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Clostridium difficile-related hospitalizations and risk factors for in-hospital mortality in Spain between 2001 and 2015

M.D. Esteban-Vasallo [a,*], J. de Miguel-Díez [b], A. López-de-Andrés [c], V. Hernández-Barrera [c], R. Jiménez-García [c]

[a] *Madrid Regional Health Authority, Public Health Directorate, Madrid, Spain*
[b] *Respiratory Department, Hospital General Universitario Gregorio Marañón, Facultad de Medicina, Universidad Complutense de Madrid, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain*
[c] *Preventive Medicine and Public Health Teaching and Research Unit, Health Sciences Faculty, Rey Juan Carlos University, Alcorcón, Madrid, Spain*

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SUMMARY

Aims: To examine trends in the incidence, characteristics and in-hospital outcomes of *Clostridium difficile* infection (CDI) hospitalizations from 2001 to 2015, to compare clinical variables among patients according to the diagnosis position (primary or secondary) of CDI, and to identify factors associated with in-hospital mortality (IHM).

Methods: A retrospective study was performed using the Spanish National Hospital Discharge Database, 2001–2015. The study population included patients who had CDI as the primary or secondary diagnosis in their discharge report. Annual hospitalization rates were calculated and trends were assessed using Poisson regression models and Jointpoint analysis. Multi-variate logistic regression models were performed to identify variables associated with IHM.

Findings: In total, 49,347 hospital discharges were identified (52.31% females, 33.69% with CDI as the primary diagnosis). The rate of hospitalization increased from 3.9 cases per 100,000 inhabitants in 2001–2003 to 12.97 cases per 100,000 inhabitants in 2013–2015. Severity of CDI and mean cost per patient increased from 6.36% and 3750.11€ to 11.19% and 4340.91€, respectively, while IHM decreased from 12.66% to 10.66%. Age, Charlson Comorbidity Index, severity, length of hospital stay and mean cost were significantly higher in patients with a primary diagnosis of CDI. Irrespective of the CDI diagnosis position, IHM was associated with male sex, older age, comorbidities, readmission and severity of CDI. Primary diagnosis of CDI was associated with lower IHM (odds ratio 0.60; 95% confidence interval 0.56–0.65).

Conclusion: CDI-related hospitalization rates are increasing, leading to a high cost burden, although IHM has decreased in recent years. Factors associated with IHM should be considered in strategies for the prevention and management of CDI.

* Corresponding author. Address: Public Health Directorate, Madrid Regional Health Authority, C/ San Martín de Porres, 6, 28035, Madrid, Spain. Tel.: +34 91 3700825.
E-mail address: maria.estebanv@salud.madrid.org (M.D. Esteban-Vasallo).

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Introduction

Clostridium difficile infection (CDI) is an intestinal infection. Colonization can be asymptomatic, and clinical symptoms can range from mild diarrhoea to toxic megacolon. Two factors exert a major influence on clinical expression of disease: the virulence of the infecting strain and the host immune response [1]. Antibiotic use remains the most important risk factor for CDI [1]. The risk of CDI and the severity of infection increase with age [2]. Other risk factors for infection are immunodeficiency, chemotherapy, organ transplantation, chronic kidney disease, inflammatory bowel disease (IBD), and exposure to an infant carrier or infected adult [3]. Frequent hospitalization and increased length of hospital stay (LOHS) are also risk factors for CDI [4].

The incidence and severity of CDI around the world have risen over the past 20 years due to the increased use and misuse of antibiotics, the rise of susceptible at-risk populations and the emergence of hypervirulent strains [5]. The impact of CDI in healthcare settings throughout the developed world is considerable in terms of mortality, morbidity and economic burden. In Spain, the mean annual incidence rate of CDI was 41.2 diagnoses per 100,000 discharges between 1997 and 2005, with a significant increasing trend [6]. In another study, the prevalence of CDI increased from 3.9 to 12.2 cases per 10,000 hospitalized patients from 1999 to 2007 [7]. The annual cost of CDI for the Spanish National Health Service was estimated to be €32.1 million in 2012, 95.6% of which was due to prolonged hospitalization [8].

Identifying factors associated with adverse outcomes of CDI would improve disease management. Several studies have identified different clinical parameters or host-related factors such as older age, underlying comorbidities and biological markers as risk factors for complicated CDI [9,10].

The objectives of this study were: to examine trends in the incidence, characteristics and in-hospital mortality of CDI hospitalizations from 2001 to 2015; to compare clinical variables according to the diagnosis position (primary or secondary) of CDI in the discharge report; and to identify factors associated with in-hospital mortality (IHM) among patients according to the diagnosis position of CDI.

Methods

A retrospective, observational study of all hospital admissions with *C. difficile* from 2001 to 2015 in Spain was undertaken. Data were obtained from the Spanish National Hospital Discharge Database (SNHDD), which compiles all public and private hospital data. The SNHDD includes patient variables (sex, date of birth), dates and circumstances of admission and discharge, up to 14 discharge diagnoses, and up to 20 procedures performed during the hospital stay [coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)]. All admissions with a primary or secondary diagnosis of CDI (ICD-9-CM code: 008.45) were collected. The primary diagnosis, coded in the first position, is the condition established at discharge as chiefly responsible for the hospitalization. The secondary diagnoses, codified in positions 2 to 14, gather all the pathological processes that are not the main reason for hospitalization, but coexist with it at the time of admission, appear during admission, or influence the duration of or treatment administered. The presence of CDI as the primary diagnosis indicates that the infection was present at admission and was its main cause, but it does not imply it is community associated as it could have been acquired in a previous hospitalization.

Comorbidity at the time of discharge was assessed by calculating the Charlson Comorbidity Index (CCI) as described by Quan et al. [11]. The presence of IBD was identified independently with diagnostic codes 555.x–556x, and surgery on the digestive system (procedure codes 42.x–54.x). Those cases suffering from toxic megacolon, perforation, colectomy, septic shock or septicaemia were considered to be severe cases of CDI, as described by Gomez-Simmonds et al. [12]. Both comorbidity and severity were detected using all the diagnoses and procedures recorded at discharge, irrespective of their position in the coding list. The hospitalization was considered to be a readmission when the patient had been discharged from the same hospital within the previous 30 days. LOHS was calculated from admission and discharge dates. IHM was defined by the proportion of patients who died during admission. Costs were calculated using diagnosis-related groups (DRGs). The mean cost of each DRG was estimated annually by the National Health Authorities, after the integration of information from the hospital's analytic accountability data and the patients' information from the SNHDD [13], and later assigned to each discharge according to the corresponding DRG. All costs shown were adjusted for the increment of inflation in the same period in Spain.

Statistical analysis

Five time periods (2001–2003, 2004–2006, 2007–2009, 2010–2012, 2013–2015) were considered. A descriptive statistical analysis was performed for all continuous variables and categories. Variables are expressed as proportions, as means with standard deviations, or as medians with interquartile ranges (LOHS). A bivariable analysis according to year was performed using the Chi-squared test for linear trend (proportions), analysis of variance (means) and Kruskall-Wallis (medians), as appropriate. Incidence rates of admission were estimated for CDI calculated per 100,000 inhabitants, according to the data from the Spanish National Institute of Statistics, as reported on 31st December each year. Trends in incidence rates were assessed using Poisson regression models adjusted by sex and age when appropriate.

Log linear Joinpoint regression was used to identify the period in which trend changes in CDI rates occurred by sex and by diagnosis position, as well as to estimate the annual percentage change. To identify variables associated with IHM among patients with CDI, three multi-variate logistic regression models were constructed: one for each diagnosis position of CDI (primary, secondary, both). The variables included in the multi-variable models were those with significant results in the bivariate analysis. Estimates are expressed as odds ratio (OR) and 95% confidence interval (CI).

All statistical analyses were performed using Stata Version 10.1, and the Joinpoint Regression Program Version 4.0.4 was used to analyse trends. Statistical significance was set at $P<0.05$ (two-tailed).

Ethical aspects

Data confidentiality was maintained at all times. Given the anonymous and mandatory nature of the dataset, it was not

necessary to obtain informed consent or approval from the ethics committee in accordance with Spanish legislation.

Results

In total, 49,347 hospitalizations were identified (52.3% in women) with CDI in Spain between 2001 and 2015 (Table I). Patients with a primary diagnosis of CDI accounted for 33.7% of the total. The incidence of CDI-related hospitalizations increased significantly from 3.9 per 100,000 inhabitants in 2001–2003 to 13.0 per 100,000 inhabitants in 2013–2015. Age increased significantly over time (68.4±20.4 years in 2001–2003 vs 69.4±20.3 years in 2013–2015), as did the proportion of women. The severity of CDI cases increased (6.4% in 2001–2003 vs 11.2% in 2013–2015), and so did the presence of CDI as the primary diagnosis (26.0% in 2001–2003 to 38.0% in 2013–2015). Distribution according to CCI showed no significant change over time. A diagnosis of IBD was identified in 3.59% of admissions. Admissions that had underdone surgery on the digestive system decreased from 27.28% in 2001–2003 to 21.91% in 2013–2015. Median LOHS for admissions for CDI was 21±26 days in 2001–2003, decreasing to 13±17 days in 2013–2015. In contrast, the mean cost per patient rose from 3750.1±2878.2€ in 2001–03 to 4340.9±2233.2€ in 2013–15. The proportion of emergency room admissions and readmissions increased from 85.1% and 28.1%, respectively, in 2001–2003 to 88.2% and 37.0%, respectively, in 2013–2015. Over the total time period, crude IHM among CDI cases was 11.5%, and this decreased significantly from 12.7% in 2001–2003 to 10.7% in 2013–2015.

The sex and age-adjusted hospitalization rate increased by 7.89% per year from 2001 to 2012, and by 21.65% per year from 2012 to 2015, with similar trends for men and women and when considering hospitalizations with CDI as the primary or secondary diagnosis (Figure 1).

The most common secondary diagnosis for patients admitted with a primary diagnosis of CDI was heart disease (5.1%), followed by hypertension (4.6%) and bacterial infection (4.5%) (Table A, see online supplementary material). The most common primary diagnoses for patients admitted with a secondary diagnosis of CDI were pulmonary disease or pneumonia (13.6%), septicaemia (5.5%) and urinary tract infection (4.5%).

The proportion of hospitalizations with CDI as the primary diagnosis increased from 26.0% in 2001–2003 to 37.9% in 2013–2015 (Table II). In total, 58.2% of patients with CDI as the primary diagnosis were women. Patients with a primary diagnosis of CDI were older (70.7 years vs 68.6 years; $P<0.001$) than patients with a secondary diagnosis of CDI, and comorbidity, IBD, operations on the digestive system, severity of CDI, LOHS and mean costs per patient were significantly lower in those with primary diagnosis. IHM was higher in patients with a secondary diagnosis of CDI than in patients with a primary diagnosis of CDI (13.8% vs 7.0%, $P<0.001$).

Table I
Characteristics of hospital admissions with *Clostridium difficile* infection (CDI) in Spain from 2001 to 2015

Variable		2001–2003	2004–2006	2007–2009	2010–2012	2013–2015	Total
Number of hospital admissions		4794	6608	9105	10,719	18,121	49,347
Incidence per 100,000 population*		3.9	5.1	6.8	7.8	13.0	7.4
CDI as primary diagnosis, *N* (%)*		1245 (26.0)	1776 (26.9)	2844 (31.2)	3890 (36.3)	6869 (37.9)	16,624 (33.7)
Female sex, *N* (%)*		2352 (49.1)	3286 (49.7)	4801 (52.7)	5653 (52.7)	9720 (53.6)	25,812 (52.3)
Age in years, mean (SD)*		68.4 (20.4)	69.16 (19.3)	69.77 (19.1)	69.21 (19.64)	69.4 (20.3)	69.3 (19.8)
Age group in years, mean (SD)*	0–14	113 (2.4)	115 (1.7)	142 (1.6)	247 (2.3)	570 (3.1)	1187 (2.4)
	15–44	563 (11.7)	712 (10.8)	935 (10.3)	1017 (9.5)	1487 (8.2)	4714 (9.5)
	45–64	718 (15.0)	1143 (17.3)	1647 (18.1)	2039 (19.02)	3351 (18.5)	8898 (18.0)
	65–74	1010 (21.1)	1332 (20.2)	1617 (17.8)	1822 (17)	3328 (18.4)	9109 (18.5)
	75–84	1470 (30.7)	2034 (30.8)	2808 (30.8)	3365 (31.39)	5323 (29.4)	15,000 (30.4)
	≥85	920 (19.2)	1272 (19.2)	1956 (21.5)	2229 (20.79)	4062 (22.4)	10,439 (21.1)
CCI, mean (SD)		1.28 (1.05)	1.29 (1.06)	1.28 (1.04)	1.30 (1.05)	1.32 (1.06)	1.30 (1.05)
CCI, *N* (%)	0	1190 (24.8)	1644 (24.9)	2214 (24.3)	2595 (24.2)	4284 (23.6)	11,927 (24.2)
	1	1835 (38.3)	2494 (37.7)	3514 (38.6)	4124 (38.5)	6899 (38.1)	18,866 (38.23)
	≥2	1769 (36.9)	2470 (37.4)	3377 (37.1)	4000 (37.3)	6938 (38.3)	18,554 (37.6)
Severity, *N* (%)*	Yes	305 (6.4)	470 (7.1)	846 (9.3)	1172 (10.9)	2027 (11.2)	4820 (9.77)
Inflammatory bowel disease	Yes	133 (2.77)	203 (3.07)	325 (3.57)	391 (3.65)	720 (3.97)	1772 (3.59)
Surgery on DS*	Yes	1308 (27.28)	1755 (26.56)	2482 (27.26)	2775 (25.89)	3970 (21.91)	12,290 (24.91)
Readmission, *N* (%)*	Yes	1345 (28.1)	1827 (27.6)	2703 (29.7)	3510 (32.7)	6703 (37.0)	16,088 (32.6)
ER admission, *N* (%)*	Yes	4081 (85.1)	5680 (86.0)	7822 (85.9)	9332 (87.1)	15,989 (88.2)	42,904 (86.94)
IHM, *N* (%)*		607 (12.7)	818 (12.4)	1159 (12.7)	1158 (10.8)	1931 (10.7)	5673 (11.5)
LOHS, median (IQR)*		21 (26)	20 (25)	17 (24)	15 (19)	13 (17)	16 (21)
Cost, mean (SD)*		3750.1 (2878.2)	4043.1 (3092.3)	4592.9 (3901.3)	4508.1 (2935.1)	4340.9 (2233.2)	4326.45 (2714.25)

CCI, Charlson Comorbidity Index; DS, digestive system; ER, emergency room; LOHS, length of hospital stay; IHM, in-hospital mortality; SD, standard deviation; IQR, interquartile range.
*$P<0.05$ to assess time trend from 2001 to 2015.
Tests used: Poisson regression (incidence), Chi-squared test (proportions), Student's *t*-test (means) and Mann–Whitney U-test (medians), as appropriate.

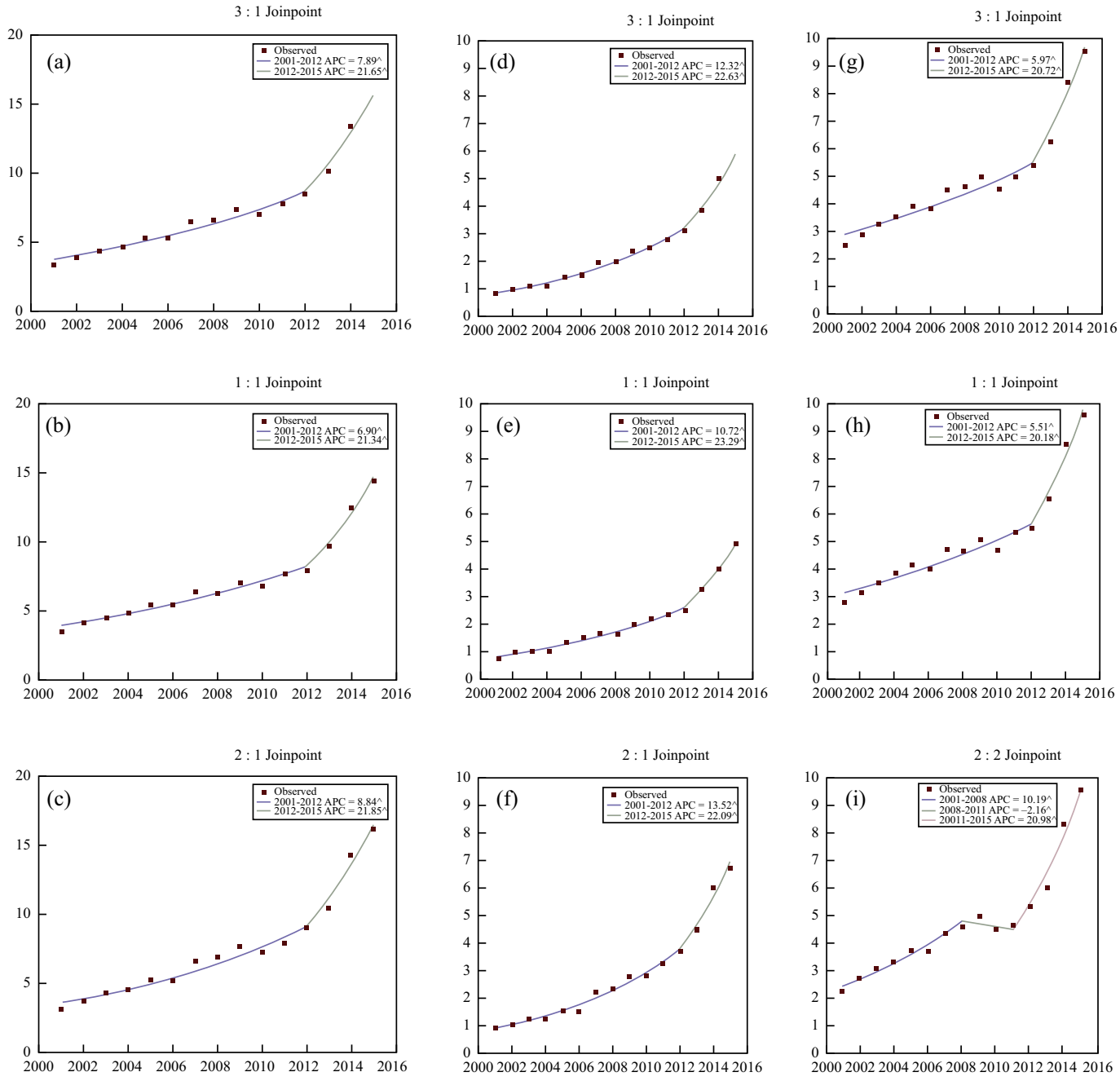

Figure 1. Joinpoint analysis in annual hospital admissions in patients with a diagnosis of *Clostridium difficile* infection (CDI) in Spain, 2001–2015. (a) Total patients with primary and secondary diagnosis of CDI. (b) Men with primary and secondary diagnosis of CDI. (c) Women with primary and secondary diagnosis of CDI. (d) Total patients with primary diagnosis of CDI. (e) Men with primary diagnosis of CDI. (f) Women with primary diagnosis of CDI. (g) Total patients with secondary diagnosis of CDI. (h) Men with secondary diagnosis of CDI. (i) Women with secondary diagnosis of CDI. APC, annual percentage change (based on rates that were age-adjusted using the Spanish National Statistics Institute Census projections) calculated using Joinpoint regression analysis. ^APC is significantly different from zero (two-sided $P<0.05$).

Regarding patients who died during hospitalization, those with a primary diagnosis of CDI were significantly older (79.8 vs 75.1 years), and had higher severity of CDI (40.7% vs 29.4%), lower proportion of operations on the digestive system (6.15% vs 12.6%), lower proportion of readmission episodes (8.2% vs 15.8%), lower emergency room admission rate (7.0% vs 13.9%), lower LOHS (12 vs 25 days) and lower cost per patient (4340.9€ vs 5862.0€) than those with a secondary diagnosis of CDI (Table III).

Among patients with CDI as the primary diagnosis, IHM increased significantly with age [adjusted OR (ORa) 1.05, 95% CI 1.04–1.05], in those with more comorbidities according to CCI (ORa 1.36, 95% CI 1.28–1.44), in those with severe CDI (ORa

Table II
Characteristics of hospital admissions of patients with a primary diagnosis and patients with a secondary diagnosis of *Clostridium difficile* infection (CDI), Spain, 2001–2015

		Primary diagnosis	Secondary diagnosis	*P*-value
Year, *N* (%)	2001–2003	1245 (26.0)	3549 (74.0)	<0.001
	2004–2006	1776 (26.9)	4832 (73.1)	
	2007–2009	2844 (31.2)	6261 (68.8)	
	2010–2012	3890 (36.3)	6829 (63.7)	
	2013–2015	6869 (37.9)	11 252 (62.1)	
Sex, *N* (%)	Male	6940 (41.7)	32,723 (66.3)	<0.001
	Female	9684 (58.2)	16,128 (49.3)	
Age in years, mean (SD)		70.67 (19.2)	68.58 (20.1)	<0.001
Age group in years, mean (SD)	0–14	274 (1.6)	913 (2.8)	<0.001
	15–44	1552 (9.3)	3162 (9.7)	
	45–64	2662 (16.0)	6236 (19.1)	
	65–74	2923 (17.6)	6186 (18.9)	
	75–84	5345 (32.1)	9655 (29.51)	
	≥85	3868 (23.3)	6571 (20.08)	
CCI, mean (SD)		1.17 (1.06)	1.37 (1.04)	<0.001
CCI, *N* (%)	0	5152 (30.99)	6775 (20.7)	<0.001
	1	5949 (35.79)	12,917 (39.5)	
	≥2	5523 (33.22)	13,031(39.82)	
Severity, *N* (%)	Yes	589 (3.54)	4231 (12.9)	<0.001
Inflammatory bowel disease	Yes	531 (3.19)	1241 (3.79)	<0.001
Surgery on DS	Yes	3789 (22.79)	8501 (25.98)	<0.001
Readmission, *N* (%)	Yes	6788 (40.8)	9300 (28.4)	<0.001
ER admission, *N* (%)	Yes	15,624 (94.0)	27,280 (83.4)	<0.001
IHM, *N* (%)		1162 (6.99)	4511 (13.8)	<0.001
LOHS, median (IQR)		9 (9)	21 (25)	<0.001
Cost, mean (SD)		3967.3 (669.4)	4961.7 (4100.5)	<0.001

CCI, Charlson Comorbidity Index; DS, digestive system; ER, emergency room; LOHS, length of hospital stay; IHM, in-hospital mortality; SD, standard deviation; IQR, interquartile range.
The *P*-value for the difference between patients with a primary diagnosis of CDI and patients with a secondary diagnosis of CDI was calculated using logistic regression adjusted by age and sex.

12.56, 95% CI 10.31–15.30), in those who underwent gastrointestinal surgery (ORa 1.78, 95% CI 1.22–2.59), and in those with a readmission episode (ORa 1.18, 95% CI 1.04–1.34) (Table IV). Older age, readmission, comorbidities and severe CDI increased the risk of IHM in patients with CDI as a secondary diagnosis. The presence of IBD was associated with lower risk of IHM in patients with CDI as either a primary or secondary diagnosis. Primary diagnosis of CDI was associated with significantly lower IHM (ORa 0.60, 95% CI 0.55–0.64) than in patients with a secondary diagnosis of CDI.

Discussion

The analysis of CDI-related hospitalizations showed a clear upward trend between 2001 and 2015 in Spain. This increase was also detected when analysing hospitalizations with CDI as the primary or secondary diagnosis, in both men and women. There was also an increasing trend in the proportion of hospitalizations with CDI as the primary diagnosis, severe cases and readmissions. Similar studies in the USA showed much higher figures for the same temporal period, whether considering total rates, by age group or primary diagnosis [14–16]. Nevertheless, in Finland, CDI-related hospitalization rates similar to those in the present study were found between 1996 and 2004 [17]. The increasing trend observed was detected previously in Spain using the SNHDD at national level for the period 1997–2005 [6]. Similarly, the same trend in CDI-related hospitalizations was detected in other studies from different countries worldwide, even when primary diagnoses alone were considered [10,14,16–18].

The increase in CDI-related hospitalizations can reflect both an increase in the incidence of the infection or in the severity of the cases affected, with a greater proportion requiring hospital care. These situations have been attributed to multiple factors, including the aging population, the increased use of broad-spectrum antibiotics and the emergence of hypervirulent strains [19]. Although in cases with CDI as the primary diagnosis, the infection might have been acquired in a previous hospitalization, they were more likely to be community associated, so the increasing trend of hospitalizations could reflect an increase in community-acquired cases.

The increase in incidence could also reflect enhanced searching for cases due to greater awareness of the problem among clinicians, and improvements in laboratory diagnostic techniques. In 2007, a national survey of laboratory procedures for *C. difficile* diagnostic testing found that CDI was underdiagnosed in most Spanish hospitals because of the widespread use of enzyme immunoassays performed directly on stool specimens as the only diagnostic procedure [20]. Since then, efforts have been made to improve the diagnostic tests used by laboratories, and to increase awareness of this disease among

Table III
In-hospital mortality according to study variables of patients with a primary diagnosis of *Clostridium difficile* infection (CDI) and patients with a secondary diagnosis of CDI, Spain, 2001–2015

		Primary diagnosis	Secondary diagnosis	*P*-value
Year, *N* (%)	2001–2003	85 (6.8)	522 (14.7)	<0.001
	2004–2006	136 (7.7)	682 (14.1)	
	2007–2009	239 (8.4)	920 (14.7)	
	2010–2012	274 (7.0)	884 (12.9)	
	2013–2015	428 (6.2)	1503 (13.4)	
Sex, *N* (%)	Male	526 (7.6)	2359 (14.2)	<0.001
	Female	636 (6.6)	2152 (13.3)	
Age in years, mean (SD)		79.8 (11.7)	75.1 (15.5)	<0.001
Age group in years, mean (SD)	0–14	0 (0)	33 (3.6)	<0.001
	15–44	21 (1.3)	176 (5.6)	
	45–64	89 (3.3)	658 (10.5)	
	65–74	169 (5.8)	812 (13.1)	
	75–84	416 (7.8)	1509 (15.6)	
	≥85	467 (12.1)	1323 (20.1)	
CCI, mean (SD)		1.60 (1.11)	1.61 (1.07)	0.897
CCI, *N* (%)	0	180 (3.5)	593 (8.7)	<0.001
	1	403 (6.8)	1692 (13.1)	
	≥2	579 (10.5)	2226 (17.1)	
Severity, *N* (%)	Yes	240 (40.7)	1243 (29.4)	<0.001
Inflammatory bowel disease	Yes	38 (7.16)	92 (7.41)	0.849
Surgery on DS	Yes	233 (6.15)	1071 (12.6)	<0.001
LOHS, median (IQR)		12 (16)	25 (30)	<0.001
Cost, mean (SD)		4340.9 (539.4)	5862.0 (4429.7)	<0.001

CCI Charlson Comorbidity Index; DS, digestive system; ER, emergency room; LOHS, length of hospital stay; SD, standard deviation; IQR, interquartile range.
The *P*-value for the difference between patients with a primary diagnosis of CDI and patients with a secondary diagnosis of CDI was calculated using logistic regression adjusted by age and sex.

Table IV
Multi-variable analysis of factors associated with in-hospital mortality among patients with *Clostridium difficile* infection according to diagnosis position, Spain, 2001–2015

		Primary diagnosis	Secondary diagnosis	Any position
		ORa (95% CI)	ORa (95% CI)	ORa (95% CI)
Year		0.96 (0.95–0.98)	0.98 (0.97–0.99)	0.98 (0.97–0.98)
Sex	Female (vs male)	0.87 (0.76–0.99)	0.90 (0.84–0.95)	0.89 (0.84–0.94)
Age		1.05 (1.04–1.05)	1.02 (1.01–1.03)	1.03 (1.03–1.03)
CCI		1.36 (1.28–1.44)	1.23 (1.19–1.27)	1.26 (1.23–1.30)
Severity	Yes (vs no)	12.56 (10.31–15.30)	3.63 (3.36–3.94)	4.38 (4.07–4.72)
Inflammatory bowel disease	Yes (vs no)	0.70 (0.59–0.83)	0.85 (0.79–0.92)	–
Surgery on DS	Yes (vs no)	1.78 (1.22–2.59)	–	0.84 (0.78–0.90)
Readmission	Yes (vs no)	1.18 (1.04–1.34)	1.33 (1.24–1.43)	1.31 (1.23–1.39)
ER admission	Yes (vs no)	0.98 (0.75–1.29)	0.89 (0.82–0.98)	0.89 (0.81–0.97)
LOHS		1.02 (1.01–1.02)	1.00 (1.00–1.01)	1.01 (1.00–1.01)
Primary diagnosis	Yes (vs secondary diagnosis)	NA	NA	0.6 (0.55–0.64)

CCI, Charlson Comorbidity Index; DS, digestive system; ER, emergency room; LOHS, length of hospital stay; aOR, adjusted odds ratio (logistic regression model); CI, confidence interval; NA, not applicable.
Only those variables that showed a significant association are shown.

clinicians and microbiologists. Changes in diagnostic testing and typing capacity for CDI performed between 2011 and 2014 could explain, at least partially, the marked accentuation of the upward trend since 2012. Despite that, according to a study performed in 2013 to evaluate the impact of these efforts, CDI remained a rather neglected disease because of the lack of sensitive diagnostic tests in some institutions and, especially, the absence of clinical suspicion [21]. In fact, a point prevalence survey of healthcare-associated infections in acute care hospitals performed by the European Centre for Disease Prevention and Control (ECDC) in 2011–2012 showed that the proportion of healthcare-associated gastrointestinal infections confirmed as CDI in Spain was among the lowest compared with other European countries [22]. In any case, the decrease in the

underdiagnosis of CDI could have an effect on the observed trend, but the upward tendency affects the entire period, indicating a real increasing trend with more factors involved.

As in other hospitalization studies, patients with CDI were predominantly women and elderly [2,6,7,10,14,17,23]. The association between age and CDI is likely to be multi-factorial, including increased exposure to antibacterials and the healthcare environment, more comorbidities and diminished immune response. The proportion of hospitalizations with CDI as the primary diagnosis (33.7%) was similar to the value reported in the analysis of hospitalizations in the USA (33%) [14,23]. As in the present study, cases with a primary diagnosis of CDI have been associated with female sex, shorter LOHS, less severe illness and lower mortality [14,23]. The increase in these cases could be associated with increased use of antibiotics (including broad-spectrum antibiotics) in primary care, and with early hospital discharges to reduce costs. The latter may also induce a higher proportion of readmissions. In the present study, one out of three CDI-related hospitalizations was a readmission, and the proportion of readmissions has increased. Readmissions in patients aged ≥65 years have been associated with comorbidities, antibiotic use and hospital exposure [24].

Over time, cases with severity criteria have doubled. This trend, apparently contradictory when compared with that of mortality, could be affected by the definition used for severe disease. Two studies among inpatients with healthcare-associated CDI found no significant trends in severity (when it was defined as death, admission to the intensive care unit or colectomy) between 2009 and 2015 in Canada, and for the period 2010–2014 in Australia [25,26]. In the present study, the frequent presence of other infections in these patients could increase the probability of developing sepsis, which, although not caused by CDI itself, would constitute a criterion of severity. Several risk factors for complicated CDI, such as older age, underlying comorbidities, acute renal failure, infection by some strain types, and some abnormal vital signs and blood tests, have been identified [9,10,27,28]. The increase in these factors could, at least partially, explain this trend, although it could also be affected by a spurious effect due to an improvement in coding.

LOHS decreased over time, reaching median values in the upper limit of the described range (five to 15 days) [29]. Concurrently, the charges per CDI-related hospitalization decreased since 2010, as described between 2005 and 2014 in the USA [10]. Nonetheless, the total costs for CDI-related hospitalizations have increased in Spain due to the increasing incidence of CDI. This is a significant economic burden, confirmed in other European countries in recent years [30], and reinforces the need for prevention and early control of CDI. Direct comparisons of costs with other studies are limited due to the use of different methodologies. Two recent reviews showed a marked variability of the costs, often due to differences between hospitals in the selection of data included in the cost estimates [29,30], emphasizing the need to estimate reliable and reproducible costs for hospitalized patients with CDI [29].

IHM in this study was at the lower range reported by other studies, which fluctuated between 8% and 37% [10,31]. With regard to the decrease in mortality detected since 2010, Luo et al. also described a significant decrease from 9.7% in 2005 to 6.8% in 2014 in a retrospective cohort study [10]. The same trend was evident when considering patients admitted with a principal diagnosis of CDI between 2004 and 2014, despite increasing infection rates [32], and for inpatient and outpatients for the period 2003–2014 [16]. This trend could simply be a result of the increase in the proportion of cases with CDI as the primary diagnosis (associated with lower mortality); however, it significantly declined independently of the diagnostic position of CDI. This could indicate improvements in care in recent years, such as the use of fidaxomicin, approved in 2012 in Spain. Recent data from the UK show its potential impact on reducing recurrences and all-cause mortality [33]. The decrease in mortality could also be partially explained by changes in the characteristics of the hospitalizations. According to the study data, the factors independently associated with mortality were male sex, age, comorbidities, severity, readmission, LOHS and presence of CDI as a secondary diagnosis.

Over the study period, the proportion of men and hospitalizations with CDI as a secondary diagnosis have decreased, but severity and readmissions have increased. Most previous studies assessing differences in CDI outcomes by sex found no dissimilarities [34], and McGowan et al. found no difference by sex in 30-day mortality in a large retrospective cohort of patients in 10 hospitals in the UK between 2002 and 2008 [35]. A retrospective analysis of the US National Hospital Discharge Surveys from 2001–2010 showed that patients with CDI as a secondary diagnosis experienced significantly higher IHM, and observed two different trends: increasing IHM in patients with CDI as a secondary diagnosis, but decreasing IHM in patients with a primary diagnosis of CDI [23]. Mortality in patients with CDI as a secondary diagnosis may be attributed to complications from other comorbid illnesses or intercurrent infections, and could also be more likely to be hospital-acquired CDI, with a higher risk of mortality [27]. As in the present study, age has been widely described as the main risk factor for mortality related to CDI [27,34–36], and other identified factors are underlying comorbidities [27,36], pre-existing corticosteroid use, colectomy, intensive care unit admission, altered laboratory parameters and ribotype 027 [27,34,36]. In hospitalized patients with CDI as the primary diagnosis, operations on the digestive system registered are subsequent to the infection and therefore probably related to treatment of complicated cases. These circumstances are related to a worse prognosis, and that could explain the association with higher mortality in these cases. IBD is a documented risk factor for CDI [1], and for the development of fulminant colitis [37]. CDI in these patients present a greater proportion of worse outcomes, with longer LOHS, higher rates of colectomies, and increased mortality than in patients without CDI [38]. However, when adjusting by other variables including age, sex, comorbidities and severity, mortality was lower than in patients without IBD, perhaps because of earlier detection and treatment.

The main limitation of this study was that the identification of cases relied on ICD-9-CM coding. Variability in the codification and recording process can occur, and improvements in the completeness and accuracy of the records can have an impact on rates. In addition, there was a lack of laboratory information on tests used to confirm the diagnosis of CDI, strain identification was not performed, and antibiotic exposure histories were not available. Additionally, an initial CDI episode could not be discriminated from a recurrent CDI episode, nor could hospital- and community-acquired infections be distinguished from each other.

Despite its limitations, the SNHDD is a valuable source of information for the surveillance of CDI. It allows analysis of an

important number of patients due to the incorporation of information from all the population. Moreover, the source is easily accessible with no additional cost, and the availability of time series allows the analysis of temporal trends.

In conclusion, CDI-related hospitalization rates are increasing in Spain, with a high cost burden, although IHM has decreased in recent years. Male sex, older age, more comorbidities, readmission with CDI, emergency room admission, severity and CDI as a secondary diagnosis were factors independently associated with higher IHM. These factors should be considered in strategies for the prevention and management of CDI. Specific surveillance systems should be implemented widely to assess trends of disease (including microbiological data to monitor strains and antimicrobial susceptibility) and adverse outcomes. The use of standardized protocols, such as the European surveillance protocol, along with the surveillance tools provided by ECDC [39], could improve CDI diagnostic practices and also allow comparisons.

Conflicts of interest statement
None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2018.09.006.

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