Clinical and Healthcare Burden of Multiple Recurrences of *Clostridium difficile* Infection

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**Background.** *Clostridium difficile* infection (CDI) is associated with a high risk of recurrence (rCDI). Few studies have focused on multiple recurrences. To evaluate the potential of novel treatments targeting recurrence, we assessed the burden and severity of rCDI.

**Methods.** This was a retrospective cohort of adults diagnosed with CDI in a hospital in Sherbrooke, Canada (1998–2013). An rCDI episode was defined by the reappearance of diarrhea leading to a treatment, with or without a positive toxin assay, within 14–60 days after the previous episode.

**Results.** We included 1527 patients. The probability of developing a first rCDI was 25% (354/1418); a second, 38% (128/334); a third, 29% (35/121); and a fourth or more, 27% (9/33). Two or more rCDIs were observed in 9% (128/1389) of patients. The risk of a first recurrence fluctuated over time, but there was no such variation for second or further recurrences. The proportion of severe cases decreased (47% for initial episodes, 31% for first recurrences, 25% for second, 17% for third), as did the risk of complicated CDI (5.8% to 2.8%). The severity and risk of complications of first recurrences decreased over time, while oral vancomycin was used more systemically. A hospital admission was needed for 34% (148/434) of recurrences.

**Conclusions.** This study documented the clinical and healthcare burden of rCDI: 34% of patients with rCDI needed admission, 28% developed severe CDI, and 4% developed a complication. Secular changes in the severity of recurrences could reflect variations in the predominant strain, or better management.

**Keywords.** *Clostridium difficile*; recurrence; complications.

Multiple recurrences of *Clostridium difficile* infection (CDI) have been observed more frequently during the past decade, and the quest for optimal management is ongoing [1]. Promising treatments include fecal microbiota transplantation, fidaxomicin, and monoclonal antibodies [2–6].

The median risk for at least 1 recurrence (rCDI) is 22% [7]. A higher proportion of patients who experience a first rCDI develop a subsequent recurrence [8]. The measures of risk of multiple recurrences were based on 2 trials on the efficacy of *Saccharomyces boulardii* conducted before emergence of the BI/NAP1/027 strain [8–12]. Other studies examined multiple recurrences in geriatric populations, in a small number of patients, and without documenting severity [13–15]. Data are lacking regarding the risk and consequences of multiple rCDIs in the general adult population. While the Society for Healthcare Epidemiology of America, Infectious Diseases Society of America, and Centers for Disease Control and Prevention define a recurrence as a diagnosis of CDI made 2 to 8 weeks after a preceding episode [16, 17], in studies that assessed risk factors for recurrence, duration of follow-up varied by up to 180 days [7].

In an era of laborious, costly treatments, the burden of multiple recurrences needs clarification in order to optimize the use of novel treatments. Through a retrospective cohort study, we aimed to describe the severity of subsequent episodes and the frequency of complications, emergency and outpatient consultations, hospitalizations, intensive care unit (ICU) stays, and use of further antibiotics or other therapeutics.

**METHODS**

Computerized medical records from the Centre Hospitalier Universitaire de Sherbrooke, a 677-bed tertiary care hospital in Quebec, Canada, were used to generate a database for CDI cases, as described previously [18–21]. Patients’ records were reviewed to expand this database by collecting additional demographics and clinical, management, and laboratory data. We included adult patients (aged ≥18 years) who had confirmed CDI between January 1998 and December 2013 and who resided in Sherbrooke. Spread over 141 square miles, the city has 162,000 inhabitants all of whom live within a 30–minute drive from the hospital. This geographic restriction allowed us to detect all cases of laboratory-proven CDI recurrences and to collect complete data on hospital care.
Definitions
Cases were identified via positive C. difficile cytotoxin assay results and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD)-9-CM or ICD-10-CM discharge codes. An initial episode of CDI was confirmed by a positive cytotoxin, endoscopic pseudomembranous colitis, or histopathology. Recurrence was defined by the reappearance of diarrhea that led to CDI treatment, with or without supporting microbiologic or endoscopic evidence, between 14 and 60 days after the previous episode. Patients who experienced 2 or more recurrences were considered to have “multiple recurrences.” An episode that occurred more than 60 days after a previous one was considered a new, distinct episode. Healthcare-associated CDI was defined as being associated with a hospital stay longer than 48 hours in the previous 4 weeks (healthcare-associated, community-onset) or occurring after 48 hours of hospitalization (healthcare-associated, healthcare-onset) [16, 17]. All other episodes were considered community-acquired.

Peak leukocytosis and creatinine were defined as the highest values within 48 hours of CDI diagnosis. Severe CDI was defined as a white blood cell count ≥15 x 10³/μL and/or an increase in creatinine ≥1.5 times the baseline level [16]. Complicated CDI was defined as at least 1 of the following: hypotension requiring vasopressors, ICU admission for a complication of CDI, ileus leading to installation of a nasogastric tube, toxic megacolon, colonic perforation, or colectomy [16]. Only outpatient visits at the hospital, including those in the emergency room, were documented.

Analyses
Data were entered in Microsoft Access, and statistical analyses were performed using SPSS Statistics 22.0 (SPSS Inc., Chicago). Proportions were compared with 2-tailed χ² or Fisher exact test when appropriate. Recurrence rates were calculated after excluding patients who died within 14 days of diagnosis. Crude and adjusted hazard ratios (AHRs) with their 95% confidence intervals (CIs) were measured using Cox regression. Time to event was defined as time until the first or second recurrence, respectively; death; or last known contact. Variables significantly associated with the outcome in univariate analyses were tested in multivariate models built sequentially, starting and continuing until no other variable reached significance. When the final model was completed, each variable was dropped in turn to assess its effect using the likelihood ratio test.

RESULTS
Initial Episodes
A total of 1527 CDI episodes that occurred in 1444 patients were included. Among the 72 patients who experienced more than 1 distinct initial episode separated by ≥2 months, 63 patients had 2 episodes, 7 patients had 3 episodes, and 2 patients had 4 episodes. The median time between episodes was 8.3 months (interquartile range [IQR], 5.1–24.9). Fifty-nine percent of patients were females (n = 903). The median age was 73 years (IQR, 54–82). Initial CDI was community-acquired in 45% of cases. Most healthcare-associated episodes occurred during a hospital stay (61%), and the rest were community-onset (39%).

Incidence of rCDI
Overall, 354 episodes of first recurrence were identified, while 128 patients experienced multiple recurrences: 93 had 2 recurrences, 26 had 3, and 9 patients had 4 or more. A positive cytotoxin confirmed 97% (n = 1484) of initial episodes, 77% (n = 271) of first recurrences (R1), 75% (n = 96) of second recurrences (R2), and 65% (n = 22) of third recurrences (R3). Pseudomembranous colitis was observed by endoscopy in 10% (n = 148) of initial episodes, 7% (n = 26) of R1, 5% (n = 6) of R2, and 9% (n = 3) of R3. A histopathological specimen confirmed the diagnosis in 0.7% (n = 11) of initial episodes and 1.7% (n = 6) of R1. In total, 21% of R1 (n = 73), 24% of R2 (n = 31), and 34% of R3 (n = 12) rCDIs were diagnosed by clinical suspicion alone. Consequently, the frequency of rCDI decreased after restricting our analysis to laboratory-confirmed cases (Supplementary Material).

After excluding patients who died within 14 days of diagnosis of the initial episode, the overall risk of R1 was 25% (Table 1). The subsequent recurrence rates varied as follows: 38% for R2, 29% for R3, and 27% for R4 or more. Multiple recurrences (R2 or more) were observed in 9% (128/1389) of all patients with follow-up. At least 1 rCDI was observed in 13% of cases between 1998 and 2002, in 30% between 2003 and 2005, in 20% between 2006 and 2009, and in 31% between 2010 and 2013 (Table 1).

Table 1. Risk of Recurrences According to Year of Diagnosis of Clostridium difficile Infection

<table>
<thead>
<tr>
<th>Year of Diagnosis</th>
<th>Initial Clostridium difficile Infection Episode</th>
<th>First Recurrence</th>
<th>Second Recurrence</th>
<th>Third Recurrence</th>
<th>Fourth Recurrence or More</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998–2001</td>
<td>253</td>
<td>31/242 (12.8%)</td>
<td>11/29 (37.9%)</td>
<td>3/10 (30.0%)</td>
<td>0/3 (0%)</td>
</tr>
<tr>
<td>2002–2005</td>
<td>727</td>
<td>198/655 (30.2%)</td>
<td>70/183 (38.3%)</td>
<td>19/65 (29.2%)</td>
<td>5/18 (27.8%)</td>
</tr>
<tr>
<td>2006–2009</td>
<td>332</td>
<td>63/319 (19.7%)</td>
<td>25/63 (39.7%)</td>
<td>9/24 (37.5%)</td>
<td>2/8 (25.0%)</td>
</tr>
<tr>
<td>2010–2013</td>
<td>215</td>
<td>62/202 (30.7%)</td>
<td>22/59 (37.3%)</td>
<td>4/22 (18.2%)</td>
<td>2/4 (50.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>1527</td>
<td>354/1418 (24.9%)</td>
<td>128/334 (38.3%)</td>
<td>35/121 (28.9%)</td>
<td>9/33 (27.3%)</td>
</tr>
</tbody>
</table>

Denominators (patients at risk) exclude those who died within 14 days after the previous episode.
Among patients who developed an R1, risk of R2 was remarkably stable over time. Although this analysis was limited by a small sample size, among patients who developed an R2, there was not much variation in the risk of a third or further recurrence during the study period. Intervals to occurrence of R1 and R2 were similar: a median of 25 days (IQR, 19–34) following the initial episode and 26 days (IQR, 21–37) following R1. The median occurrence of an R3 after an R2 was 38 days (IQR, 22–48) in the context of longer courses of oral vancomycin.

To determine the extent to which we might have underestimated the risk of recurrence by examining only a strict 60-day interval after the diagnosis of the previous episode regardless of the duration of its treatment, we measured this risk using an interval of 60 days after the last dose of the previous treatment (whether this had been an R1 or more). The risk of recurrence increased to 41% (138/334) for R2 and 37% (49/131) for R3 but decreased to 26% for R4 (12/47).

Characteristics of rCDI

Almost half (47%) of initial episodes were severe [16], mostly defined by a leukocytosis $\geq 15 \times 10^3/\mu\text{L}$, which was at least twice as frequent as acute renal failure (Table 2). Severity was seen in almost one third of R1 but progressively declined with further rCDIs. Similarly, the frequency of complicated episodes as well as the 30-day all-cause mortality rate somewhat decreased as recurrences accrued, although a few cases of toxic megacolon or shock were seen during second or third recurrences.

As shown in Table 3, the severity of initial CDI episodes declined modestly in 2010–2013 compared with earlier periods, but there was no change in the proportion that were deemed complicated. For R1, there was a progressive decrease over time in the proportion that were severe, as well as a concomitant reduction in the frequency of complications. When these analyses were restricted to patients with a toxin-positive recurrence, very little change was seen in the frequency of severe CDI, complications, readmission, and mortality (see Supplementary Material).

### Treatment of rCDI

While most initial episodes were treated with metronidazole for 10–14 days (Table 4), vancomycin was preferred for rCDI with increased duration of therapy through tapering. Physicians rarely resorted to fecal microbiota transplantation. Three of 15 patients who received a fecal transplantation experienced an additional episode. Antibiotics given for an indication other than CDI were prescribed for 25% (n = 88) of patients between the initial episode and R1, for 16% (n = 21) between R1 and R2, and for 14% (n = 7) of cases with subsequent recurrences.

Treatments of R1 and R2 changed dramatically over time; metronidazole was replaced by vancomycin, which was increasingly used as a long course with tapering of dosage (Table 5). Overall, when all periods and all recurrences are combined, patients treated with vancomycin were marginally less likely to

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**Table 2. Severity, Complications, and Mortality for Each Episode of Clostridium difficile Infection**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Initial Episode (N = 1527)</th>
<th>First Recurrence (n = 354)</th>
<th>Second Recurrence (n = 128)</th>
<th>Third Recurrence (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe episodes</td>
<td>710 (46.5%)</td>
<td>108 (30.5%)</td>
<td>32 (25.0%)</td>
<td>6 (17.1%)</td>
</tr>
<tr>
<td>Leukocytosis*</td>
<td>571 (37.4%)</td>
<td>90 (25.4%)</td>
<td>30 (23.4%)</td>
<td>5 (14.3%)</td>
</tr>
<tr>
<td>Acute renal failureb</td>
<td>256 (16.8%)</td>
<td>33 (9.3%)</td>
<td>9 (7.0%)</td>
<td>1 (2.8%)</td>
</tr>
<tr>
<td>Complicated episodes</td>
<td>89 (5.8%)</td>
<td>15 (4.2%)</td>
<td>6 (4.7%)</td>
<td>1 (2.8%)</td>
</tr>
<tr>
<td>Clostridium difficile Infection-related intensive care unit admission</td>
<td>87 (5.7%)</td>
<td>16 (4.5%)</td>
<td>4 (3.1%)</td>
<td>1 (2.8%)</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>33 (2.2%)</td>
<td>4 (1.1%)</td>
<td>1 (0.8%)</td>
<td>1 (2.8%)</td>
</tr>
<tr>
<td>Ileus</td>
<td>32 (2.1%)</td>
<td>9 (2.5%)</td>
<td>2 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Toxic megacolon</td>
<td>23 (1.5%)</td>
<td>0</td>
<td>3 (2.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Perforation</td>
<td>5 (0.3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Colectomy</td>
<td>18 (1.2%)</td>
<td>2 (0.6%)</td>
<td>2 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>All-cause 30-day mortality</td>
<td>166 (10.9%)</td>
<td>27 (7.6%)</td>
<td>9 (7.0%)</td>
<td>2 (5.7%)</td>
</tr>
</tbody>
</table>

* White blood cell count $\geq 15 \times 10^3/\mu\text{L}$ within 48 hours of diagnosis.

* Increase in creatinine 1.5 times the normal value within 48 hours of diagnosis.

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**Table 3. Changes in Severity and Complications of Clostridium difficile Infection Over Time**

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Severity</strong></td>
<td></td>
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</tr>
<tr>
<td>Initial episodes</td>
<td>113/221 (51.1%)</td>
<td>343/627 (54.7%)</td>
<td>166/287 (57.8%)</td>
<td>88/200 (44.0%)</td>
<td>.02</td>
</tr>
<tr>
<td>First recurrences</td>
<td>14/23 (60.9%)</td>
<td>63/148 (42.6%)</td>
<td>17/46 (37.0%)</td>
<td>14/46 (30.4%)</td>
<td>.05</td>
</tr>
<tr>
<td>Second recurrences</td>
<td>4/7 (57.1%)</td>
<td>14/33 (42.4%)</td>
<td>8/16 (50.0%)</td>
<td>6/10 (60.0%)</td>
<td>.77</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial episodes</td>
<td>11/253 (4.3%)</td>
<td>44/725 (6.1%)</td>
<td>22/332 (6.6%)</td>
<td>12/215 (5.6%)</td>
<td>.67</td>
</tr>
<tr>
<td>First recurrences</td>
<td>3/31 (9.7%)</td>
<td>10/198 (5.1%)</td>
<td>1/63 (1.6%)</td>
<td>1/62 (1.6%)</td>
<td>.01</td>
</tr>
<tr>
<td>Second recurrences</td>
<td>0/10 (0%)</td>
<td>6/67 (9.0%)</td>
<td>0/25 (0%)</td>
<td>0/22 (0%)</td>
<td>.59</td>
</tr>
</tbody>
</table>
develop complications (8/308, 2.6%) than were those given metronidazole (3/75, 4.0%), while complications developed in 11 of 56 patients (19.6%) who received both vancomycin and metronidazole (concomitantly or sequentially).

Risk Factors for rCDI
In multivariable analysis, a number of risk factors for R1 were identified. Using the 18- to 64-years age group as baseline, R1 was associated with being aged 65–74 years (AHR, 1.5; 95% CI, 1.1–2.1; \( P = .01 \)) or \( \geq 75 \) years (AHR, 1.8; 95% CI, 1.4–2.4; \( P < .001 \)). R1 was also associated with the period of initial diagnosis (using 1998–2001 as baseline: 2002–2005: AHR, 2.3; 95% CI, 1.5–3.3; \( P < .001 \) and 2010–2013: AHR, 2.5; 95% CI, 1.6–3.9; \( P < .001 \)) and with the severity of initial CDI (AHR, 1.6; 95% CI, 1.3–2.0; \( P < .001 \)). Within the subset of patients who developed an R1, age was not a risk factor for a second or additional recurrences. Overall, 13% (n = 192) of patients were immunocompromised, but no associations were observed between recurrence and immune status.

Healthcare Burden of Initial and rCDI
For their initial episode, 807 patients (53%) were treated as outpatients, 199 (13%) were later hospitalized, and 517 (34%) were hospitalized at the time of CDI diagnosis. The median length of stay for patients admitted for the management of their initial CDI episode was 9 days (IQR, 5–21 days). After excluding patients already hospitalized at the time of recurrence, 34% (148/434) of recurrences prompted hospital admission, with a median length of hospital stay of 7 days. This proportion did not change whether this was an R1, R2, or R3 (Table 6). With further recurrences, the proportion of patients who were hospitalized at the time of diagnosis decreased, with a corresponding increase in the proportion of patients managed as outpatients. Among patients managed at Centre Hospitalier Universitaire de Sherbrooke as outpatients, 43% (50/115) were seen more than once, perhaps avoiding unnecessary hospitalizations. Among 695 patients hospitalized at some time during their initial episode, 101 (15%) were readmitted to the hospital after diagnosis of R1, 80 (12%) of whom with CDI as their principal diagnosis. These proportions were 19% (33/171) and 15% (25/171), respectively, after diagnosis of R2.

DISCUSSION
Our study addresses multiple recurrences of CDI and their clinical and healthcare burden, following community- and hospital-
associated CDI over a long period in a single center. Our facility provides all hospital care and laboratory assays to the 162,000 inhabitants of the city of Sherbrooke [18], enabling us to measure almost all CDI recurrences, in contrast with other studies in which patients have access to several facilities. Most prior studies have measured accurately the risk of a first recurrence (12%–30%) [7] because patients could be closely followed for a short period of time, often during trials [4,22,23]. However, few studies measured the risk of additional recurrences after R1. The most frequently cited study was a post hoc cohort of patients who re-measured the risk of additional recurrences after R1. The most plausible explanation for this result is that earlier studies [25] had little impact on the risk of R2 (41% vs 38%) and R4 (26% vs 27%) while increasing the risk of R3 (37% vs 29%).

Our study demonstrates the significant burden of rCDI on healthcare systems [25]. Combining all recurrences, more than one third of patients not already hospitalized required hospital admission, where they remained for a median of 7 days, as in the United States [26]. Given that a day of hospitalization in Quebec is valued at $820 and that this figure does not take into consideration the 3-fold higher cost for patients in the ICU or physicians’ billing, the total cost of each hospital admission for rCDI is approximately $6500. For those already in the hospital at the time of recurrence, we did not attempt to quantify the prolongation of hospitalization, but this must have generated substantial costs. Comparison with recent studies on the burden of rCDI is difficult as they either focused on a select population of patients who received intensive care [27] or used an administrative database with limited clinical information [24].

Overall, risk of at least 1 recurrence was 25%, while 9% of patients experienced 2 or more recurrences. Our measures may be somewhat underestimated because we used a time frame of 14–60 days to define rCDI [16], and the increasing use of tapered vancomycin regimens might have deferred the onset of a recurrence beyond the 60-day limit. However, extending the period of observation to 60 days after the last dose of the previous treatment had little impact on the risk of R2 (41% vs 38%) and R4 (26% vs 27%) while increasing the risk of R3 (37% vs 29%).

The risk of developing a first rCDI varied over time. The higher risk in 2002–2005 may have reflected the emergence of the BI/NAP1/027 strain [18]. During this period, the burden of *C. difficile* spores in our hospital must have been higher, increasing the potential for reinfections. Furthermore, some studies suggested that BI/NAP1/027 is associated with a higher risk of recurrence [22, 28, 29]. Established since 2004, the Quebec CDI surveillance program collects, in addition to incidence data, a limited number of samples from many hospitals for typing [30]. Throughout Quebec, the proportion of *C. difficile* strains that corresponded to BI/NAP1/027 remained stable at

### Table 6. Healthcare Burden of Recurrences

<table>
<thead>
<tr>
<th>Healthcare Burden</th>
<th>First Recurrences (n = 354)</th>
<th>Second Recurrences (n = 128)</th>
<th>Third Recurrences (n = 35)</th>
<th>Fourth Recurrences or More (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Managed as outpatient at CHUS*</td>
<td>72 (20.3%)</td>
<td>26 (19.5%)</td>
<td>12 (34.3%)</td>
<td>6 (40.0%)</td>
</tr>
<tr>
<td>One visit to CHUS</td>
<td>45 (12.7%)</td>
<td>12 (9.4%)</td>
<td>5 (14.3%)</td>
<td>3 (20.0%)</td>
</tr>
<tr>
<td>≥2 visits to CHUS</td>
<td>27 (7.6%)</td>
<td>13 (10.2%)</td>
<td>7 (20.0%)</td>
<td>3 (20.0%)</td>
</tr>
<tr>
<td>Admission for rCDI</td>
<td>97 (27.4%)</td>
<td>37 (28.9%)</td>
<td>10 (28.6%)</td>
<td>4 (26.7%)</td>
</tr>
<tr>
<td>Median length of stay, days (interquartile range)</td>
<td>7 (4–14%)</td>
<td>7 (3–13.5%)</td>
<td>6 (3–10%)</td>
<td>4.5</td>
</tr>
<tr>
<td>Admitted mainly for reason other than CDI</td>
<td>34 (9.6%)</td>
<td>7 (5.5%)</td>
<td>0</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Already hospitalized at diagnosis of rCDI</td>
<td>75 (21.2%)</td>
<td>19 (14.8%)</td>
<td>2 (5.7%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>Managed as outpatient, not CHUS</td>
<td>76 (21.5%)</td>
<td>40 (31.3%)</td>
<td>11 (31.4%)</td>
<td>3 (20.0%)</td>
</tr>
</tbody>
</table>

Abbreviations: CDI, *Clostridium difficile* infection; CHUS, Centre Hospitalier Universitaire de Sherbrooke; rCDI, recurrent *Clostridium difficile* infection.

* Outpatient visit alone, not followed by admission at CHUS.
55% in 2007–2013 [30]. We lack information about the distribution of strains at our center in recent years and cannot rule out the possibility that a novel, recurrence-prone strain took hold in 2010–2013.

In contrast, among patients with an R1, the probability of developing an R2 or R3 remained stable over time (Table 1). It may be that at this stage in the natural history of CDI, host characteristics such as immune senescence might matter more than variations in infecting strains or risk of reinfection.

Our study had limitations. Missing data were inevitable due to its retrospective design. Physicians occasionally did not provide precise information regarding the duration of treatments in an outpatient setting. Medical records outside the hospital or telephonic prescriptions could not be reviewed. Nevertheless, we had access to laboratory results ordered outside the hospital since our laboratory is the only one offering the cytotoxin assay. Furthermore, all but 1 medical specialist who managed most patients with multiple CDI recurrences in Sherbrooke had a hospital-based practice, even for their outpatients. Thus, we believe our results accurately reflect the recurrence rate in our population despite missing data on empirical prescriptions outside the hospital. An information bias could have been introduced by retaining rCDI diagnosed solely by clinical suspicion. As these episodes were not proven, some patients could have had an alternate cause of diarrhea; however, the exclusion of unconfirmed cases would have eliminated many genuine cases of rCDI and underestimated the true risk of recurrence. The proportion of unconfirmed cases increased after R2, as clinicians found it less useful to confirm diagnoses in patients who presented with the same symptoms shortly after discontinuation of the previous CDI treatment. Finding no difference in the frequency of adverse outcomes between all CDI patients and those with laboratory-confirmed CDI suggests that this aforementioned information bias was inconsequential.

Multiple rCDIs are a plague to patients, a challenge to physicians, and a substantial burden on healthcare resources. The quest for optimal management of rCDI is ongoing, and fidaxomicin seems more effective than vancomycin for the treatment of a first recurrence [31]. A recent study mentioned that fecal microbiota transplant is the most cost-effective option, while fidaxomicin and monoclonal antibodies are more expensive [32]. However, bacteriotherapy is unattractive to many. Use of fidaxomicin as a chaser or taper regimen seems promising but needs further evaluation [6]. A trial on tapered fidaxomicin is ongoing (www.clinicaltrials.gov; NCT02395848). Pharmacoeconomic studies are needed to evaluate all options in light of the burden data provided in the current study. Given the decreasing risk of complications over time and over the natural history of the disease, for novel therapeutic options to be cost-effective, they would need to reduce the risk of first and further recurrences and of hospital readmissions, rather than the risk of complications.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes


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