C H A P T E R 3

HOST FACTORS ARE MORE IMPORTANT IN PREDICTING RECURRENT *CLOSTRIDIUM DIFFICILE* INFECTION THAN RIBOTYPE AND USE OF ANTIBIOTICS

Yvette H. van Beurden, Shabir Nezami, Chris J.J. Mulder, Christina M.J.E. Vandenbroucke-Grauls

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ABSTRACT

Objective

A frequent complication of *Clostridium difficile* infection (CDI) is recurrent disease. The aim of this study was to determine whether early recurrence risk was higher after infection with ribotype 027 (outbreak strain) compared to infection with endemic strain types of *C. difficile.*

Methods

Consecutive patients diagnosed with CDI between May 2013 and March 2014 were included (outbreak strain, and non-outbreak strains). Patients who developed recurrent CDI within 30 days after completion of CDI treatment, were compared to patients without a recurrence. Medical charts were reviewed for demographic and clinical characteristics. General practitioners were contacted to complete data about the occurrence of recurrent CDI, and the use of medication after hospital discharge.

Results

In total, 135 patients were at risk for the development of recurrent CDI; 74 patients were infected by ribotype 027, and 61 patients by other ribotypes. Thirty-nine patients (29%) developed recurrent CDI within 30 days after completion of CDI treatment. In multivariable analysis, age ≥70 years (HR 3.05; 95% CI 1.54-6.03), and a duration of CDI treatment ≥11 days (HR 1.92; 95% CI 1.00-3.69) were clearly associated with recurrence; infection with ribotype 027 showed a HR of 1.72 (95% CI 0.97-3.33).

Conclusion

During this outbreak of *C. difficile* in a tertiary care center, age, and a prolonged duration of CDI therapy (which is most likely a marker of underlying disease severity) were the main risk factors for recurrent CDI. This points to host factors as more important predictors for recurrent CDI than strain type or antibiotic use.

INTRODUCTION

A major challenge in the management of *Clostridium difficile* infection (CDI) is the high recurrence rate.[1] This rate has increased since early 2000, coincident with the emergence of *C. difficile* ribotype 027, a more virulent ribotype.[2]

It is generally assumed that the inability of the gut microbiota to re-establish colonization resistance after initial CDI adds to recurrence risk.[3,4] Alternatively, recurrent CDI may reflect failure of the host to mount a protective immune response against *C. difficile.*[4] Recurrent CDI is usually treated with (a tapered regimen of) vancomycin, fidaxomicin or fecal microbiota transplantation (FMT).[5] Fidaxomicin and FMT both appear associated with less recurrences.[6,7]

The increased recurrence rate of CDI since the emergence of ribotype 027 suggests a possible link between ribotype 027, and the development of recurrent disease. However, this relationship is not clearly established yet.[8] Between May 2013 and July 2014 an outbreak of *C. difficile* ribotype 027 occurred at a 750-bed tertiary care center in The Netherlands.[9] Primary aim of this follow-up study was to determine whether early recurrence risk was higher after CDI infection with ribotype 027 compared to infection with endemic strain types of *C. difficile.*

METHODS

General study outline

The present study was based on a study cohort described previously.[9] In this study we compared CDI patients who developed a recurrence after successful treatment, with CDI patients who did not develop a recurrence. This study was approved by the Medical Ethics Committee of the VU University medical center.

Participants

Consecutive patients diagnosed with CDI (outbreak strain ribotype 027, and other ribotypes) between May 2013 and March 2014 were included. Whole genome sequencing of a random selection of 10 strains of ribotype 027 isolated at different time points during the outbreak, showed that the cases of CDI 027 were likely caused by a single strain of *C. difficile* (two or less single-nucleotide variants between isolates).[9]

Patients diagnosed at the outpatient clinic, and patients who were lost to follow-up during CDI treatment were excluded. CDI was defined as the presence of diarrhea in combination with a positive stool (culture plus toxin) for *C. difficile*. Recurrent CDI was defined as a new episode of diarrhea with a positive stool for *C. difficile* within 30 days after completion of CDI treatment.

Data collection

We reviewed medical charts, reports of computerized tomography (CT) scans, and reports of colonoscopies or sigmoidoscopy for demographic and clinical characteristics. In our hospital whenever a (pseudomembranous) colitis is suspected, a CT scan or colonoscopy/sigmoidoscopy is performed. Therefore, when a CT scan or colonoscopy/sigmoidoscopy was not performed, we presumed that patients had no (pseudomembranous) colitis. In addition, data on outcome parameters within 30 days after completion of CDI treatment were collected. General practitioners were contacted to complete data about occurrence of recurrent CDI, and the use of antibiotics, proton pump inhibitors, and immunosuppressant's after hospital discharge.

Follow-up time

Person time at risk for recurrent CDI and death were calculated. For analysis of risk factors for recurrent CDI, follow-up started one day after completion of antibiotic CDI

treatment. To estimate mortality rates after primary and recurrent infection, follow-up started at time of CDI diagnosis. Follow-up time before the development of a recurrence was added to the denominator of the non-recurrent CDI mortality rate estimation, thereby accounting for immortal time bias. Follow-up was censored upon death, when patients were lost to follow-up, or 30 days after completion of CDI treatment.

Statistical analysis

Cox regression was used for time-to-event analysis, and hazard ratios (HR) and their 95% confidence intervals (95% CI) were estimated. The choice for a Cox model over logistic regression was based on the setting (cohort design with frequent outcome), because in such setting the odds ratio is a clear overestimation of the relative risk. The proportional hazards assumption was assessed for each variable, and no violation of the assumption was found.[10] The multivariable model included all factors associated with recurrent CDI in univariate analysis (95% CI > 1.0), as well as putative risk factors from earlier studies. The incidence of recurrences and all-cause mortality was expressed as the number of events per 1000 patient risk days and accounted for immortal time bias.

RESULTS

Patient characteristics and risk factors for recurrent *C. difficile* infection

In total, 144 patients with CDI were included. Nine patients died during CDI treatment; the remaining 135 patients were at risk for the development of a recurrence (Table 1). Of this group, 39 patients (15/1000 patient risk days) developed recurrent CDI within 30 days after completion of initial CDI treatment (Figure 1). The

mean time period between completion of CDI treatment, and the development of recurrent disease was 10 days (± 7 days).

In multivariable analysis, age ≥ 70 years, and a prolonged duration of CDI treatment (≥ 11) were associated with recurrent CDI (Table 2). Infection with *C. difficile* ribotype 027 showed a HR of 1.72 (95% CI 0.88-3.33).

Table 1. Patient characteristics and crude hazard ratios of potential risk factors for development of recurrent CDI

	Recurrent CDI N = 39		**Non recurrent CDI N = 96**		**Crude HR (95% C.I.)**
	N	**(%)**	**N**	**(%)**	
Age ≥ 70 years	25	(64%)	35	(37%)	2.9 (1.5-5.5)
Male gender	28	(72%)	58	(60%)	1.4 (0.7-2.9)
Charlson's comorbidity index, mean (±SD)	2.67	(±2.14)	2.55	(±2.34)	1.0 (0.9-1.1)
Ribotype 027	24	(62%)	50	(52%)	1.6 (0.8-3.0)
Pseudomembranous colitis initial CDI**	7	(18%)	8	(8%)	1.9 (0.8-4.3)
Use of medication during follow-up*					
Antibiotics	20	(53%)	38	(40%)	1.2 (0.6-2.3)
Proton pump inhibitors	25	(68%)	46	(48%)	1.3 (0.7-2.4)
Immunosuppressant's	6	(15%)	11	(12%)	1.0 (0.4-2.4)
Duration of CDI treatment (days)					
0 – 10 days	20	(51%)	69	(72%)	Reference
≥ 11 days	19	(49%)	27	(28%)	2.0 (1.1-3.8)

*Data were missing for 1 patients; **Colonoscopy/sigmoidoscopy performed in 4 patients, computerized tomography (CT)-scan performed in 21 additional patients. Abbreviations: CDI: *Clostridium difficile* infection; HR: Hazard Ratio; CI: confidence interval

Table 2. Adjusted hazard ratios of risk factors for recurrent CDI

	Adjusted HR (95% C.I.)[#]
Age ≥ 70	3.05 (1.54-6.03)
Charlson's comorbidity index	1.03 (0.89-1.19)
Ribotype 027	1.72 (0.88-3.33)
Use of antibiotics during follow-up	0.97 (0.50-1.86)
Duration of CDI treatment	
0 – 10 days	Reference
≥ 11 days	1.92 (1.00-3.69)

[#]Model adjusted for age, Charlson comorbidity index, *C. difficile* ribotype, use of antibiotics, number of days between stop CDI treatment and hospital discharge, duration of CDI treatment. Abbreviations: (r)CDI: (recurrent) *Clostridium difficile* infection; HR: Hazard Ratio; CI: confidence interval

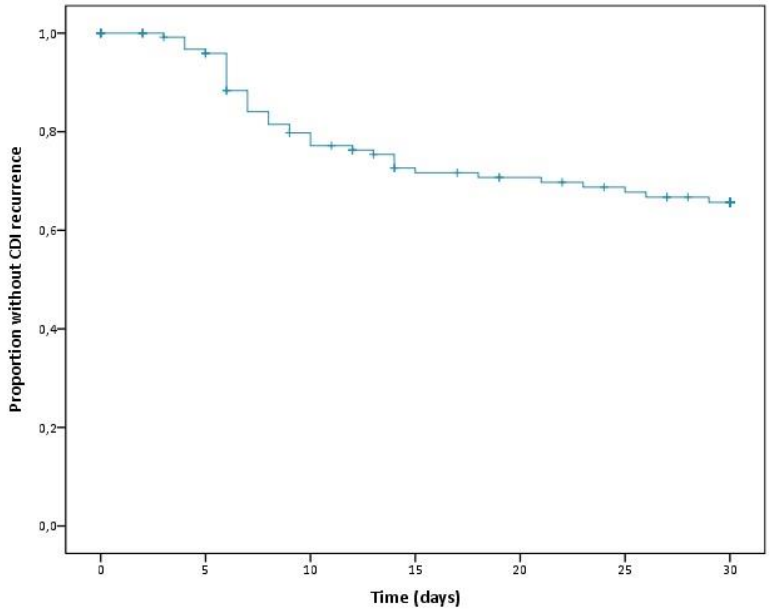

Figure 1. Kaplan Meier curve**.** Survival was calculated from end of CDI treatment. Abbreviations: CDI: *Clostridium difficile* infection. The y-axis represents the cumulative proportion of patients that has not developed recurrent CDI during follow-up; the x-axis represents time.

Clinical course of patients with recurrent *Clostridium difficile* infection

Of the 39 patients who developed a recurrent infection, 8 patients (21%) were readmitted due to recurrent CDI. Four patients (10%) with recurrent CDI had a (pseudomembranous) colitis (CT-scan performed in six patients; no colonoscopies/sigmoidoscopies performed), of which three also had a (pseudomembranous) colitis during the initial CDI episode. No patient needed abdominal surgery or had to be admitted to the intensive care unit due to recurrent CDI. Of patients with recurrent CDI, four patients died within the follow-up period (5.8/1000 patient risk days), compared to 25 non-recurrent CDI patients (5.7/1000 patient risk days).

DISCUSSION

During this outbreak of *C. difficile* in a tertiary care center, demographic and clinical parameters (e.g. age, and duration of CDI therapy), appeared as stronger predictors for recurrent CDI than strain type or use of antibiotics.

Advanced age, extensive comorbidity, and a prolonged hospitalization are well known risk factors for the development of recurrent CDI.[11] In older people, various age-related innate immune response changes, increased comorbidities, and polypharmacy, in combination with a less stable and diverse gut microbiota contribute to (recurrent) CDI susceptibility.[4,12] Patients who needed prolonged CDI therapy represented a highly vulnerable population. Therefore, duration of CDI therapy is most likely a marker of disease severity. That older patients who received prolonged CDI therapy were most at risk for recurrent CDI during this outbreak is therefore not surprising.

Additionally, it has been shown that recurrence risk is increased in patients who receive non-CDI antibiotics during follow-up.[13] Avoidance of unnecessary antimicrobials in patients with recent CDI has therefore been recommended to prevent recurrence.[14,15] In our cohort, only half of patients who developed a recurrence had used non-CDI antibiotics after completion of CDI treatment. Most patients developed recurrent CDI within 10 days after completion of treatment. This suggests that, during a period of high CDI incidence in a tertiary care center, where usually severely ill patients with extensive comorbidity are hospitalized, there is no time for the gut microbiota to reestablish colonization resistance, even if no antibiotics are used.

Ribotype 027 is a typical outbreak strain that has become endemic in many hospitals worldwide. However, the intrinsic virulence of ribotype 027 has been debated

because it disproportionately affects older, weaker, and hospitalized patients.[16] That in our study, age, and duration of CDI therapy (which is most likely a marker of underlying disease severity) were stronger predictors for recurrent CDI than ribotype 027 adds to this debate. However, given a hazard ratio of 1.72 (95% CI 0.88-3.33) in multivariable analysis, despite the confidence interval that encompasses unity, an additive role for a more virulent ribotype 027 cannot be ruled out.

Several previous studies have provided valuable insights into the role of different risk factors for recurrent CDI.[17] However, to our knowledge, we are the first to provide insight in the risk factors for the development of recurrent CDI during an outbreak. Limitations of our study include the retrospective design, and small sample size. Due to the outbreak setting of our study the prevalence of ribotype 027 was higher than that of other ribotypes. Therefore, our results may not generalizable to settings with lower ribotype 027 prevalence.

In conclusion, during an outbreak of CDI in a tertiary care center, older patients who needed prolonged CDI therapy were most at risk for an early recurrent infection. This points to host factors as more important predictors for recurrent CDI than strain type and the use of antibiotics during a CDI outbreak. These patients might benefit from treatment with FMT or fidaxomicin, which is associated with a lower recurrence risk.[6,7]

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