Official journal of the Spanish Society of Chemotherapy

Brief report

Revista Española de Quimioterapia
doi:10.37201/req/085.2020

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Clostridioides difficile infection in a long-term convalescence hospital: A real tale of pitfalls and outdated therapy

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Article history
Received: 29 July 2020; Revision Requested: 22 September 2020; Revision Received: 30 September 2020; Accepted: 6 October 2020; Published: 1 December 2020

ABSTRACT

Objective. The aim of the study was to know the characteristics and risk factors of *Clostridioides difficile* infection (CDI) in a long-term hospital is key to improve its management.

Material and methods. Retrospective study with 37 patients, along 43 months. We describe demographic variables, clinical data, time to diagnosis, treatment, and evolution.

Results. Analysis of 46 episodes (37 patients, mean age=82.2 years). 77.8% were absolutely dependent, 41.7% had chronic kidney disease, 64.9% had received antibiotics in the previous three months, 40.5% received antibiotics at diagnosis. It was the first episode in 78.4%, and first recurrence in 21.6%. Therapy was started in the first 24 hours after diagnosis in 89.2%, mostly metronidazole. 83.3% recovered, 3 patients died from CDI, diagnosis was registered in the discharge report in 91.1%.

Conclusions. Previous antibiotic therapy, high grade of dependency and renal failure were the main risk factors. There is room for improvement in CDI management at our hospital.

Keywords *Clostridium difficile*, *Clostridioides difficile*, nosocomial infection, recurrent infection, management.

Infección por *Clostridioides difficile* en un hospital de convalecencia: una historia real de trampas y tratamiento anticuado

RESUMEN

Objetivo. Conocer las características y factores de riesgo de infección por *Clostridioides difficile* (ICD) en un hospital de convalecencia es clave para mejorar su manejo.

Material y métodos. Estudio retrospectivo con 37 pacientes, durante 43 meses. Describimos variables demográficas, datos clínicos, tiempo hasta el diagnóstico, el tratamiento y la evolución.

Resultados. Análisis de 46 episodios (37 pacientes, edad media=82,2 años). 77,8% tenían dependencia absoluta, 41,7% enfermedad renal crónica, 64,9% habían recibido antibióticos en los 3 meses previos, 40,5% recibían antibióticos en el momento del diagnóstico. Fue el primer episodio en 78,4%, y la primera recidiva en 21,6%. En el 89,2% se comenzó tratamiento en las primeras 24 horas tras el diagnóstico, mayoritariamente metronidazol. El 83,3% se recuperaron. 3 pacientes murieron por ICD. El diagnóstico figuraba en el informe de alta en 91,1%.

Conclusiones. El tratamiento antibiótico previo, un alto grado de dependencia, y el fracaso renal, fueron los factores de riesgo principales. Hay margen de mejora en el manejo de ICD en nuestro hospital.

Palabras clave: *Clostridium difficile*, *Clostridioides difficile*, infección nosocomial, infección recurrente, manejo

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INTRODUCTION

Clostridioides difficile infection (CDI) is the most frequent cause of nosocomial diarrhoea. It is a global health problem, with most cases acquired in hospital but also described in the community. Reported mortality rate ranges between 3-15%, and recurrence rate, 12-40% [1,2].

Hospital San Juan de Dios (HSJD) is a long term-acute care hospital with 188 beds, holding units of palliative care, neurorehabilitation, haemodyalisis for chronic patients, convalescence, and an acute geriatric unit. Patients are admitted from acute care hospitals of the region, and directly from nearby centres of primary care, with a catchment area of 500.000 inhabitants. These types of health facilities have their own features and challenges concerning CDI [3,4].

MATERIAL AND METHODS

We have performed a retrospective study of all CDI cases since 5th May 2016 to 31st December 2019. We used the definitions of nosocomial, community-acquired and recurrent CDI reported in updated guidelines [5,6]. In every patient with a clinical picture suggestive of CDI (diarrhoea, abdominal pain, fever), a faecal sample was collected and analysed at the microbiology laboratory of the hospital, using *C. difficile quik check complete* (Techlab® Blacksburg) test. This is a fast membrane enzyme-immunoassay which simultaneously detects the bacterial antigen glutamate dehydrogenase (GDH) and also toxins A and B. Samples which were GDH+/Tox- were sent to the reference hospital (Hospital Miguel Servet) for Polymerase Chain Reaction –PCR- testing (GenXpert®Cepheid), which detects a toxin-producer gen [7]. Data obtained from clinical records were fully anonymised and collected using a specifically designed database. For the statistical study, qualitative variables are presented according to distribution of frequencies, and expressed as number and percentage. Quantitative variables are presented as means, median, mode and standard deviation. We did all statistical analysis using SPSS (IBM SPSS Statistics 25.0 2017). The Ethics Committee of Clinical Research of Aragón (CEICA) approved the study project (ruling 31/01/2020), as did the Ethics Committee of HSJD.

RESULTS

Patients, risk factors and clinical data. We describe 37 patients diagnosed of CDI during the study period (24 men/13 female), mean age 82.8 +/- 9.6 years (56-100). Patient´s demographics and clinical data before and on admission appear in Table 1.

CDI diagnosis, treatment and clinical outcome. (Table 2) There were 46 episodes of CDI (29 first episodes and 17 recurrences). In 29 patients (78.4%) the infection was the 1st episode, and in 8 cases (21.6%), the debut episode in our hospital was the first recurrence of CDI. 12 patients out of the 37 presented recurrent CDI during their hospital stay: 8, first recurrence after an initial episode (21.6%), 8 as second recurrence, and 1 as third recurrence (overall, 17 episodes in 12 patients). Data concerning the characteristics of the infection (clinical data, treatment, evolution) appear in Table 2.

In 15 patients with CKD and age > 65 years, CDI was qualified as severe, with a high risk of recurrence according to the guidelines.

The anti-CDI therapy of the first episode was metronidazole in 24/29 (82.8%), vancomycin in 4/29 (13.8%), and fidaxomicin in one. The first CDI recurrence was treated with metronidazole in 5 cases, and with vancomycin in 3 cases. The second CDI recurrence was treated with metronidazole in 1 case, vancomycin 2 cases, fidaxomicin 1 case. The third recurrence received fidaxomicin.

DISCUSSION

We describe in this study the characteristics of 37 patients with CDI in a long term-acute care hospital, trying to confirm if the well-known reported risk factors are also present in our patients, and if the diagnostic and therapeutic approaches employed fit with current guidelines. Most studies have been performed in health facilities of very different profile (tertiary hospitals [8,9], multicentric studies [10], or extensive epidemiological studies [2]). After a thorough bibliographical search, we have not found any study performed in a hospital of our profile.

In our series, almost 60% of patients came from emergency departments of other hospitals, for convalescence and/or rehabilitation after infections or cerebrovascular disease. As symptoms may be scarce or not reported, and given the high index of dependency in this population, diagnosis may be a difficult challenge. It is also worth mentioning, as it has been reported in other series [10], the association between CDI and chronic renal insufficiency (15 from 36 patients, 41.7%, had an eGFR<50mL/min). All these factors confer to our patients a high degree of frailty and a high risk of CDI recurrence, a finding also previously described [8,11,12]. We also found in our patients a wide use of PPIs, drugs that modify the pH of the bowel and disrupt bowel microbiota, as well as an association of CDI with previous antibiotic use, also described in previous studies [3,4,8-11]. It is important to remark that 40.5% of patients were on antibiotics at the time of diagnosis, and they were withdrawn in only 53.5% of them, which may indicate a pitfall in the management of CDI in our patients.

Concerning clinical presentation, most (83.8%) patients did not refer any symptoms or signs. This scarcity of clinical data indicates that CDI is clinically silent in this population, even in severe cases. Though there are no registered data regarding the number of leukocytes, applying the GEIH Score [12] (age, number of diarrhoeal episodes and renal insufficiency), 40.5% of patients had severe CDI, with a high risk of recurrence.

Regarding the analysis of the episodes, in 78.4% of cases CDI presented as the first episode. In 21.6% of cases, the epi-

Table 1 **Patients´ demographics, clinical data before and on admission.**

Variable	Number (n)	Percentage (%)
Patients´ demographics		
Gender		
Female	24/37	64.9%
Male	13/37	35.1%
Age	Mean ± SD = 82.8 ± 9.6	
Origin		
Emergency department	22/37	59.5%
Neurology	4/37	10.8%
Pre-diagnosis data		
Patients with infections in the previous 3 months	24/37	64.9%
Number of infections	N=28	
Respiratory infection	8/28	28.6%
CDI	8/28	28.6%
Urinary tract infection	6/28	21.4%
Patients with antibiotics in the previous 3 months	24/37	64.9%
Number of antibiotics	N=38	
Beta-lactams	20/38	52.6%
Glucopeptides	5/38	13.2%
Macrolides	5/38	13.2%
Clinical data on admission		
Diagnosis on admission		
Respiratory infection	7/37	18.9%
Unspecified diarrhoea	6/37	16.2%
Sepsis	5/37	13.5%
Stroke	4/37	10.8%
Days of disease that led to admission	Mean ± SD =17.8 ± 21.2	
Patients with antibiotics on admission	21/37	56.8%
Number of antibiotics	N=23	
Beta-lactams	16/23	69.6%
Quinolones	2/23	8.7%
Barthel on admission	Mean ± SD =15.8 ± 24.4*	
CKD	15/36*	41.7%*
PPIs	29/37	78.4%

CKD=chronic kidney disease, (estimated Glomerular Filtration Rate<50mL/min); PPIs=proton pump inhibitors.
***Data about clinical outcome was missing in one patient.**

sode during hospital stay was a recurrence, as the initial episode had happened previously. According to the current definition of recurrence given by IDSA-SHEA [6], it can be said that 32.4% suffered from recurrent CDI, and 67.5% (n=25), only an initial episode of CDI, without further recurrences during the length of the hospital stay. This recurrence rate is between 20 and 30% in the study by Lessa et al. [2] and similar in other studies [8,11]; it is reported as high as 57.1% in one of the studies performed in Spain [11].

In most cases, treatment was started within the same day or the following day after reception of the laboratory diagnosis, which can be a good quality indicator. Considering

Table 2 **Clinical data of CDI, treatment and evolution until discharge.**

Variable	Number (n)	Percentage (%)
Clinical data of CDI		
Distribution patients-year		
2016	2/37	5.4%
2017	9/37	24.3%
2018	10/37	27%
2019	16/37	43.2%
CDI origin		
Nosocomial	32/37	86.5%
Community	5/37	13.5%
Patients with antibiotics on diagnosis	15/37	40.5%
Number of antibiotics	N=19	
Beta-lactams	11/19	57.9%
Cotrimoxazole	3/19	15.8%
Withdrawal of antibiotics on diagnosis	8/15	53.3%
Clinical findings		
Haemodynamic instability	0	0%
Tachycardia	1/37	2.7%
Nausea/vomiting	3/37	8.1%
Abdominal pain	6/37	16.2%
Fever	10/37	27%
Diarrhoea	35/37	94.6%
>2 days	20/37	54.1%
Initial episode during hospital stay		
First episode of CDI	29/37	78.4%
First recurrence	8/37	21.6%
Recurrent CDI	12/37	32.4%
Treatment		
Started ≤ 1 day after diagnosis	33/37	89.2%
Antimicrobials		
First episode		
Metronidazole	24/29	82.8%
First recurrence		
Metronidazole	8/12	66.6%
Contact precautions	26/37	70.3%
Evolution until discharge		
Recovery	31/36*	86.1%*
Derivation to other center	1/37	2.7%
Death attributable to CDI	3/37	8.11%
Days of hospital stay	Mean ± SD = 43.6 ± 30.0	
Days diagnosis-discharge	Mean ± SD = 23.0 ±19.2	
Microbiological control	4/37	10.8%
CDI as principal diagnosis in discharge report	7/37	18.9%
CDI specified in discharge report	34/37	91.9%

CDI = *Clostridioides difficile* infection; * Data about clinical outcome was missing in one patient.

therapeutic approach, 78.4% of individuals with an initial episode were treated with metronidazole, which was the drug of choice until 2017. However, last guidelines [5,6] advise about the use of vancomycin or fidaxomicin as first line in all patients with first episode of CDI [13-15]. So, it could be said that the degree of penetrance of current therapeutic guidelines is poor in our hospital. Recurrent episodes were also treated inadequately, mostly with metronidazole again.

Despite this, 83.8% of the patients recovered, a similar high rate is reported by Aljafel et al. [9] and others [8] 8.1% of deaths in our series were attributable to CDI. This figure is similar to the rate reported by Olsen et al. [15] and also by Lessa et al. [2] and it is even higher in other series [1,8,10]. It is worthwhile to remember that all publications belong to health facilities with very different characteristics from our hospital. Mean hospital stay of our patients was 43.6 days (standard deviation: 30.1 days), which is longer than the duration reported by other authors [8,9]

We acknowledge the limitations of the study: retrospective, with a small sample, and patients who are far from representative of the general population, as are aged (mean age 82 years) and with multiple comorbidities. It means that CDI is bound to be more severe and the risk of recurrences, higher. However, it has also strengths: it can inspire further research about CDI in the hospital, within the frame of a stewardship team and infection control approach. Moreover, it analyses a type of patients which is specific to this profile of hospitals, scarcely represented in current literature.

FUNDING

None to declare.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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