville, Spain) approved the protocol and each patient's informed consent (or the next of kin) was mandatory before enrolment.

Patients who subsequently developed diarrhea (defined as ≥3 unformed stools within 24 h[7]) during their ICU stay were included. For every patient different clinical and analytical variables were recorded. Information was also collected on CDI recurrence, the prevalence of complications, and mortality either in hospital or within 60 days from CDI diagnosis for all patients analyzed.

Definitions

Immunosuppression was considered in those who had undergone organ transplantation, active malignancy, immunodeficiency due to any primary disease, HIV or treatment with radiation or cytotoxic or corticosteroid drugs use or haematologic disease. The rest of factors were defined as currently accepted. The severity of diarrhea was defined as: mild disease, 4–5 unformed stools per day or white blood cell (WBC) count ≤12,000/μL; moderate disease, 6–9 unformed stools per day or WBC count of 12,000–15,000/μL; severe disease, ≥10 unformed stools per day or WBC count ≥15,000/μL.[8] Recurrence was defined as the return of symptoms and a positive stool sample separated from the former by between 15 and 60 days after recovery from a previous episode (at least 3 days without diarrhea and clinical improvement).[9]

Microbiological diagnosis

Participating ICUs provided cases and incidence data, and local laboratories sent all unformed stool specimens received on a single day to a central reference laboratory regardless with patient age/origin (inpatients and outpatients), the diagnosis requested by the clinician, or the transport medium (except when this contained sporicides, *e.g.* formaldehyde).

A microbiological diagnosis of CDI was made initially at the local laboratory. At weekly intervals, samples were sent to the reference laboratory located in the Microbiology Department of Hospital General Universitario Gregorio Marañón (Madrid, Spain) and the results were reported 2–5 days later.

Statistical analysis

Discrete variables were expressed as counts (percentage) and continuous variables as means ± standard deviation. The chi-squared test or Fisher exact test was used for categorical variables, and the Mann–Whitney *U* test or Kruskal–Wallis test was used for continuous variables. To identify independent variables associated with CDI development, we performed a multivariate analysis using a binomial logistic regression.

Results

During the study period, 4258 patients were admitted to the participant ICUs. One-hundred and ninety patients (4.5%) developed diarrhea and met the study inclusion criteria. Only 11 out of the 26 participant centers provided positive CDI cases. Sixteen patients were diagnosed with CDI, representing an accumulated incidence of 0.37%. The baseline characteristics are described in Table 1.

When patients with confirmed CDI were compared with those without CDI 1only chronic renal failure had higher prevalence in those with CDI compared with those without CDI (31.3% *vs*. 6.9%). The median number of unformed stools in patients diagnosed with a CDI per day was 5 (3–6) with a median duration of diarrhea of 2 days (range 2–3). Three patients with CDI (18.8%) presented with paralytic ileus. In addition, two cases of pseudomembranous colitis were reported. The infection was considered severe in seven cases (43.7%). The median length of stay in the ICU, measured in infected survivor patients, was 5 days (3–38). Only two patients (12.5%) suffered a recurrence of CDI, one infected by ribotype 027 and the other one by 014/020. The crude in-ICU mortality was 37.5% (6/16) in patients with CDI compared to 21.8% (38/174) in patients without CDI ($p = 0.155$). One death was reported to be attributable to CDI.

The antibiotics prescribed before the episode of diarrhea are shown in Table 2. Following multivariate statistical analysis, adjusting by age, gender, APACHE II score, and previous antimicrobial

Table 1
Baseline characteristics of patients with and without *Clostridium difficile* infection.

Variable	Total cohort N = 190	CDI N = 16	No CDI N = 174	p-value
Age (years), median (IQR)	64 (52–74)	65 (56–73)	63 (52–74)	0.530
Gender (female), n (%)	65 (34.2)	7 (43.8)	58 (33.3)	0.440
APACHE II at admission to ICU, median (IQR)	19 (15–25)	17 (13–19)	20 (16–25)	0.723
SOFA score, median (IQR)	5 (3–7)	5 (4–7)	5 (2–7)	0.739
Patients with underlying disease, n (%)				
Diabetes mellitus	41 (21.6)	4 (25.0)	37 (21.3)	0.765
Heart failure	25 (13.2)	–	25 (14.4)	0.135
COPD	45 (23.7)	6 (37.5)	39 (22.4)	0.223
Chronic renal failure	17 (8.9)	5 (31.3)	12 (6.9)	0.008
Chronic liver failure	18 (9.5)	2 (12.5)	16 (9.2)	0.657
Immunosuppression	13 (6.8)	–	13 (7.5)	0.608
Corticosteroids	15 (7.9)	1 (6.3)	14 (8.0)	1
HIV infection	1 (0.5)	–	1 (0.6)	1
Solid cancer	22 (11.6)	4 (25.0)	18 (10.3)	0.102
Hematological neoplasia	7 (3.7)	–	7 (4.0)	1
Others	104 (54.7)	7 (43.8)	97 (55.7)	0.305
Prior infection with *Clostridium difficile*	2 (1.1)	1 (6.3)	1 (0.6)	0.156
Characteristics of primary episode of diarrhea				
Hospitalization >48 h, *n* (%)	179 (94.2)	15 (93.8)	164 (94.3)	0.473
Number of unformed stools/day	4 (3–6)	5 (3–6)	4 (3–5)	0.394
Bloody diarrhea, *n* (%)	7 (3.7)	0	7 (4.0)	1
Median (IQR) duration of diarrhea (days)	2 (2–3)	2 (2–3)	2 (2–3)	0.322
SOFA score	6 (3–8)	5 (3–9)	6 (4–8)	0.797
Temperature (°C)	36.8 (36–37.6)	36.5 (36.1–37.6)	36.9 (36–37.5)	0.922
Leukocytes ($\times 10^3$ cells/mm^3)	11 (7–19)	3 (2–18)	11 (8–19)	0.211
Creatinine (mg/dL), median (IQR)	0.80 (0.51–1.70)	1.71 (0.73–5.60)	1.07 (0.71–1.69)	0.306
Days from hospital admission to diarrhea	15 (8–25)	27 (12–44)	15 (8–24)	0.061
Days from ICU admission to diarrhea	9 (4–19)	6 (1–28)	10 (5–27)	0.208
Risk factors, n (%)				
MV 48 h before infection	141(74.2)	9 (56.3)	132 (75.9)	0.069
Proton pump inhibitor	171 (90.0)	16 (100)	155 (89.1)	0.608
Histamine-2-receptor antagonist	15 (7.9)	0	15 (8.6)	0.367
Opiates (i.v.)	125 (65.8)	8 (50.0)	117 (67.2)	0.091
Enteral nutrition	125 (65.8)	7 (43.8)	118 (67.8)	0.077
Parenteral nutrition	56 (29.5)	8 (50.0)	48 (27.6)	0.101
Antimicrobials 30 days prior to diarrhea	178 (93.7)	13 (81.3)	165 (94.8)	0.019
Outcome				
Death, *n* (%)	44(23.2)	6 (37.5)	38 (21.8)	0.155

APACHE II = Acute Physiology and Chronic Health Evaluation II; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; IQR = inter-quartile range; SOFA = Sequential Organ Failure Assessment.

Table 2
Prescription of empiric antimicrobial therapy prior to onset of diarrhea[a]

Antimicrobial class	No CDI N = 165		CDI N = 13		p-value
	N	%	N	%	
Carbapenem	43	26.1	9	69.2	0.001
Piperacillin-tazobactam	33	20.0	6	46.2	0.831
Cephalosporins	24	14.5	1	7.7	0.493
Quinolones	21	12.7	0	0.0	0.170
Linezolid	17	10.3	3	23.1	0.160
Penicillins	16	9.7	1	7.7	0.812
Glycopeptides	10	6.1	2	15.4	0.196
Antifungals	5	3.0	0	0.0	0.524
Aminoglycosides	4	2.4	0	0.0	0.570
Daptomycin	2	1.2	1	7.7	0.080
Tetracyclines	3	1.8	0	0.0	0.168
Metronidazole	2	1.2	0	0.0	0.689
Macrolides	1	0.6	0	0.0	0.335
Colistin	2	1.2	0	0.0	0.689
Others	9	5.5	0	0.0	0.387

[a] Sixty-nine patients received more than one antimicrobial agent.

therapy, only chronic renal insufficiency was identified in the final model as a factor independently associated with development of CDI (adjusted odds ratio [OR] 5.45 [95% confidence interval {CI} 1.72–25.42]; $p = 0.035$) in this patient cohort. In a second model adjusting by the same variables and as well as prior carbapenem usage, the factors independently associated with development of CDI were the same as in the first regression model.

The most frequently isolated *C. difficile* ribotypes were 078/126 ($n = 4$; 25.0%), 001 ($n = 3$; 18.7%), 014/020 ($n = 2$; 12.5%), and 027 ($n = 2$; 12.5%) The rest f them (070, 157, 106, R156 and R64) we identified in one case. The two patients with ribotype 027 were both women with a similar APACHE II score at ICU admission.

Discussion

This is the first multicenter, prospective study describing the incidence, general characteristics, risk factors and complications of patients infected with *C. difficile* in Spanish ICUs. The present study demonstrates that real incidence of CDI appears to be low in Spain. Chronic renal failure was the only factor independently associated with CDI development which is similar to previously reported by a recent Mayo Clinic findings.[10]

Accurate diagnosis of CDI is a prerequisite for obtaining consistent epidemiologic data. To avoid this potential limitation, we centralized all sample analyses to a reference laboratory. Our accumulated incidence of CDI was 0.37%, lower than reported in a retrospective study carried out in a tertiary referral hospital in Barcelona, with 3.6% in 2 years.[11] A retrospective analysis

of patients included in the Spanish nosocomial infection surveillance registry in 2012 revealed an accumulated incidence of CDI of 0.35%.[12] In our cohort, only three patients with CDI presented with some form of associated complication, all with paralytic ileus. Regarding mortality among the patients with diarrhea, we found no differences when comparing patients with and without CDI, which was perhaps related to the low severity of the majority of these infections, with 64.3% classified as mild or moderate. These findings are consistent with previous studies.[6]

Some limitations of our study should be acknowledged. First, we evaluated follow-up of all patients only until day 60 from CDI diagnosis, so CDI may have occurred beyond this timeframe. Secondly, the small number of cases of infection precluded certain statistical comparisons, and may have led to a type II error. Thirdly, we recognize that incidence density is the most accurate indicator. However, in our multicenter study the number of patients with ICU stays was not available for every participating hospital.

Conclusions

In summary, the key finding of our study was that CDI incidence was lower than expected. There were no clinical or analytical data that distinguished between CDI and other types of diarrhea. Our study highlighted the potential importance of chronic renal insufficiency as a risk factor for the development of CDI in these patients.

Conflict of interests

The authors declare that they have no conflicts of interest.

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