Risk of Clostridioides difficile infection recurrence in the VINCat hospitals: a prospective observational cohort study

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Short communication

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ABSTRACT

Background

The 2016 cumulative incidence of Clostridioides difficile infection (CDI) in Spain was reported by European Center for Disease Control (ECDC) to be above the mean of other European countries. The aim of this multicenter prospective observational cohort study was to examine the risk factors that determine 90-day CDI recurrence in Catalonia, Spain.

Methods

The study included 558 consecutive adults admitted to hospital who had a symptomatic, first positive, CDI diagnosis. Sociodemographic, clinical, and epidemiological variables were recorded. The primary outcome was 90-day CDI recurrence.

Results

In this Catalan population, having received more than 1 course of antibiotics in the 30 days prior to CDI diagnosis (OR=2.459, 95% CI: 1.195; 5.060, *p*=0.015) and active chemotherapy (OR=4.859, 95% CI: 1.495; 15.792, *p*=0.009) are significant predictors of 90-day CDI recurrence.

Conclusions

The identification of independent risk factors of 90-day CDI recurrence will enable the optimization of preventive measures in at-risk populations.

KEYWORDS

Clostridioides difficile infection, colitis, recurrence, risk factors

Introduction

Clostridioides difficilele, is a Gram-positive, spore-forming, strict anaerobic bacterium that causes *C. difficile* infection (CDI). It is transmitted via the oral-fecal route and it is the main cause of healthcare-related infective diarrhea, as well as often being associated with community-acquired cases of colitis [1].

C. difficile spores are highly resistant to environmental conditions, including alcohol-based hand washes and many disinfectants, allowing them to remain on surfaces for long periods of time. This is extremely problematic in health-care settings [2], with transmission of *C. difficile* spores occurring for the most part via the contaminated hands of health-care professionals, but also through contact with contaminated surroundings or contaminated medical utensils and devices [3]. In Spain, the mean hospital incidence density of CDI reported in 2016 was 4,26 episodes/10.000 patients- days above the mean European incidence [4].

Recurrence of CDI is very common, and it leads to significant morbidity and increased healthcare costs. After successful treatment of an initial episode, up to 15-35% patients experience disease recurrence with a relapse of CDI symptoms within 3 months [5–7]. Key risks have been previously analyzed, with several factors including age >65 years, severe underlying disease, concomitant use of non-CDI active antibiotics, renal failure, history of previous CDI, possibly continued use of antacid medications, initial disease severity and recent hospitalization being associated with increased risk of recurrence [6,8,9]. Ideally, these risk factors could be used as clinical prediction tools that allow the attending physicians to respond quickly and effectively to reduce the risk of subsequent recurrences [6].

In Catalonia (Spain), the VINCat program (Vigilancia de les Infeccions Nosocomials als hospitals de Catalunya - Infection Control and Antimicrobial Stewardship Catalan Program), a nosocomial infection surveillance and control program, has been in operation at acute care hospitals since 2006. It consists of a network of multidisciplinary hospital teams with the common goal of reducing hospital acquired infection rates in the region. The program includes an antibiotic stewardship module in which data of

the annual antibiotic consumption by families and molecules are monitored and compared between hospitals (benchmarking). In addition, different actions are in place to limit the duration of antibiotic prescription and the use of broad-spectrum antibiotics, especially carbapenems and quinolones in the general digestive surgery and urology services. experience [10,11].

The objective of the present study carried out at the hospitals in the VINCat program, was to analyze the clinical characteristics of adult patients with CDI in Catalonia and to examine the risk factors that determine 90-day recurrence, to design a risk prediction tool and other future strategies of CDI prevention tailored to the population in this region. This study also aimed to provide recurrence information that may be of use in other geographical areas with populations of similar characteristics to those of Catalonia.

Methods

Study design and setting

This multicenter prospective observational cohort study was carried out at the 28 hospitals participating in the VINCat program, that comprise a representative sample of the 3 levels of acute-care hospitals included in the Catalan Health Care System (high-tech hospitals, tertiary referral hospitals and district general hospitals). They account for 40.9% of all adult acute-care hospital beds in Catalonia and amounted to a total of 1,740,846 hospital-days during the study period. The infection prevention and control team within each participating hospital was responsible for *C. difficile* surveillance and appointed an investigator responsible for the recording and validating of all the studied variables in a standardised questionnaire. Sociodemographic, clinical and epidemiological variables and disease evolution at discharge and after 90 days were recorded for each case. New CDI cases were identified following diagnostic and microbiological testing in addition to reviews of the patients' clinical histories and discussions with the referring teams. Diagnosis and classification of CDI was made following VINCat criteria already described elsewhere [12]. The participating clinical

laboratories were periodically audited to ensure that all CDI cases were consecutively reported. All data was reviewed by the study coordinator.

Population and definitions

The study included all consecutive adults (≥18 years at diagnosis) admitted to any hospital area from 1st January until 31st December 2018 that met the study definition of CDI which strictly met VINCat criteria. CDI was defined as the presence of diarrhea (≥ 3 loose stools in ≤ 24 hours) or toxic megacolon without any other known cause while meeting at least one of the following criteria: (a) the isolation of a toxin-producing strain in a laboratory stool sample or a positive test result for *C. difficile* toxins A or B in a laboratory stool specimen [13]; (b) confirmed pseudomembranous colitis by endoscopic, surgical or histological examination. Microbiological testing was performed at each participating hospital's microbiology laboratory. Toxigenic culture of the stool samples was the technique of choice in this study because of its high sensitivity (>95%) [14]. Samples were cultured on selective medium like cycloserine-cefoxitin fructose agar (CCFA), on chromogenic medium like ChromID® C. difficile (bioMérieux), or on non-selective medium like brucella agar or Schaedler agar with 5% sheep blood, vitamin K and hemin, always under anaerobic conditions at 37°C for 48 - 72 hours. This was followed by testing of the isolates via immunoassays to determine their ability to produce *C. difficile toxins* A and B [13,15].

Colonised but asymptomatic patients (even if they were carriers of a toxin-producing strain), patients that had suffered previous CDI episodes and those admitted to specific convalescence and palliative care units were excluded.

Three possible scenarios of CDI acquisition were considered in this study: (i) Hospital-acquired (HA) CDI: infection identified >48 hours after admission to the hospital and before discharge. (ii) Healthcare-associated (HCA) CDI: infection starting in the community or within 48 hours of admission, in patients admitted to a health centre (hospital, nursing home, outpatient dialysis or community health centre) in the 4 weeks prior to the onset of symptoms. (iii) Community-acquired (CA) CDI:

infection starting in the community or within 48 hours of admission, with no admission to a health centre in the previous 4 weeks.

Previous antibiotic treatment was defined as the administration of more than 48 hours of antibiotics during the 30 days preceding hospital admission. This information was obtained from the patients' electronic clinical record.

Patients were followed up for 90 days post-diagnosis of CDI. Recurrence was defined as a second episode (following the same VINCat criteria as the first episode) occurring within 90 days from the onset of a previous episode, provided that CDI symptoms from the first episode had resolved [7]. Cure was defined as treatment response without recurrence of CDI during the follow-up period [16]. Deceased patients during the follow up period were excluded from this analysis.

No diagnostic tests were made, or samples taken from any participant in addition to those required by routine care. This study complies with the principles of the Declaration of Helsinki and the legal structure according to international human rights and biomedicine and personal data protection legislation. The Ethics Committee of XXXXXX approved the study (ref: *(Blinded for review)*). All data were treated as confidential, and records were accessed anonymously.

Statistical analysis

Categorical data were presented as frequency (n) and proportions (%) and were analyzed using a Pearson $\chi 2$ test or Fisher's exact test. 2-tailed *p* values of <0.05 were considered statistically significant.

To develop the risk prediction model for 90-day CDI recurrence, variables that were significantly associated with recurrence in the univariate analyses (i.e., $p< 0.05$) and that were clinically relevant were considered in the multivariate Cochran-Mantel-Haenszel test. Results were presented as estimate odd ratios (ORs) and corresponding 95% confidence intervals (CIs). All analyses were two sided, and significance level was set to 0.05.

The analysis was performed using the IBM SPSS v20 statistical package and R v4.0.4 statistical software.

Results

Description of patients with CDI

Of the 558 inpatients with CDI included in this analysis, 351 (62.9%) were > 65 years old and 256 (45.9%) were men. 230 (41.2%) infections were HA, 170 (30.5%) were CA and 158 (28.3%) were HCA. 285 (51%) patients had been admitted to a healthcare facility in the year prior to the CDI. 142 (25.4%) patients had diabetes mellitus, 93 (16.7%) presented with oncological disease and 48 (8.6%) were on active chemotherapy at the time of the infection (Table 1).

372 (66.7%) patients had received previous antibiotic treatment within 30 days; of them, 184 (49.5%), had received more than one course of antibiotics in the 30 days prior to the CDI diagnosis. 193 (34.6%) patients received a penicillin antibiotic, 116 (20.8%) cephalosporins antibiotic, 113 (19.7%) patients received a course of quinolone antibiotics and 69 (12.4%) patients received carbapenems (Table 1) To treat the CDI episode, 285 (51%) patients received metronidazole and 198 (35.5%) received vancomycin (Table 2). During the episode of CDI and the 90-day follow-up period, 262 (47%) patients received antibiotic treatment for reasons other than to treat CDI. Of them, 135 patients (51.5%) received more than 1 antibiotic course in that 90-day period. 95 (17.0%) patients received a penicillin antibiotic, 99 (17.7%) received cephalosporins, 78 (14%) received quinolones and 77 (13.8%) were prescribed carbapenems. Furthermore, during this period, 378 (67.7%) patients were taking proton pump inhibitors (Table 2).

30 (5.4%) patients were admitted to the intensive care unit (ICU) due to CDI. 66 (12%) patients presented with a recurrence of the disease within 90 days from the index CDI (Table 1). Recurrence rates were 9%, 10% and 17% for CA, HA and HCA, respectively.

Characteristics associated with 90-day recurrence

Patients who had a recurrence within 90 days following their index CDI were more likely to be > 65 years old (74.2% vs 61.4%, p=0.000), to have an HCA infection (40.9% vs 26.6%, *p*=0.009), to have been admitted to a healthcare facility in the previous year (66.7% vs 49%, *p*=0.000), be suffering from oncological disease (24.2% vs 15.7%, *p*=0.005) or to be on active chemotherapy at the time of the infection (18.2% vs 7.3%, *p*=0.010).

In relation to antibiotic treatment, patients developing recurrent infections were also more likely to have received more than 1 course of antibiotics in the 30 days prior to the CDI diagnosis (73.1% vs 45.6%, *p*<0.001), or to have received a recent quinolone (31.8% vs 18.1%, *p*=0.008) or cephalosporin (34.8% vs 18.9%, *p*=0.003) course compared with those in which the CDI had resolved (Table 1). No differences in recurrence rate were observed among patients receiving initial therapy for CDI with vancomycin or with metronidazole (OR 1.1 95%CI 0.6-2.0)

Risk prediction model for 90-day recurrence

In the multivariate model, age >65 years, oncological disease, active chemotherapy, admission to a healthcare facility in the previous year, HCA of the infection, more than 1 course of antibiotics prior to diagnosis and recent treatment with quinolones or cephalosporins were included. Of them, only having received more than 1 course of antibiotics in the 30 days prior to the CDI diagnosis (OR=2.459, 95% CI: 1.195; 5.060, *p*=0.015) and active chemotherapy (OR=4.859, 95% CI: 1.495; 15.792, *p*=0.009) were significant predictors of 90-day CDI recurrence (Table 3).

Discussion

To the best of our knowledge, this is the largest epidemiological study to investigate predictors for 90-day recurrence of CDI in Catalonia [17]. 558 CDI cases were analyzed with 66 (12%) experiencing a recurrent episode within the 90-day follow-up period.

Although risk factors for CDI among hospitalized patients such as age, prior hospital admission and antibiotic use has been recently reassessed [18] anticipating which patients may suffer from recurrent CDI continues to be a subject of debate. An extensive range of risk factors for severe or recurrent CDI have been described in the literature [6,19] and the aim of our study was to identify which ones were specific to the characteristics of the population in Catalonia to create a rigorous clinical prediction tool that would help the patients in this region. The results from our study are in line with previously published international studies that determined that older age [20–23], continued use of antibiotics after CDI diagnosis or after CDI treatment [20,21] and underlying disease [20,24] are prognostic markers of an increased risk of recurrent CDI. On the other hand initial CDI severity [20,23] and continued use of proton pump inhibitors (PPIs) [20,23] have also been widely reported to increase the risk of CDI and recurrence. In fact, PPIs are among the most commonly used medications and the Food and Drug Administration issued a warning with respect to the utilization of PPIs and risk of developing CDI [25]. However, the use of PPIs did not show statistical significance in our study.

Our multivate model determined that having received more than 1 course of antibiotics in the 30 days prior to the CDI diagnosis was a significant predictor of 90-day CDI recurrence. Thus, these results, we believe that the cumulative exposure and antimicrobial selection caused by the administration of more than one antibiotic group has played a relevant role towards recurrence of CDI. This aligns with previous studies that established that cumulative antibiotic exposure prior to admission is the greatest contributor to the risk of subsequent CDI [26,27]. This could be related to antibiotics altering the intestinal microbiota and subsequently producing an environment where CDI is easily developed [28]. Actions such as antimicrobial stewardship that actively modify prescription behavior for high-risk antimicrobials like cephalosporins and quinolones have been described as an effective method for decreasing *C. difficile* recurrence rates [29]. In our study, nearly 20% of patients received quinolones which might have contributed to the increased risk of CDI. However, following the formal recommendation against the generalized use of quinolone therapy, from 2017 to 2020 quinolone consumption steadily decreased in VINCat hospitals (data not shown). Furthermore, antimicrobial

stewardship programmes, when implemented alongside infection control measures, have shown to have a synergistic effect and are therefore recommended for future antimicrobial stewardship planning [30].

Malignancy is also a widely recognized risk factor for primary and recurrent CDI [31,32]. Chemotherapy, immunosuppression and frequent exposure to broad-spectrum antibiotics, coupled with regular visits to healthcare facilities, are the most probable cause for the increased risk of CDI in this group of patients [33]. In our study, malignancy itself was not found to be an independent risk factor for recurrent CDI, however, oncological patients undergoing chemotherapy treatment presented a significantly higher risk of recurrence probably due to chemotherapy agents altering the normal gut microbiota composition by causing mucosal inflammation, decreasing the repair capacity of the mucosal epithelium or promoting an anaerobic environment which favors CDI [34–37].

The originality of our study lies in its assessment of the risk of recurrence based on the location of the initial infection. Previous hospitalization is a known risk factor for CDI [1], however, recent studies have reported that a substantial proportion of CDI occurs in the community and its incidence has been increasing [38]. Bearing this in mind, our study investigated whether the location of acquisition of the infection was a key factor in the risk of future recurrence in the Catalan population. The results showed that patients who suffered a recurrence were more likely to have attended a healthcare facility in the previous year. This does not mean that patients had acquired the toxigenic CD in a previous facility. It is not proof of acquisition; it only denotes that they were at higher risk. In fact, this association was not confirmed in the multivariate analysis.

Our study has several limitations that warrant mention. Even if this is a multicenter study, all participating hospitals are located in Catalonia (seven and a half million inhabitants) and the results may not be generalizable. As it is an observational study, treatment decisions are made at the discretion of the treating physician and therefore biased selections may be present in relation to the severity of the disease and the use of metronidazole or vancomycin. Importantly, since 2021,

metronidazole is only recommended in CDI when the preferred options, fidaxomicin and vancomycin, are not available [16]. Since our study was carried out before this recommendation, 51% of the patients received metronidazole. In addition, when analyzing the impact of the use of different antibiotics in CDI recurrence risk, all antibiotics from the same class were grouped together and no differentiation was made between narrow and broad spectrum antibiotics or different generations within the same class.The sample size does not allow us to identify strong correlations between clinical factors and the risk of recurrence, despite some of them being well known CDI recurrence risk factors. Furthermore cumulative amount of antibiotics as defined daily doses were not compared between patients with and without recurrence. And finally, the results of this study may be affected by the exclusion of deceased patients from this analysis since death is considered a competing risk and its occurrence hinders analysis of the results..

Besides limitations, the results of our study show the importance of CDI surveillance with data collection and analysis to identify infection trends and risk factors for recurrence. Addressing these factors, might be critical to tailor individualized therapy such as vancomycin tapering or monoclonal antibodies against CD toxins that will keep at-risk patients safe. .

Conclusions

Our prospective observational study has identified several risk factors linked to CDI recurrence in the Catalan population that will increase the awareness of infection prevention and control teams within the participating organizations, so that policies and preventive measures can be optimized, and recurrence rates can be reduced through prevention protocols in these at-risk populations. Further studies with larger sample sizes are required to dispel any uncertainties regarding the role of the different risk factors in the recurrence of CDI in the Catalan population.

Summary Points

- CDI is the main cause of healthcare-related infective diarrhea, as well as often being associated to community-acquired cases of colitis.
- Up to 15-35% patients experience disease recurrence with a relapse of CDI symptoms within 3 months.
- An extensive range of risk factors that determine CDI recurrence have been described and identifying the specific ones that are more likely to affect different populations would be useful.
- Among the patients admitted to the VINCat hospitals in Catalonia, Spain, having received more than 1 course of antibiotics in the 30 days prior to CDI diagnosis and active chemotherapy are significant predictors of 90-day CDI recurrence.
- The identification of these 2 risk factors will enable the optimization of preventive measures in the at-risk populations.

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Risk of *Clostridioides difficile* infection recurrence in the VINCat hospitals: a prospective observational cohort study

Table 1. Baseline demographic and epidemiological characteristics of adult inpatients with CDI.

Demographic variables	**Total N=558**	**Resolved CDI N=492**	**Recurring CDI N=66**	**P value**
Age >65	**351 (62.9%)**	**302 (61.4%)**	**49 (74.2%)**	**0.000**
Gender (Male)	256 (45.9%)	222 (45.1%)	34 (51.5%)	0.121
Comorbidity factors				
Diabetes Mellitus	142 (25.4%)	123 (25%)	19 (28.8%)	0.398
Renal replacement therapy	22 (3.9%)	17 (3.5%)	5 (7.6%)	0.578
Inflammatory Bowel Disease	31 (5.5%)	25 (2.5%)	6 (9.1%)	0.310
HIV infection	6 (1.1%)	5 (1%)	1 (1.5%)	0.705
Solid organ transplant	17 (3%)	16 (3.3%)	1 (1.5%)	0.492
Oncological disease	**93 (16.7%)**	**77 (15.7%)**	**16 (24.2%)**	**0.005**
Active chemotherapy	**48 (8.6%)**	**36 (7.3%)**	**12 (18.2%)**	**0.010**
Immunosuppressive therapy#	51 (9.1%)	46 (9.3%)	5 (7.6%)	0.891
Previous Antibiotic administration*	372 (66.7%)	320 (65%)	52 (78.8%)	0.070
Penicillins	193 (34.6%)	166 (33.7%)	27 (40.9%)	0.250
Cephalosporins	**116 (20.8%)**	**93 (18.9%)**	**23 (34.8%)**	**0.003**
Quinolones	**113 (19.7%)**	**89 (18.1%)**	**21 (31.8%)**	**0.008**
Carbapenems	69 (12.4%)	57 (11.6%)	12 (18.2%)	0.126
>1 previous antibiotic (N=372 patients)	**184 (49.5%)**	**146 (45.6%)**	**38 (73.1%)**	**<0.001**
Etiological variables				
Acquisition				
HCA	**158 (28.3%)**	**131 (26.6%)**	**27 (40.9%)**	**0.009**
HA	230 (41.2%)	206 (41.9%)	24 (36.4%)	0.301
CA	~~160~~ 170 (~~28.7~~30.5%)	155 (31.5%)	15 (22.7%)	**0.001**
PAHCF in the last year	**285 (51%)**	**241 (49%)**	**44 (66.7%)**	**0.000**
Severity level				
ICU	30 (5.4%)	30 (6.1%)	0%	0.125
Antibiotics treatment				
Metronidazole	285 (51%)	245 (49.8%)	40 (60.6%)	0.095
Vancomycin	198 (35.5%)	174 (35.4%)	24 (36.4%)	0.937
Other treatments during CDI and the follow-up period				

Antibiotic treatment (Not for CDI)	262 (47.0%)	226 (45.9%)	36 (54.5%)	0.188
Cephalosporins	99 (17.7%)	86 (17.5%)	13 (19.7%)	0.658
Penicillins	95 (17.0%)	83 (16.9%)	12 (18.2%)	0.790
Quinolones	78 (14.0%)	70 (14.2%)	8 (12.1%)	0.643
Carbapenems	77 (13.8%)	65 (13.2%)	12 (18.2%)	0.272
>1 antibiotic (N=262 patients)	135 (51.5%)	116 (51.3%)	19 (52.8%)	0.872
Proton pump inhibitors	378 (67.7%)	326 (66.9%)	49 (74.2%)	0.229

CA: community acquired; CDI: *Clostridioides difficile* infection; HA: hospital acquired; HCA: healthcare associated; HIV: human immunodeficiency virus; ICU: intensive care unit; PAHCF: previous admission to a healthcare facility
*Previous antibiotic administration is defined as the administration of antibiotic treatment for >48h during the 30 days prior to CDI diagnosis
For the purposes of this study the term immunosuppressive therapy includes being on chemotherapy for cancer, being within one year out from receiving a hematopoietic stem cell or solid organ transplant, untreated HIV infection with CD4 T lymphocyte count < 200, combined primary immunodeficiency disorder, and receiving >20mg/day prednisolone for more than 14 days.

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Risk of *Clostridioides difficile* infection recurrence in the VINCat hospitals: a prospective observational cohort study

Table 2. CDI treatment and other treatments during CDI and the follow-up period

Treatment	Total N=558	Resolved CDI N=492	Recurring CDI N=66	P value
Antibiotics treatment				
Metronidazole	285 (51%)	245 (49.8%)	40 (60.6%)	0.095
Vancomycin	198 (35.5%)	174 (35.4%)	24 (36.4%)	0.937
Other treatments during CDI and the follow-up period				
Antibiotic treatment (Not for CDI)	262 (47.0%)	226 (45.9%)	36 (54.5%)	0.188
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For the purposes of this study the term immunosuppressive therapy includes being on chemotherapy for cancer, being within one year out from receiving a hematopoietic stem cell or solid organ transplant, untreated HIV infection with CD4 T lymphocyte count < 200, combined primary immunodeficiency disorder, and receiving >20mg/day prednisolone for more than 14 days.

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Table 3. Multivariate analysis of the risk factors associated with 90-day CDI recurrence.

Variables	OR	95% CI	p-value
Age>65	2.024	0.996;4.11	0.051
Oncological disease	0.602	0.225;1.609	0.312
Active chemotherapy	**4.859**	**1.495;15.792**	**0.009**
Previous Cephalosporins administration	1.568	0.815;3.018	0.178
Previous Quinolone administration	1.512	0.769;2.974	0.230
>1 Previous antibiotic	**2.459**	**1.195;5.060**	**0.015**
PAHCF in the last year	0.487	0.220;1.080	0.077
HCA	1.308	0.630;2.716	0.472
CA	1.031	0.420;2.530	0.947

CA: community acquired; CI: confidence interval; HCA: healthcare associated; OR: odds ratio; PAHCF: previous admission to a healthcare facility within the last year