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Economic burden of recurrent *Clostridioides difficile* infection in adults admitted to Spanish hospitals. A multicentre retrospective observational study

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ABSTRACT

Introduction. *Clostridioides difficile* infection (CDI) is associated with increased hospital stays and mortality and a high likelihood of rehospitalization, leading to increased health resource use and costs. The objective was to estimate the economic burden of recurrent CDI (rCDI).

Material and methods. Observational, retrospective study carried out in six hospitals. Adults aged ≥18 years with ≥1 confirmed diagnosis (primary or secondary) of rCDI between January 2010 and May 2018 were included. rCDI-related resource use included days of hospital stay (emergency room, ward, isolation and ICU), tests and treatments. For patients with primary diagnosis of rCDI, the complete hospital stay was attributed to rCDI. When diagnosis of rCDI was secondary, hospital stay attributed to rCDI was estimated using 1:1 propensity score matching as the difference in hospital stay compared to controls. Controls were hospitalizations without CDI recorded in the Spanish National Hospital Discharge Database. The cost was calculated by multiplying the natural resource units by the unit cost. Costs (euros) were updated to 2019.

Results. We included 282 rCDI episodes (188 as primary diagnosis): 66.31% of patients were aged ≥65 years and 57.80% were female. The mean hospital stay (SD) was 17.18 (23.27) days: 86.17% of rCDI episodes were isolated for a mean (SD) of 10.30 (9.97) days. The total mean cost (95%-CI) per episode was €10,877 (9,499-12,777), of which the hospital stay accounted for 92.56%.

Conclusions. There is high cost and resource use associated with rCDI, highlighting the importance of preventing rCDI to the Spanish National Health System.

Keywords: *Clostridioides difficile*, recurrence, cost analysis.

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Carga económica de la infección por *Clostridioides difficile* en pacientes adultos tratados en hospitales españoles. Estudio observacional, retrospectivo, multicéntrico

Introducción. La infección por *Clostridioides difficile* (ICD) está asociada a un aumento de la estancia hospitalaria y de la mortalidad y a una alta probabilidad de reingreso, lo que conlleva un aumento de uso de recursos sanitarios y por tanto un incremento de costes. El objetivo del estudio fue estimar la carga económica de la ICD recurrente (ICDr).

Material y métodos. Estudio observacional, retrospectivo y multicéntrico. Se incluyeron pacientes adultos (≥18 años), que tuvieran registrado al menos un episodio diagnóstico confirmado (primario o secundario) de ICDr durante enero 2010 y mayo 2018. El uso de recursos relacionado con la ICDr incluyó la estancia hospitalaria (urgencias previas, planta, aislamiento y UCI), así como pruebas y tratamientos. Para episodios que ingresaron por ICDr (diagnóstico principal) se consideró la estancia completa registrada. Cuando la ICDr se registró como diagnóstico secundario se estimó la estancia hospitalaria debida a ICDr mediante emparejamiento (1:1) utilizando la técnica "propensity score". Se consideraron como controles (episodios sin ICD) las hospitalizaciones registradas en Conjunto Mínimo Básico de las Altas Hospitalarias. El coste total se calculó multiplicando las unidades naturales de los recursos por el coste unitario correspondiente. Todos los costes fueron actualizados a euros de 2019.

Resultados. Se incluyeron 282 episodios ICDr (188 como diagnóstico principal): 66,31% de los pacientes tenían más de 65 años y 57,80% eran mujeres. La estancia media (DE) hospitalaria fue de 17,18 (23,27) días. Un 86,17% de los episodios fueron aislados debido a ICDr con una media (DE) de 10,30 (9,97) días. El coste medio (IC-95%) total por episodio fue de 10.877€ (9.499-12.777), siendo la duración de la estancia hospitalaria el 92,56% del coste total.

Conclusiones. Tanto el uso de recursos como el coste debido a la ICDr tienen un alto impacto para el sistema nacional de salud lo que pone de relieve la importancia de prevenir las ICDr.

Palabras clave: *Clostridioides difficile*, recurrencia, análisis de costes.

INTRODUCTION

Clostridioides difficile infections (CDI) range from uncomplicated diarrhoea and pseudomembranous colitis to fulminant colitis, resulting in sepsis and death in 2-3% of patients [1–5]. Cytotoxins produced by *C. difficile* (toxin A, toxin B), which may inflame the colon and damage the surface of the epithelial mucosa [6] are responsible for most cases of antibiotic-associated pseudomembranous colitis [1–4] and 15-25% of antibiotic-associated diarrhoeas [1].

In Spain, CDI is the most common nosocomial infection of the digestive system [7] and the most common cause of diarrhoea in hospitalized patients [8, 9]. In recent decades there has been an increase in cases of diarrhoea associated with CDI, probably due to increased clinical suspicion and greater diagnostic sensitivity. According to the VINCat register (a Catalan Health Service programme that established a unified surveillance system for nosocomial Infections in Catalan hospitals), the incidence rate increased from 2.20 cases/10,000 hospital stays in 2011 to 3.41 in 2016 [10]. The increase was significant for all types of CDI: nosocomial, health care-related and community-acquired [11]. In Spain, the rate of hospitalizations due to CDI has increased from 3.9 cases per 100,000 persons in 2003 to 12.97 in 2013-15 [12]. The incidence may be up to 2.5 times higher in patients aged ≥ 65 years [9]. The increased frequency of CDI correlates with increased antibiotic use, prolonged hospital stays and older age [13, 14].

Despite the progressive increase in the incidence of CDI, it remains an underdiagnosed pathology, a European study found that only 52% of hospitals used an optimal algorithm for the diagnosis of CDI [15]. In Spain, Alcalá et al., found that 66.6% of patients infected with *C. difficile* are not well diagnosed [16], although this may have improved in recent years due to molecular diagnostic techniques.

The treatment of CDI is based on the administration of antibiotics, the application of preventive measures to control the infection, hydration and the avoidance of opiates and drugs that inhibit intestinal peristalsis. Approximately 85% of patients diagnosed respond to treatment. However, in 10-35% of patients, despite treatment and the resolution of symptoms, CDI recurs within 8 weeks of the first episode [1, 17–19]. Antibiotic use after the diagnosis of CDI, the use of antacid agents, older age [17, 20–23], the persistence of spores, loss of diversity of the gut microbiota [4, 24–26] and previous episodes of CDI [27], severe CDI episodes, an insufficient immune response and the persistence of diarrhoea >5 days [14], are the main risk factors for rCDI. The first recurrence increases the percentage of new recurrences by up to 50-60% [28–30]. Recurrence is one of the main complications of CDI because, in addition to increasing the risk of more recurrences, it worsens health outcomes [4, 23], including increased morbidity and mortality [31–33], leading to increased health resource use and, therefore, increased health costs. The cost of an inpatient with CDI is increased by 33% to 54% compared with the cost of a patient without CDI [34].

Few Spanish studies have analysed the economic impact of CDI. Asensio et al., estimated the annual expenditure for the Spanish National Health System (NHS) as € 32,157,093. The high costs were mainly due to the prolonged length of hospital stay. The cost per episode of *C. difficile*-associated diarrhoea was € 3,901 (initial infection), € 4,875 (first recurrence) and € 5,916 (second recurrence) [35]. Other analyses estimated that the cost attributable to CDI varied from € 3,750 to € 4,396 / patient, depending on the severity of the episodes [12, 36].

Given the lack of observational studies to estimate the burden of rCDI in Spanish patients in both resource use and costs, this study analysed the economic impact of rCDI in real clinical practice.

MATERIAL AND METHODS

Design and study population. A descriptive, retrospective, multicentre observational study was conducted to estimate the economic burden of hospitalized episodes of rCDI. The study was carried out under conditions of usual clinical practice in six hospitals representative of the Spanish geography. The study was classified by the Spanish Agency for Medicines and Health Products as a non-post-authorization observational study and was approved by the Clinical Research Ethics Committee of the Hospital General Universitario Gregorio Marañón (study code: MSD-CDI-2016-01).

Researchers consecutively identified all the most recent episodes of rCDI that met the selection criteria within the inclusion period and these were collected in the electronic case report form (eCRF) designed for the study, the patient's sociodemographic and clinical data, as well as the episodes of rCDI associated with each patient and their use of resources. The unit of analysis was rCDI episodes. The economic assessment was conducted from the NHS perspective and the inclusion period was January 2010 to May 2018.

The study population included patients aged ≥ 18 years of both sexes with ≥ 1 confirmed diagnostic episode of rCDI during the inclusion period. Patients in whom it was not possible to obtain clinical and/or resource use data and those with episodes of rCDI, but who did not meet the study definition of rCDI were excluded.

Data collection. We collected sociodemographic characteristics such as age and sex, the characteristics of hospitalization (type of admission, hospitalization service, primary diagnosis, secondary diagnoses and discharge destination), characteristics of each rCDI episode, including the number of recurrences, episode severity, the Charlson Comorbidity Index (CCI) and McCabe-Jackson index, if the patient was immunocompromised, antibiotic use and the use of proton pump inhibitors in the 30 days prior to diagnosis of rCDI. Diagnoses were recorded using the coding of the Spanish version of the International Classification of Diseases, Clinical Modification ninth revision (CIE-9-MC).

The use of rCDI-related resources included the hospital stay, testing, treatments (pharmacological and/or faecal microbiota transplant (FMT)) and surgical intervention due to rCDI.

Definitions.

— CDI diagnosis. A diagnosed CDI episode was defined using two criteria: a) diarrhoea, defined as ≥ 3 evacuations of unformed faeces within 24 consecutive hours or less; b) a positive stool test for toxigenic *C. difficile* or its toxins [25, 37].

— rCDI. According to the European Society of Clinical Microbiology and Infectious Diseases [37] a recurrence was defined as a new episode of CDI within 8 weeks of the resolution of signs and symptoms of the previous episode.

Due to the difficulty in clinical practice of distinguishing between recurrences due to a recurrence of the infection by the original strain or a re-infection of patients who remained susceptible and were exposed to new strains [1], both mechanisms were considered as a recurrent episode.

Episodes that occurred during the first two days after the end of treatment for CDI or rCDI were considered therapeutic failures, and all resource consumption identified during that period was considered as resource use corresponding to that episode (Figure 1).

— Hospital stay. In the case of CDI as a primary diagnosis, the days spent in the emergency room prior to the ward stay and the ward stay recorded in the eCRF were attributed to recurrence.

In the case of CDI as a secondary diagnosis, the days spent in the emergency room prior to the ward stay and the ward stay attributed to recurrence were considered to be the difference in days of stay for the patient compared to a control patient without CDI (control group). Cases and controls were matched using the propensity score.

The days of isolation room and the days in the ICU recorded in the eCRF were attributed to the recurrence in all episodes.

— Spanish National Hospital Discharge Database (SNHDD) – Controls. Hospital discharges registered with the minimum basic data set (SNHDD) of the Ministry of Health, Consumer Health and Social Welfare were included as controls. The SNHDD gathers information on patient characteristics (age and sex), hospitalization (type of admission and discharge, and hospital stay), diagnoses and some relevant therapeutic interventions, especially surgical interventions, used to treat the patient during hospitalization (procedures). Diagnoses and procedures were recorded using the CIE-9-MC coding. The SNHDD register is mandatory and includes all acute hospital discharges from the NHS [38]. The CCI calculation [39] was adapted for use with an administrative database [40].

Costs. Direct health costs were included to estimate the economic impact of rCDI on adult patients in Spain from the NHS perspective.

The unit costs of resource use were obtained from the ESALUD database [41] and drug treatments from the website of the General Council of Official Colleges of Pharmacists (Bot PLUS) [42]. All costs were updated to 2019 euros.

Direct health costs included resource use during hospitalization due to rCDI (previous emergency room admissions, ward, isolation room, and ICU stays; testing and treatment). The costs of tests were calculated by multiplying the natural units of the resources used by the associated unit cost. The

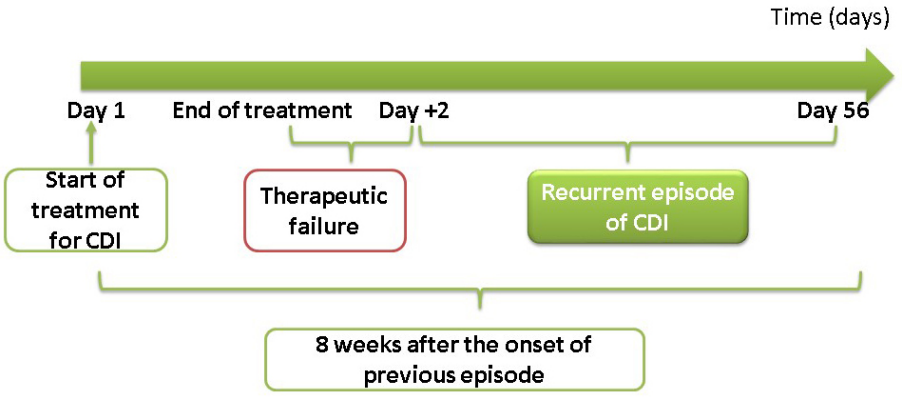

Figure 1 Definition of an rCDI episode

cost of the hospital stay (ward, isolation room, ICU) was obtained by multiplying the days of stay by the corresponding unit cost.

The total dose was calculated for each active substance used during hospitalization by multiplying the dose by the length of treatment. The cost of each treatment was obtained by multiplying the total dose that each patient received during hospitalization by the unit cost of each treatment. The wholesale price without Value Added Tax was applied according to the presentation of the medicine.

Stratifications. Stratified analyses were made to estimate the cost of rCDI according to age (≤ 65 years, >65 years), sex, severity of the episode (mild or moderate, severe, severe-complicated), immunosuppressive status and number of recurrences (1, 2, ≥3).

Statistical analysis. A descriptive analysis was made of the study variables. Quantitative variables were described using means and standard deviation (SD) and qualitative variables using absolute and relative frequencies. Confidence intervals (CI) were calculated using bootstrapping techniques employing replacement samples of the same size as the original sample [43, 44]: 10,000 simulations were made and the 2.5th and 97.5th percentiles of the distribution were used to determine the 95% CI.

rCDI episodes and the control group were matched (1:1) using the propensity score employing the greedy matching algorithm. I.e., once a control episode was selected, that control was not reconsidered [45]. A logistic regression model adjusting for covariates was developed to estimate propensity to develop CDI among patients in the case and control cohorts. The covariates included were sex and age, comorbidities during hospitalization, type of admission and discharge and primary diagnosis. Each propensity score included the hospital admission date for cases and controls to ensure the length of hospital stay before the event was similar in the two groups and was not a confounding factor.

The matching of the two groups was restricted by the primary diagnosis. In the event of more than one control being available for the case, selection was carried out randomly. The analysis was performed only in matched episodes. Episodes of rCDI without a comparable control were excluded from the study. Differences in characteristics between rCDI episodes and controls were evaluated using standardized differences [46].

Sensitivity analysis. To validate the analysis, a sensitivity analysis of the matching technique was made. Secondary diagnoses were considered in this analysis in addition to the covariates included in the main analysis (sex and age, comorbidities during hospitalization, type of admission and discharge, and primary diagnosis): i.e., the case and control coincided in as many secondary diagnoses as was possible.

The analysis was conducted using the R statistical package (version 3.6.1) [47].

RESULTS

The initial cohort included 230 hospitalized patients with rCDI, of whom 224 patients with 290 recorded rCDI episodes were valid for the analysis. Of these 290 recurrent episodes, 188 had a primary diagnosis of CDI and 102 a secondary diagnosis of CDI. These 102 episodes were matched with episodes without CDI using propensity scores: controls were found for 94 episodes and 8 episodes were excluded from the analysis. The standardized differences in baseline characteristics for comparisons of the two groups were <0.2 (small effect), suggesting that pro-

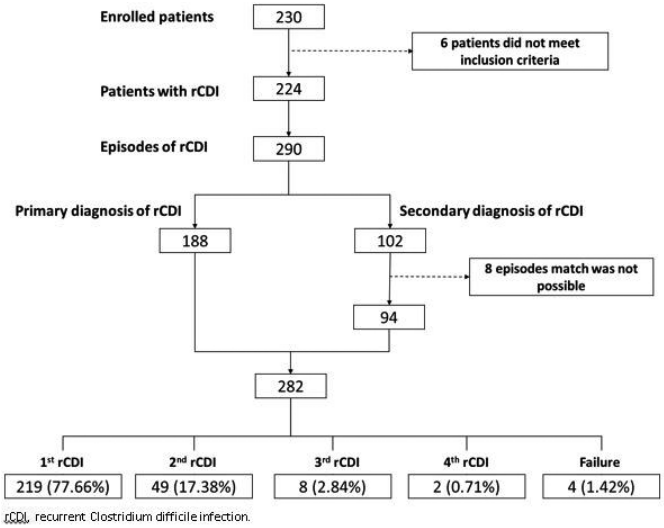

Figure 2 | **Flow chart of rCDI episodes**

Table 1 Sociodemographic data, and clinical and hospitalization characteristics due to rCDI

	rCDI	N
Sociodemographic features		
Age [years][a] – Mean (SD)	70.71 (18.16)	282
Female – n (%)	163 (57.80%)	282
Clinical characteristics		
Episode severity – n (%)		282
Mild or moderate	168 (59.57%)	
Severe	92 (32.62%)	
Severe-complicated	22 (7.80%)	
Comorbidities[b,c] – n (%)		282
Chronic kidney failure	100 (35.46%)	
Heart failure	68 (24.11%)	
Chronic respiratory disease	57 (20.21%)	
Tumour or solid neoplasm without metastasis	46 (16.31%)	
Diabetes with target organ injury	44 (15.60%)	
Cerebrovascular disease	41 (14.54%)	
Diabetes without target organ injury	39 (13.83%)	
Peripheral artery disease	34 (12.06%)	
Moderate-severe chronic liver disease	32 (11.35%)	
Dementia	29 (10.28%)	
Other	104 (36.88%)	
Charlson index score – n (%)		282
<3 points	33 (11.70%)	
≥3 points	249 (88.33%)	
McCabe-Jackson index – n (%)		282
I (Rapidly fatal)	14 (4.96%)	
II (Ultimately fatal)	118 (41.84%)	
III (Non-fatal)	150 (53.19%)	
Immunocompromised patient – n (%)	88 (31.21%)	282
Previous use of antibiotics[d] – n (%)	221 (81.55%)	271
Previous use of proton pump inhibitors[d] – n (%)	230 (82.44%)	279

Table 1 Sociodemographic data, and clinical and hospitalization characteristics due to rCDI (cont.)

	rCDI	N
Characteristics of hospitalization		
Type of admission – n (%)		282
Urgent	267 (94.68%)	
Programmed	15 (5.32%)	
Type of hospitalization service discharge[e]– n (%)		282
Medical	259 (91.84%)	
Surgical	16 (5.67%)	
Other service	7 (2.48%)	
Discharge destination – n (%)		282
Home	180 (63.83%)	
Transfer to social health centre	41 (14.54%)	
Hospital deaths	35 (12.41%)	
Other	17 (6.03%)	
Transfer to another hospital	8 (2.84%)	
Voluntary discharge	1 (0.35%)	

[a]Age at the time of assignment of ward bed. [b]Mutually non-exclusive categories. [c]Others: leukaemia (n= 18); myocardial infarction (n= 18); lymphoma (n= 17); tumour or solid neoplasm with metastasis (n= 16); gastroduodenal ulcer (peptic) (n= 12); connective tissue disease (n= 7); mild chronic liver disease (n= 7); hemiplegia (n= 5); AIDS (n= 4). [d]During the 30 days prior to the diagnosis of rCDI episode. [e]Medical service: Digestive, cardiology, dermatology, endocrinology, infectious diseases, neurology, geriatrics, haematology, internal medicine, nephrology, pneumology, medical oncology, paediatrics, rehabilitation, rheumatology, internal medicine. Surgical service: Angiology and vascular surgery, cardiac surgery, general and digestive surgery, maxillofacial surgery, chest surgery, gynaecology, neurosurgery, urology, obstetrics, ophthalmology, otolaryngology, trauma and orthopaedic surgery.
rCDI, recurrent *Clostridioides difficile* infection; SD, standard deviation; IQR interquartile range.

pensity score matching was effective in minimizing the baseline differences (Supplementary table A-1). Finally, 282 episodes of rCDI (corresponding to 217 patients) were analysed, of which 77.66% were a first recurrence (Figure 2).

The mean age was 71 years (SD: 18.16), 57.80% of patients were female, and 60% of episodes were mild or moderate in severity. In 88.33% of episodes, patients had high comorbidity (CCI ≥3 points). The most common comorbidities were chronic kidney failure (35.46%), heart failure (24.11%) and chronic respiratory disease (20.21%). In 31.21% of episodes patients were immunocompromised, 81.55% and 82.44% used antibiotics (any reason) and proton pump inhibitors, respectively, during the 30 days before the diagnosis of rCDI. In 63.83% of episodes, the discharge destination was home, and there were 12.41% hospital deaths (Table 1).

Resource use. The total mean hospital stay (SD) due to rCDI, including the days of stay in the emergency room prior to the hospitalization, was 17.18 (23.27) days. In 86.17% of episodes, an isolation room due to rCDI was required, with a mean stay (SD) of 10.30 (9.97) days. The most common tests

Table 2 **Resource use and total cost per episode of rCDI.**

	Episodes (%)	Mean resource use (SD)	Total cost (€) Mean (95% CI)
HOSPITAL STAY DUE TO rCDI [days][a]			
Emergency room before assignation of ward bed	15.60%	1.48 (0.63)	
Isolation room	86.17%	10.30 (9.97)	
Ward stay	62.77%	12.12 (23.72)	
ICU	2.84%	16.50 (18.34)	
Total	**100.00%**	**17.18 (23.27)**	**10,068 (8,717 – 11,920)**
TESTS DUE TO rCDI [n][a]			
Biochemistry	35.82%	2.95 (2.62)	
Diagnostic imaging	28.37%	1.25 (0.56)	
Cultures	22.34%	2.75 (0.62)	
Colonoscopies	6.03%	1.00 (0.00)	
Other tests	7.09%	1.15 (0.49)	
Total	**100.00%**		**155 (134 - 181)**
TREATMENT DUE TO rCDI[a,b,c]			
Vancomycin [mg]	65.48%	621.31 (522.82)	
Metronidazole [mg]	50.89%	1,480.54 (195.96)	
Fidaxomicin [mg]	26.69%	397.40 (22.79)	
Faecal microbiota transplant [n]	4.27%	na	
Rifaximin [mg]	1.42%	800.00 (0.00)	
Tigecycline [mg]	0.36%	100.00 (na)	
Non-specific immunoglobulin [mg]	0.36%	2,500.00 (na)	
Total	**99.65%**		**484 (403 – 580)**
OTHER RESOURCE USE DUE TO rCDI [n]			
Surgery	0.35%	1 (na)	
Total			**24.69 (0 – 74.07)**
Therapeutic failure	1.42%	na	
Total			**145 (32.38 – 411)**
TOTAL COST PER rCDI EPISODE			**10,877 (9,499 – 12,777)**

rCDI, recurrent *Clostridioides difficile* infection; SD, standard deviation; CI, confidence interval; na, not applicable.

[a]Mutually non-exclusive resources. [b]One episode received no treatment for rCDI. [c]Percentage of episodes calculated from episodes that received treatment.

for rCDI were biochemistry (35.82%), imaging (28.37%) and cultures (22.34%), with a mean (SD) of 2.95 (2.62); 1.25 (0.56); and 2.75 (0.62) tests per episode, respectively. All other recorded tests were made in less than 7% of episodes (Table 2).

The most common pharmacological treatments prescribed for rCDI were vancomycin (65.48%), metronidazole (50.89%) and fidaxomicin (26.69%). All other drugs were prescribed in < 2% of episodes. One episode received no treatment for CDI. FMT was carried out in 4.27% of episodes (Table 2).

Costs. The mean total cost (95% CI) per episode was € 10,877 (9,499-12,777): 92.56% of the total cost was due to the length of the hospital stay, while the remaining 7.44% was distributed between treatments (4.45%), testing (1.43%), therapeutic failure (1.33%) and surgery (0.23%) (Table 2).

The hospital stay was the greatest contributor to the total cost (mean [95% CI]: € 10,068 [8,717 – 11,920]), of which 51.05% was due to the need for an isolation room, 37.30% to the ward stay, 7.10% to the ICU stay, and 4.55% to pre-hospitalization emergency room stays.

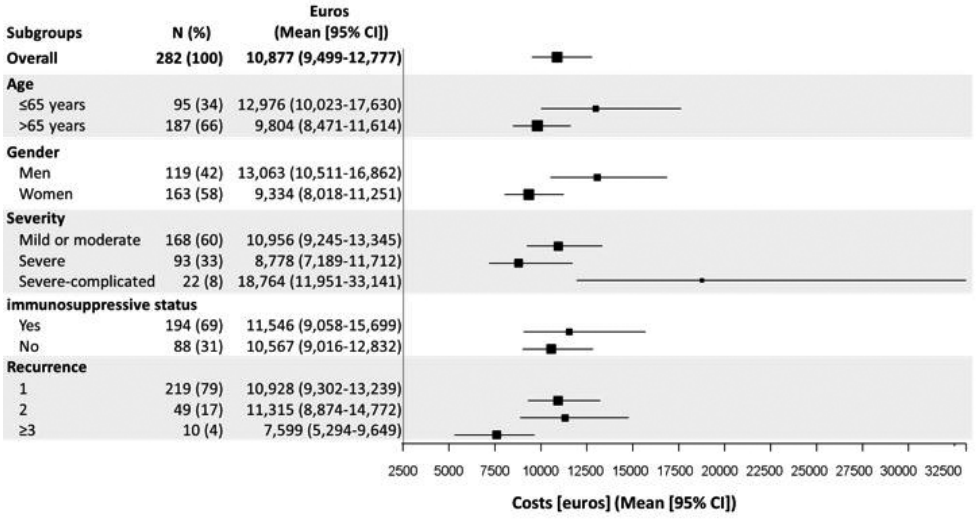

Figure 3 | **Total cost per episode of rCDI stratified according to age, sex, severity, immunosuppression and severity**

Figure 3 shows the total cost, stratified by subgroups. The total mean cost per rCDI episode was higher in patients aged ≤65 years (€ 12,976 vs. € 9,804, in patients aged ≤65 years and > 65 years, respectively), in men (€13,063 vs. €9,334, in men vs women, respectively), and in immunosuppressed patients (€11,545 vs. €10,567, in immunosuppressed and non-immunosuppressed patients, respectively). These results should be interpreted with caution due to the small sample size in some subgroups.

Sensitivity analysis. We included the 188 episodes with a primary diagnosis. Of the 102 episodes with a secondary diagnosis of CDI, 66 episodes were matched with controls fulfilling the established criteria. Therefore, 254 episodes (188 rCDI episodes as the primary diagnosis) were analysed. Both the total mean stay (SD) and the mean cost (SD) due to rCDI was very similar to the main analysis, resulting in 17.53 (23.84) days of hospital stay and €11.151 (9.649 – 13.244) per rCDI episode.

DISCUSSION

This study assessed the economic impact and burden of hospitalizations due to rCDI in real clinical practice in Spain. Unlike other studies, we took into account the cost of the pre-hospitalization emergency room stay and the cost of patient isolation due to infection. In addition, episodes of rCDI recorded as both primary and secondary diagnoses were included. Therefore, we were able to estimate the resource use and cost of rCDI episodes that require hospital management in real clinical practice.

Our results showed a mean hospital stay of 17.18 days per rCDI episode. Studies have shown that the mean stay in Spain ranges from 9.1 to 45.0 days per recurrent episode [35, 36], while in Europe it ranges from 20.1 to 33 days [36, 48, 49]. In general, while there are wide variations in the length of hospital stay, most studies agree that rCDI has a longer hospital stay than initial episodes of CDI. Wilcox et al. [50] observed a median hospital stay of 15.5 days for initial episodes and 21 days for recurring episodes, while Tresman and Goldenberg [49] found a mean stay of 17 and 33 days, for initial and recurring episodes, respectively.

The mean cost per rCDI episode in our study was € 10,877, of which approximately 93% corresponded to the hospital stay (€ 10,068). The costs found are clearly higher than those obtained in previous reports on the cost of rCDI in Spain. Asensio et al. [35] found a mean cost per CDI episode of €4,875 and €5,916 for the first and second recurrences, respectively, half the estimated costs found in our study. One of the main reasons for this difference may be the study design: we used a retrospective, multicentre observational design in real clinical practice, while Asensio et al. used the Delphi method, with a panel of three experts estimating the cost per episode. Although the Delphi method has proven useful in reaching consensus in areas of uncertainty or when empirical evidence is lacking, the results stem from the opinions and perceptions of experts. Our results are in line with similar European studies that found the cost of an episode of rCDI ranges from € 7,539 to € 31,121 [36, 48–50]. We observed that isolation rooms accounted for 47% of the total cost, results similar to those of other European studies, where isolation rooms contributed between 26% and 46% of the total cost of the episode [51, 52]. Despite its high contribution to the total cost, an isolation room of patients with symptoms of CDI is one of the key infection control measures [25].

The incidence rate of CDI in Spain has increased from 2.20 cases/10,000 patients in 2011 to 3.41 in 2016 [10]. *C. dif-*

ficile infections have a high rate of recurrence after the end of treatment, which may complicate the prognosis due to increased morbidity and mortality. In recent decades, in Europe the recurrence rate has increased to 35% [37] while, in Spain, descriptive studies have reported a recurrence rate of 12-18% [6, 13, 23]. The risk of recurrence increases after each new episode, increasing morbidity, health resource use and 90-day mortality [53], as shown by the stratification of the cost per episode of the first recurrence (€10,928) and the second recurrence (€11,315) in our study, although these results should be interpreted with caution due to the small sample size in some subgroups.

Some limitations of the study may have influenced the results. First, the methodology used to estimate additional days due to rCDI in episodes with rCDI recorded as a secondary diagnosis. Matching using the propensity score was successful in adjusting the imbalances observed between the two cohorts (rCDI episodes and episodes without CDI). However, this methodology cannot correct possible imbalances between the two cohorts due to potentially important unobserved characteristics.

Secondly, the use of the SNHDD administrative database to search for episodes without CDI (controls), means results were conditioned on the quality of the data record in the discharge reports. In addition, although this database is very useful in hospital management, it does not record potentially important information such as resource use during hospitalization (tests, treatments) or patient characteristics (weight, comorbidity, clinical characteristics).

Thirdly, the impact of rCDI could be underestimated because we analysed only hospitalized rCDI episodes and therefore the resource use due to a recurring episode after hospital discharge (if any) was not considered, nor were episodes that were moved to another hospital or long-stay centre considered. Neither was the cost of infection control measures, such as disposable gloves, gowns and thermometers or room cleaning after patient discharge considered.

In conclusion, until now, no Spanish study has been specifically designed to assess the impact of the hospital management of rCDI in real clinical practice. Therefore, our results may represent the first contribution on this topic available in Spain. Despite the limitations of the study, the results show that the recurrence of CDI represents a significant burden on the NHS, highlighting the importance of preventing CDI recurrences.

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CONFLICTS OF INTEREST

EB, has participated in clinical trials and advisory boards sponsored by MSD, Pfizer and Astellas. JC received fees as a speaker in conferences and advisory board meetings from Astellas and MSD. MJR-H received fees as a speaker and participant in advisory board meetings from Astellas and MSD. MS has lectured at meetings organized by pharmaceutical companies (MSD, Janssen, Pfizer and Gilead) or participated in some medical advice. He has not received direct grants or scholarships. JPH has received fees as a speaker and participant in advisory board meetings from Pfizer, MSD, Menarini and Zambon and a research grant from MSD. JAI reported no conflicts of interest. EO is an employee of Merck & Co. VL is an employee of Merck Sharp & Dohme. SM was an employee of Merck Sharp & Dohme. MC and EU are employees of Oblikue Consulting. EL declares he has been a speaker in a symposium organized by MSD.

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