Research articles

INCREASING RATES IN *CLOSTRIDIUM DIFFICILE* INFECTION (CDI) AMONG HOSPITALISED PATIENTS, SPAIN 1999-2007

A Asensio (aasensio.hpth@salud.madrid.org)¹, J Vaque-Rafart², F Calbo-Torrecillas³, J J Gestal-Otero⁴, F López-Fernández⁵, A Trilla-García⁶, R Canton⁷, EPINE Working Group

1. Department of Preventive Medicine, Hospital Universitario Puerta de Hierro. Madrid, Spain

2. Department of Preventive Medicine, Hospital Vall d'Hebron. Barcelona, Spain

3. Department of Preventive Medicine, Hospital Carlos Haya. Málaga, Spain

4. Department of Preventive Medicine and Public Health, University of Santiago de Compostela, Spain

5. Department of Preventive Medicine, Hospital Universitario Puerto del Mar, Cádiz, Spain

6. Epidemiology Unit. Hospital Clinic. Barcelona, Spain

7. Department of Microbiology. Hospital Universitario Ramón y Cajal. Madrid, Spain

Limited information is available on the burden and epidemiology of *Clostridium difficile* infection (CDI) in Spain. The present report communicates the secular trends in prevalence of CDI among hospitalised patients in Spain from 1999 through 2007. Data were obtained through the EPINE study (Estudio de prevalencia de las infecciones nosocomiales en los hospitales españoles), a point prevalence study series of nosocomial infections among patients admitted to hospital in Spain.

A total of 378 cases with CDI were identified. Median age was 74 years. Prevalence rates of CDI increased from 3.9 to 12.2 cases per 10,000 hospitalised patients and showed a significantly increasing secular trend from 1999 through 2007 (prevalence rate ratio per each year increment 1.09; 95% CI 1.05 – 1.14). Percentage of hospitalised patients receiving antimicrobials increased linearly from 36.0% in 1999 to 40.7% in 2007 ($p < 0.001$) and was strongly correlated to CDI prevalence (R square = 0.73; regression coefficient = 1.194, 95% CI = 1.192 – 1.196).

Introduction

Clostridium difficile is the most commonly diagnosed cause of infectious hospital-acquired diarrhoea [1]. Since 2003, outbreaks of severe nosocomial diarrhoea, caused by a new virulent strain of *C. difficile* Type O27, characterised as toxinotype III, North American pulsed-field type 1 (NAP1), restriction-endonuclease analysis group type BI and PCR-ribotype O27 have been recognised in Canada and the USA, and soon thereafter in several European countries, as well as in Japan, evoking great concern among public health authorities [2-5]. Limited information is available on the burden and epidemiology of *C. difficile* infection (CDI) in Spain. The present report communicates the secular trends in prevalence of CDI among hospitalised patients in Spain from 1999 through 2007 and factors associated with CDI prevalent cases.

Methods

Since 1990, a point prevalence study series of nosocomial infections among patients hospitalised in acute care facilities have been conducted in Spain (Estudio de prevalencia de las infecciones nosocomiales en los hospitales españoles – EPINE study).

Each year in May, acute care hospitals in Spain are requested to voluntarily join the EPINE prevalence study. Participating hospitals fill a standardised questionnaire on each hospitalised patient as well as overall data on the hospital and the hospital's wards.

CDI diagnosis relies on CDC case-definitions for nosocomial infections (note: the EU case definitions were not available at the time of the start of the study), and includes cases of either clinical diarrhoea or toxic megacolon with laboratory evidence of positive stool culture and/or toxin assay for *C. difficile*. Thus our analysis encompassed a symptomatic population with a positive microbiological confirmation of CDI by culture, toxin assay or both.

In addition to information on nosocomial infections, the patient forms collected from the hospitals included demographic data (age and gender); information on underlying clinical conditions such as diabetes mellitus, renal failure, immunosuppression, chronic pressure ulcers and hypoalbuminemia; healthcare exposures such as previous surgery, enteral feeding, immunosuppressive therapy, use of antibiotics (as the proportion of patients receiving any antimicrobial on the day of the survey); type of ward (general medical as opposed to a surgical, intensive care, paediatric or obstetric ward); and size of the hospital as measured by number of beds (small: lesser than 200 beds; medium: 200-500 beds; large: greater than 500 beds). Hospital validated forms were sent to an independent central analysis unit for further validation and analysis. A hospital report was sent back to every participating hospital to avoid possible disagreements before final integration of the collected results in a centralized database. We focused our analysis on the period 1999-2007.

Prevalence rates were expressed as the number of patients with CDI per 10,000 hospitalised patients. Comparisons of facilities, clinical conditions, exposures and demographic features were made by chi-square test, likelihood ratio test, Student's *t* test or Mann-Whitney test if appropriate. Secular trends were evaluated by Poisson regression. For factors associated with CDI, prevalence rate ratios and 95% confidence intervals were computed. For correlation of the use of antimicrobial and the annual prevalence

rates Spearman correlation coefficient and regression coefficient along 95% confidence intervals were calculated. All calculations were performed with Stata/SE 9.0 statistical software.

Results

Between 1999 and 2007 on average 249 hospitals per year participated in the EPINE survey yielding a representative sample of almost 57,000 hospitalised patients per year. Most of the hospitals

(82-85%) participating in the survey at any given year took part in the entire nine-year series. The mean age of patients increased from 56.2 years in 1999 to 58.7 years in 2007. A total of 378 CDI cases were identified. Prevalence rates of CDI ranged from 3.9 cases/10,000 patients in 1999 to 12.2 cases/10,000 patients in 2007, and showed a significantly increasing trend from 1999 through 2007 (prevalence rate ratio for one year increment 1.09; 95% CI 1.05 – 1.14) (Table 1). Prevalence rates were consistently

TABLE 1

Prevalence rates of *Clostridium difficile* infection (CDI) and use of antimicrobials in hospitals in Spain, by year of the survey

	1999 (N=233)	2000 (N=243)	2001 (N=243)	2002 (N=246)	2003 (N=241)	2004 (N=258)	2005 (N=257)	2006 (N=253)	2007 (N=266)	Prevalence ratio*	95% CI
Age group											
18-64 years											
Cases	6	9	11	11	12	11	14	8	26		
Patients	23,077	23,357	23,369	22,690	22,565	24,130	23,823	23,857	25,042		
Prevalence rate	2.6	3.9	4.7	4.8	5.3	4.6	5.9	3.4	10.4	1.12	(1.04-1.21)
65-79 years											
Cases	8	11	14	16	10	15	19	14	24		
Patients	18,569	19,164	19,718	18,752	18,542	19,488	19,256	18,513	19,466		
Prevalence rate	4.3	5.7	7.1	8.5	5.4	7.7	9.9	7.6	12.3	1.09	(1.03-1.18)
≥ 80 years											
Cases	7	17	10	13	9	17	13	17	23		
Patients	7,170	7,649	8,342	8,493	8,738	9,468	9,975	10,624	11,786		
Prevalence rate	9.8	22.2	12.0	15.3	10.3	18.0	13.0	16.0	19.5	1.03	(0.96-1.10)
All age groups											
Cases	21	39	35	40	33	45	50	40	75		
Patients	53,689	55,323	56,321	54,882	54,864	58,672	58,379	57,989	61,496	1.09	(1.05-1.14)
Prevalence rate	3.9	7.0	6.2	7.3	6.0	7.7	8.6	6.9	12.2		
Patients receiving antimicrobials (%)	36.0	36.7	36.4	37.0	36.9	38.6	39.4	39.4	40.7		

Prevalence rates are given per 10,000 hospitalised patients

N = number of participating hospitals

*Prevalence ratio for one year increment, estimated by Poisson regression

TABLE 2

Clinical and demographic characteristics of patients with *Clostridium difficile* infection (CDI) in comparison with non-CDI patients, hospitals in Spain 1999-2007

	CDI patients N = 378	non- CDI patients N = 511,237	Prevalence ratio (95% CI)	p value
Age in years, median (range)	74 (4-97)	64 (1-99)	10*	<0.001
Age > 65 years	207 (68.3%)	216,361 (48.1%)	2.3 (1.8-3.0)	<0.001
Male gender	203 (54.4%)	259,068 (51.6%)	1.1 (0.9-1.4)	0.273
Renal failure	80 (22.2%)	41,787 (8.5%)	3.1 (2.4-3.9)	<0.001
Diabetes mellitus	95 (26.1%)	97,475 (19.8%)	1.4 (1.1-1.8)	<0.003
Immunodeficiency	40 (11-1%)	18,305 (3.7%)	3.2 (2.3-4.5)	<0.001
Hypoalbuminemia	107 (30.3%)	29,093 (6.1%)	6.7 (5.3-8.4)	<0.001
Pressure ulcers	69 (19.1%)	24,051 (5.0%)	4.5 (3.5-5.9)	<0.001
Previous surgery	57 (15.5%)	151,639 (30.2%)	0.4 (0.3-0.6)	<0.001
Enteral feeding	60 (16.4%)	31,990 (6.5%)	2.8 (2.2-3.7)	<0.001
Immunosuppressive therapy	62 (17.2%)	41,468 (8.4%)	2.3 (1.7-3.0)	<0.001
Hospital size**				
< 200 beds	75 (19.8%)	147,521 (28.9%)	Reference	< 0.001
200-500 beds	145 (38.4%)	213,673 (41.8%)	1.3 (1.0-1.8)	
> 500 beds	158 (41.8%)	149,930 (29.3%)	2.1 (1.6-2.7)	
Medical wards***	266 (70.4%)	209,276 (40.9%)	3.4 (2.7-4.3)	<0.001

* Median difference

** Likelihood ratio test=30.7

*** In this study, we use the term "medical ward" to indicate internal medicine (and its subspecialties) wards as opposed to "non-medical wards" including surgical, intensive care, paediatric and obstetric wards.

higher in older age groups for every year. Furthermore, for adults, prevalence rates showed a statistically significant increasing time trend for every age group except for the group of patients aged 80 years and older (Table 1).

The prevalence of use of antimicrobials in the hospitalised population (given as the number of patients on antimicrobials per 100 hospitalised patients) increased linearly from 36.0% in 1999 through 40.7% in 2007 ($p < 0.001$) (Table 1) and showed a strong correlation with CDI prevalence rates ($R^2 = 0.73$; regression coefficient for percentage of use of antimicrobials 1.194, 95% confidence interval 1.192 – 1.196).

Comparison of CDI and non-CDI patients by main characteristics is displayed in Table 2. No differences were found for gender. However, CDI patients were older, presented more frequently underlying conditions such as renal failure, diabetes mellitus, immunodeficiency, pressure ulcers or hypoalbuminemia. CDI patients were also more frequently exposed to enteral feeding, and to immunosuppressive therapy, but significantly less often exposed to surgical procedures. Furthermore, being admitted to a general medical ward (such as internal medicine or its subspecialties: cardiology, pulmonology, etc.), as opposed to a surgical, intensive care, paediatric or obstetric ward was associated with a higher prevalence of CDI, and so was the size of the hospital (rate ratio 1.3 and 2.1 for medium and large size hospitals, respectively, compared with small size hospitals) (Table 2).

Discussion

One of the strengths of this prevalence series is that it represents more than half of the population hospitalised in acute care centres in Spain in a given day, and most data come from hospitals that have regularly participated in the survey every year. These data indicate that prevalence rates of CDI per 10,000 hospitalised patients over the period 1999-2007 increased significantly from 3.9 to 12.2, at an annual rate of 9%. Furthermore, this increase could also be demonstrated for patients pertaining to the age group of 18-79 years (the average annual increases for 18-64-year-olds and 65-79-year-olds were 12% and 9% respectively).

Several factors could explain this increase in CDI rates. When looking for potential outbreaks that could account for the differences between the various years, we were able to identify one hospital in 2002, two hospitals in 2004, another hospital in 2006 and three hospitals in 2007 showing point prevalence rates higher than 40 per 10,000 patients. Thus, even if prevalence surveys are not a powerful tool to detect outbreaks, the hypothesis of increasing trends related to more frequent hospital outbreaks in most recent years cannot be ruled out on the basis of our data.

Exposure to several classes of antimicrobials has been consistently found to be associated with CDI [6]. During the study period the proportion of patients receiving antimicrobials increased significantly and was found strongly correlated to the CDI prevalence rates. This increase in the use of antimicrobials suggests it could be one of the causes of the observed increase in CDI rates. Nevertheless, this hypothesis can not be proven from the ecological trend presented in our study since individual exposition should be taken into account for a causal association and we lacked data on individual patients' exposures to antimicrobials before their developing CDI.

It has been previously shown that the older and the sicker the patients the more prone they are to CDI. In fact, in our study, CDI patients were older than the patients not infected, and CDI rates were consistently higher for older age groups during the entire study period. Furthermore, the mean age of patients increased by almost 2.5 years from 1999 to 2007. The severity of the main underlying disease and/or the number of comorbidities also increased during the period [7] and could be another factor accounting for the increase in CDI.

The possibility that the new virulent strain of *C. difficile* Type O27 could account for the increasing trend observed is extremely remote. This strain has been identified in Spain in two cases only: an imported case of CDI in a patient transferred from a hospital in the United Kingdom, and another one in a laboratory technician who had worked with *C. difficile* isolates and subsequently developed CDI. However, no outbreaks associated with this strain have been communicated to date [8].

As previously reported, the underlying diseases and certain clinical characteristics were associated with a higher risk of CDI. We found diabetes mellitus, renal failure, immunodeficiency or hypoalbuminemia as well as being subjected to enteral feeding or immunosuppressive therapy to be associated with CDI. Furthermore, being admitted to a general medical ward and a large hospital, were both associated with a higher rate of CDI, whereas a history of previous surgery was associated with a lower rate of CDI. However, higher rates of CDI in larger hospitals could also be related to the more complex case-mix and to better awareness of CDI by clinicians in third care, including many referral, centres.

Our study has several limitations. Prevalence rates are not directly comparable to incidence rates that have been proposed for surveillance of CDI. Estimation of incidence rates from prevalence rates in the hospital framework is risky and has not been recommended [9]. A calculation from the formula proposed by Rhame and Sudderth [10] yielded an average incidence rate of 9.8 cases/10,000 patient-days for the whole period studied (1999-2007). This estimate would be within the range of other incidence estimates [11-14] before the emergence of the new virulent *C. difficile* Type O27.

It is also likely that the figures we obtained underestimate the actual prevalence, since testing for *C. difficile* is not a routine clinical practice in less severe cases, and is performed at the discretion of the attending physician. On the other hand, in recent years, clinicians have shown increased awareness of CDI in endemic situations and have more frequently tested for *C. difficile* toxins thus yielding a higher number of CDI diagnoses.

Further limitation of our study is that we lack information on strain identification therefore the importance of *C. difficile* Type O27 can not be definitely ruled out. Both cross-sectional and ecological studies are not a valid study design for risk factor research as they do not allow for establishing causal inferences, but they can point out potential risk factors for further evaluation. Another concern is seasonality. As the survey was performed every year during May, seasonal variations in time could not be assessed. Other studies have observed seasonality with rates peaking in winter months and lower rates in summer [15]. However, the fact that we performed the survey in the same month each year, although precluding a study of seasonality, allowed us to measure trends.

To conclude: over the 1999-2007 period prevalence rates of CDI increased significantly in Spanish hospitals. On-going surveillance systems are needed to closely monitor incidence, *C. difficile* strains characteristics, as well as the changing epidemiology of CDI in Spain.

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