Infectious Diseases Now 52 (2022) 267–272

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Original article

Clostridioides difficile infection (CDI) epidemiology and patient characteristics in Switzerland

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INFO ARTICLE

Historique de l'article :
Reçu le 1er février 2022
Accepté le 2 mai 2022
Disponible sur Internet le 7 May 2022

Keywords :
Outcomes
Recurrence
Mortality
Treatment
Predictive factors

ABSTRACT

Objectives. – *Clostridioides difficile* infection (CDI) is a disease with high morbidity and mortality rates. The objective of this study was to describe CDI epidemiology and patient characteristics over a 5-year period in Switzerland and assess risk factors for mortality, recurrence and severe CDI.
Patients and methods. – We retrospectively included all consecutive CDI cases having occurred in adult patients hospitalized in two tertiary centers: the Lausanne University Hospital (1000 beds) and the University Hospital of Zurich (900 beds), between 2014 and 2018. Suspected cases of CDI were identified from the microbiology laboratory database on the basis of a positive test and confirmed by records review.
Results. – During first CDI episodes, the median age was 67 years and the median Charlson comorbidity index (CCI) score was 5. All in all, 299 out of 826 patients (36.2%) had severe infection based on the Infectious Diseases Society of America criteria. In the multivariable analysis, CCI was associated with increased risk of mortality. None of the factors recorded on admission were significantly associated with increased risk of recurrence. In the multivariable analysis, male sex and CCI were associated with severity, while immunosuppression was associated with less severe presentation.
Conclusions. – If we did not identify any criteria on admission that could be predictive of recurrences, this could be explained the retrospective nature of the study. A higher comorbidity index is a key driver for severe CDI and mortality. Reporting of CDI is not mandatory in Switzerland; structuration of CDI reporting should be a short-term priority.

1. Introduction

Clostridioides (formerly *Clostridium*) *difficile* is the leading cause of healthcare-associated diarrhea. The prevalence of the disease differs widely from one country to another; in the USA, for example, *C. difficile* has been shown to cause 12.1% of all health care-associated infections [1], with 462,100 cases reported in 2017 (95% CI, 428,600 to 495,600) [2]. The numbers observed in Europe are lower; a recent prevalence survey performed in France showed that *C. difficile* represented 2.31% of healthcare-associated infection [3]. Interestingly, only a limited number of studies provide objective data regarding *C. difficile* epidemiology in Switzerland. A point prevalence survey performed in 2017 focusing on healthcare-associated infections found that *C. difficile* contributed to 4.3% of all infections [4]. In 2015, a prevalence study included all routinely collected stool samples from hospitalized patients with diarrhea in 76 hospitals in Switzerland on 2 days, 1 in winter and 1 in summer [5]; the results showed that enzyme immunoassay (EIA) *C. difficile* detection rates came to 6.4 cases/10,000 patient bed-days in winter and 5.7 cases/10,000 patient bed-days in summer. This work did not report any data on the clinical presentation or the treatment proposed as first-line.

Recurrences and severe CDI are the main challenges in *C. difficile* infections (CDI) and justified the recent revision of the clinical guidelines published by the Infectious Diseases Society of America

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https://doi.org/10.1016/j.idnow.2022.05.002

Table 1
First episode characteristics by center.

Characteristics	Global (n = 826)	Lausanne (n = 420)	Zurich (n = 406)
Demographics	826	420	406
Age (mean, standard deviation)	67 (54–78)	70 (58–80)	62 (50–74)
Sex % (n)			
Female	44.6% [368]	43.8% [184]	45.3% [184]
Male	55.4% [458]	56.2% [236]	54.7% [222]
Comorbidities			
Charlson comorbidity index (mean, SD)	5 (3–7)	5.5 (3–8)	4 (2–6.8)
Laboratory findings % (n)			
Leucocytes (G/L)			
< 0.5 G/L	5.6% [41]	4.5% [15]	6.5% [26]
0.5–15 G/L	74.0% [545]	66.5% [222]	80.3% [323]
> 15 G/L	20.4% [150]	29.0% [97]	13.2% [53]
Creatinine (μmol/L)			
< 133 μmol/L	76.4% [608]	75.9% [302]	76.9% [306]
> 133 μmol/L	23.6% [188]	24.1% [96]	23.1% [92]
Treatments % (n)			
Antacid treatment (PPI)	64.9% (526)	58.3% (236)	71.4% (290)
Antibiotic treatment (≤ 3 months)	81.4% (649)	84.1% (329)	78.8% (320)
Concomitant chemotherapy	18.5% (153)	19.8% (83)	17.2% (70)
IDSA CDI severity group % (n)	826	420	406
Non-severe	63.8% [527]	60.2% [253]	67.5% [274]
Severe	36.2% [299]	39.8% [167]	32.5% [132]

(IDSA) [6] and the European society (ECCMID) [7]. The IDSA defines severity using only leucocytes and serum creatinine and does not provide factors associated with increasing probability of developing severe CDI. This definition is based on expert opinions that are not discussed in the recommendations [6]. Recurrences are also discussed in terms of treatment, but risk factors and at-risk populations are not defined. Interestingly, the approach of the European society is different, including several prognostic factors that could optimally identify patients at risk for severe as well as recurrent CDI. Regarding severity, age and comorbidities are key factors found in the literature with an age limit of 65 years [7]. Age remains a strong factor for recurrence, as do prior CDI, prior hospitalization, non-CDI antibiotic use and proton pump inhibitor (PPI) use. The current literature does not provide specific data on the Swiss population and its comparability to other countries. Our primary objective was therefore to describe CDI epidemiology and patient characteristics over a 5-year period in Switzerland, focusing on 2 university tertiary hospitals located in Zurich and Lausanne. Secondary objectives were to describe risk factors for mortality, and recurrent and severe infections in this cohort based on admission criteria.

2. Methods

We performed a retrospective study of patients with CDI episodes admitted to two Swiss University Hospitals from 2014 to 2018 (2015–2018 for Zurich and 2014–2018 for Lausanne). Patients were included if they had received a CDI diagnosis (meeting the IDSA/SHEA criteria of diarrhea and positive CDI test [6]) and were treated for CDI. The tests used, depending on the center, were combinations of glutamate dehydrogenase, polymerase chain-reaction test for toxigenic *C. difficile* (GeneXpert *C. difficile*, Cepheid CA/USA) and Enzyme immunoassays for toxins.

We collected demographic, clinical and biological data from Electronic Medical Record (EMR) and chart review. We evaluated severity criteria as defined by the IDSA/SHEA guidelines: elevated serum creatinine level > 1.5 mg/dL (133 μmol/L) and/or marked leukocytosis (15 G/L) [6]. The date of diagnosis was defined as Day 0 (D0). We collected all variables available on D0 or the 'worst variable' available in the 48-hour interval around the time of diagnosis. Treatment regimen, dosing and duration were at the discretion of the treating physicians. The study was approved by local ethics committees (ID 2018-01330; KEK Zurich Nr. 2016-00145).

Data collection and statistical analysis: data were collected through a 'case report form (CRF)' made on RedCap. Descriptive analyses are presented as mean (±SD) for symmetric continuous variables, median (interquartile range, IQR) for asymmetric continuous variables and as percentages for categorical variables. Wilcoxon rank sum test, Pearson's Chi-squared test, and Fisher's exact test were performed when adequate. All variables with $P < 0.2$ in univariable analysis were included in a multivariable model. Results are presented as odds ratios (ORs) with their 95% confidence intervals (95% CIs) calculated using the generalization of ordinary linear regression method. A value of $P < 0.05$ was considered statistically significant. Variance inflation factor (VIF) was calculated to quantify multicollinearity. All analyses were performed using R software version 3.6.0 (2019) (R Foundation for Statistical Computing, Vienna, Austria; URL https://www.R-project.org/).

3. Results

From January 2014 to December 2018, we identified 857 hospitalized patients who met sample selection criteria, of whom 243 (28.4%) were diagnosed at most 72 hours after admission and 612 (71.6%) during hospitalization. In total, 826 patients presented as a first episode (96.3%) and 31 as a recurrence (3.7%). Demographic and clinical data are displayed in Table 1. Focusing on first episodes, the median age was 67 years and the median value for Charlson comorbidity index (CCI) score was 5. All in all, 649 patients (81.4%) had received antibiotics within the previous 3 months and 153 patients (18.5%) had active malignancies and were receiving concomitant chemotherapy upon CDI diagnosis. All in all, 299 patients (36.2%) had severe infection based on the IDSA criteria. The majority of patients were admitted in the internal medicine service (32.1%).

We performed a univariate analysis to determine the factors associated with mortality at 8 weeks based on the initial clinical presentation as described previously (Table 2). Age higher than 65 years was associated with increased mortality (69.1% vs. 30.9%, $P = 0.013$). The second variable associated with mortality was the presence of comorbidities assessed by the Charlson comorbidity index (CCI), which was measured at a median of 5 vs. 7 comparing living and dead patients respectively. Other factors such as sex, leucocytes, and IDSA severity score did not reach statistical significance. The multivariable analysis showed that only the CCI was

Table 2
Univariate analysis of mortality at 8 weeks.

Characteristics	Alive, $n = 577$[a]	Dead, $n = 55$[a]	Overall, $n = 632$[a]	P-value[b]
Age group				0.013
< 65	48.4% [279]	30.9% [17]	46.8% [296]	
> 65	51.6% [298]	69.1% [38]	53.2% [336]	
Sex				0.8
Female	46.8% [270]	45.5% [25]	46.7% [295]	
Male	53.2% [307]	54.5% [30]	53.3% [337]	
Charlson comorbidity score	5.0 (3.0, 7.0)	7.0 (4.0, 8.5)	5.0 (3.0, 7.0)	< 0.001
Concomitant chemotherapy	21.8% [126]	18.2% [10]	21.5% [136]	0.5
Immununosuppression	25.1% [145]	36.4% [20]	26.1% [165]	0.070
Serum creatinin	79 (59, 133)	86 (68, 127)	79 (59, 132)	0.3
IDSA severity group				0.6
Non-severe	63.4% [366]	60.0% [33]	63.1% [399]	
Severe	36.6% [211]	40.0% [22]	36.9% [233]	
Leucocytes classes				0.4
0.5, 15 G/L	74.0% [385]	74.0% [37]	74.0% [422]	
0.02, 0.49 G/L	6.7% [35]	2.0% [1]	6.3% [36]	
> 15 G/L	19.2% [100]	24.0% [12]	19.6% [112]	

[a] Median (IQR); % [n].
[b] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

Table 3
Multivariable analyses of mortality at 8 weeks.

Characteristic[a]	OR	95% CI	P-value	VIF
Charlson comorbidity score	1.27	1.13, 1.43	< 0.001	1.3
Age group			0.7	1.3
< 65	1.00	—		
≥ 65	0.89	0.44, 1.84	0.7	

OR: odds ratio; CI: confidence interval; VIF: variance inflation factor.
[a] All the factors with $P < 0.2$ from the univariate analysis were included in the initial model.

Table 4
Univariate analysis of recurrences at 8 weeks.

Characteristic	No recurrence 8 weeks, $n = 444$[a]	Recurrence 8 weeks, $n = 78$[a]	Overall, $n = 522$[a]	P-value[b]
Age	65 (53, 76)	62 (52, 74)	65 (53, 75)	0.4
Age group				0.2
< 65	48.6% [216]	56.4% [44]	49.8% [260]	
≥ 65	51.4% [228]	43.6% [34]	50.2% [262]	
Sex				0.4
Female	47.1% [209]	52.6% [41]	47.9% [250]	
Male	52.9% [235]	47.4% [37]	52.1% [272]	
Charlson comorbidity score	5.0 (3.0, 7.0)	4.5 (3.0, 6.8)	5.0 (3.0, 7.0)	0.8
Concomitant chemotherapy	22.7% [101]	16.7% [13]	21.8% [114]	0.2
Immununosuppression	27.3% [121]	20.5% [16]	26.2% [137]	0.2
Serum creatinin	78 (59, 122)	87 (60, 153)	79 (59, 130)	0.10
IDSA severity group				0.087
Non severe	66.4% [295]	56.4% [44]	64.9% [339]	
Severe	33.6% [149]	43.6% [34]	35.1% [183]	
Leucocytes (G/L)	8 (5, 13)	8 (5, 13)	8 (5, 13)	> 0.9
Leucocyte classes				0.7
0.02, 0.49 G/L	6.5% [27]	8.3% [6]	6.8% [33]	
0.5, 15 G/L	76.1% [315]	72.2% [52]	75.5% [367]	
> 15 G/L	17.4% [72]	19.4% [14]	17.7% [86]	

[a] Median (IQR); % [n].
[b] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

associated with an increased risk of mortality at 8 weeks (OR: 1.27, CI: 1.13–1.43, $P < 0.001$) (Table 3).

In the second part of the analysis, we focused on recurrences and the associated factors based on the initial characteristics of the patients. Among the 826 first episodes analyzed, 522 were evaluable and 78 presented a recurrent episode within 8 weeks. None of the factors recorded on admission were significantly associated with an increased risk of recurrence in the univariate analysis (Table 4). Multivariable analysis did not show any factor associated with recurrence.

In the last part of our study, we focused on the factors associated with the severity as defined by the IDSA [6]. Three factors were associated with severity in the univariate analysis: age over 65 years, male sex, and higher CCI score. Severe forms were more frequently observed in males compared to females, 63% vs. 37% respectively ($P < 0.001$). Interestingly, the percentage of non-severe forms was significantly higher in patients with concomitant chemotherapy and immunosuppression. All of the results are presented in Table 5. The multivariable analysis confirmed an increased risk of severity on two factors: male sex and CCI. As summarized in Table 6, immunosuppression was significantly associated with non-severe forms.

4. Discussion

In a large-scale retrospective cohort of 826 first CDI episodes from two tertiary care hospitals in Switzerland over a 5-year

Table 5
Univariate analysis of factors associated with severe CDI.

Characteristic	Non-severe, $n = 451$[a]	Severe, $n = 284$[a]	Overall, $n = 735$[a]	P-value[b]
Age group				< 0.001
< 65	52.5% [237]	30.6% [87]	44.1% [324]	
> 65	47.5% [214]	69.4% [197]	55.9% [411]	
Sex				< 0.001
Female	51.4% [232]	37.0% [105]	45.9% [337]	
Male	48.6% [219]	63.0% [179]	54.1% [398]	
Charlson comorbidity score	4.0 (2.0, 7.0)	6.0 (4.0, 8.0)	5.0 (3.0, 7.0)	< 0.001
Concomitant chemotherapy	26.2% [118]	10.9% [31]	20.3% [149]	< 0.001
Immununosuppression	31.3% [141]	16.2% [46]	25.4% [187]	< 0.001
Antacid[c]				0.063
No	35.7% [161]	27.8% [79]	32.7% [240]	
Yes	63.0% [284]	70.1% [199]	65.7% [483]	
Previous use of non-CDI antibiotics (3 months)[c]				0.4
No	18.4% [83]	15.5% [44]	17.3% [127]	
Yes	79.4% [358]	81.0% [230]	80.0% [588]	

[a] Median (IQR); % [n].
[b] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.
[c] Excluding patients for which information is missing.

Table 6
Multivariable analyses of factors associated with severe CDI.

Characteristic[a]	OR	95% CI	P-value	VIF
Sex			< 0.001	1.0
Female	1.00	—		
Male	1.74	1.26, 2.42	< 0.001	
Charlson comorbidity score	1.24	1.17, 1.32	< 0.001	1.1
Immununosuppression	0.27	0.18, 0.40	< 0.001	1.1

OR: odds ratio; CI: confidence interval; VIF: variance inflation factor.
[a] All the factors with $P < 0.2$ from the univariate analysis were included in the initial model.

period, we describe the factors associated with mortality at 8 weeks, recurrence, and severity based on the initial presentation. Our main results underline that mortality is primarily associated with the comorbid conditions of the patients as assessed by the Charlson comorbidity index. No factor on admission can clearly predict recurrences, or severity of CDI, consistent with mortality. Conversely, mortality is mostly driven by comorbidities and age.

While CDI epidemiology has been widely described in the international literature, very few data are available on disease characteristics and prognostic factors in Switzerland. This retrospective study was an initial approach designed to identify potential patterns liable to improve CDI recognition and severity classification. Our goal was to describe patient characteristics and to detect factors upon admission that could predict mortality, recurrence, and severity. For the purposes of this study, we did not include proposed treatment and response to treatment.

C. difficile is a major healthcare-associated pathogen; the demographic characteristics of our patients are consistent with the current literature. A recent cohort of 414 CDI patients from France presented a mean age of 71 (18–100) which is close to the mean age of 68 (54–78) in our study [8]. In this French cohort, 78% of CDI cases were healthcare-associated infections compared to 71.6% in our study; prior exposure to antibiotic treatment was 73.8% compared to 81.4% in our study. The study by Khanafer et al., 2021 also compares these numbers to other studies published in France and different European countries and highlights clear differences [8]. Our data are closer to the general European profile including an older patient population, a higher number of healthcare-associated cases and more frequent exposure to antibiotics. In our cohort, there were 36.2% of severe CDI cases using the IDSA definition involving only leucocytes and renal function. This percentage is lower than that measured in a 3-year French cohort study with 233 patients [9]. Comparing several definitions of severity, the authors combined severe and complicated forms. When selecting the definitions including leucocytes and creatinine, the percentage of severe forms ranged between 45.5% to 59.2%, which is higher than in our population.

The mortality rate observed in our cohort at week 8 was 8.7% (55/632 patients evaluable), which is lower than the rates observed in France or Europe, 17.1% and 18.6% respectively [8]. A Spanish study on 362 patients reported a mortality rate of 14% [10]. Another study performed in the US retrospectively evaluated 285 patients stratified by severity, and all-cause mortality varied from 16.7% in mild and moderate forms to 32% in severe forms [11]. The factors associated with mortality were severe CDI, age and CCI. In our study, only age and CCI were associated with mortality in univariate and multivariable analysis. The lower mortality probably reflects the lower percentage of severe forms in our cohort.

Recurrences usually occur in 15–25% of CDI cases following the initial episode [12]. A patient presenting a first recurrence has a higher risk of subsequent recurrence and risks entering a cycle of multiple episodes of recurrence, leading to exhaustion and long courses of antimicrobial therapy. In our study, we observed a comparable rate of recurrence at 15% (78/522). Numerous factors have been associated with recurrences such as age, leucocytes, proton pump inhibitors, albumin level, primary diagnosis with EIA, treatment with metronidazole, treatment with antibiotic, and renal insufficiency [13–15]. The ESCMID guidelines underlined two major predictors for CDI recurrence: age > 65-years-old, and prior CDI episode. In our study we did not find any statistical relationship (age, sex, CCI, leucocyte count, serum creatinine or severity) in univariate and multivariable analysis at time of diagnosis. It is therefore difficult to estimate the potential risk of recurrence based on the initial presentation. This absence of relationship could be related to the absence of systematic follow-up of recurrences at 8 weeks due to the retrospective study design and the lack of data on treatment.

In the most recent guidelines published by the European Society of Infectious Diseases (ESCMID), several prognostic factors were associated with risk of severe CDI [7]. Older age defined as more than 65 years and the presence of comorbidities were identified as the most important risk factors. Our results are consistent with these data. The univariate analysis identified age (> 65), sex (male), and CCI as key factors, while only sex and CCI were retained in the multivariable analysis. Interestingly, we observed that immunosuppression was associated with less severe forms, which was an unexpected result not previously reported in the literature. Guevara et al recently published a prospective cohort study of 227 cancer patients with CDI [16]. In this cohort, only 19% (43/227) of the patients presented IDSA severity criteria which is lower than the percentage of severe forms observed in our total cohort (36.2%). No clear explanation was found for this difference, and the association needs to be confirmed insofar as it could potentially represent bias related to the retrospective design of the study.

This study presents several limitations that must be acknowledged and could potentially explain some of the differences observed with regard to the current literature. First, it was a retrospective study based on the positive results of the laboratory tests; second, there was no common validated algorithm between the two laboratories in Lausanne and Zurich. In addition, the diagnostic procedures in use between 2014 and 2018 have been subject to substantial modification based on the international recommendations and, more specifically, on the 2016 publication in of the ESCMID recommendations for CDI diagnosis [17]. Some data, such as previous exposure to antibiotics or PPI, were not necessarily mentioned in the patients' electronic records and may have been underestimated. Finally, and probably most importantly, there was no systematic follow-up of the patients designed to actively monitor recurrence or report mortality, both of which are important limitations to the analysis of this data.

5. Conclusion

In this study we have shown that the characteristics of patients with CDI in Switzerland are comparable to those of the general European population. Mortality at 8 weeks is associated with age and CCI. We did not identify criteria on admission that could be predictive of recurrences, but this could be related to the retrospective nature of the study, which may have led to underestimation of classical factors such as antibiotic or PPI exposure. Finally, CDI severity is driven by comorbidities and gender. Reporting of CDI is not mandatory in Switzerland. As a result, it is very complicated to obtain reliable information on patient demographics and disease evolution. While the patients under consideration in this study are comparable to those of other cohorts, we are lacking in accurate data on CDI outcomes, assessment of severity, occurrence of recurrences, and treatment choice. Structuration of CDI reporting should be a short-term priority. In an era of antibiotic resistance and stewardship promotion, CDI is a strong indicator reflecting both disease and antibiotic overuse, and represents a factor that should not be ignored by national entities.

Ethical Approval

All procedures performed in studies involving human particpants were in accordance with the 1964 Helsinki declaration and its later amendments.

Disclosure of interest

EK reports receiving grants from the Swiss National Science Foundation (SNSF grant nº P500PM_202961) and SICPA Foundation. AT is an employee of MSD Merck Sharp & Dohme AG, Lucerne, Switzerland. BG has participated in advisory boards with Pfizer and MSD Merck Sharp & Dohme AG.

Funding

This study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Contribution of authors

Benoit Guery: conceptualization, Bruno Grandbastien, Benoit Guery: formal analysis, Erika Kampouri, Paraskevas Filipidis, Maxime Wolfle: investigation, Erika Kampouri, Paraskevas Filipidis, Benoit Guery, Aline Taveira: writing original draft, Tina Badinski, Antony Croxatto, Tatiana Galperine, Y. Achermann: writing-Review & Editing.

Informed consent and patient details

The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article and that this report does not contain any personal information that could lead to their identification.

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