MAJOR ARTICLE

Management and Outcomes of a First Recurrence of *Clostridium difficile*–Associated Disease in Quebec, Canada

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(See the editorial commentary by Louie on pages 765–7)

Background. During an epidemic of *Clostridium difficile*–associated disease (CDAD) caused by a strain that is a hyper-producer of toxins A and B, the frequency of a first recurrence after metronidazole treatment of the initial episode doubled in 2003–2004, compared with 1991–2002.

Methods. To examine whether administration of metronidazole as treatment for a first recurrence of CDAD remained appropriate, we reviewed data for patients with CDAD diagnosed in a hospital in Quebec, Canada, during 1991–2005, who experienced a first recurrence. The frequency of a second recurrence within 60 days after the first one was measured using Kaplan-Meier analysis. Cox regression was used for multivariate analysis.

Results. A total of 463 patients had a first recurrence of CDAD, of whom 154 (33.3%) experienced a second recurrence. Independent predictors of a second recurrence were age and duration of hospitalization after the first recurrence; this latter finding suggested that many such episodes were reinfections rather than relapses. Neither choice of treatment drug (metronidazole or vancomycin) nor use of the same drug for treatment of first recurrence, as had been used during the initial episode, was associated with increased risk of a second recurrence. However, 51 patients (11.0%) developed at least 1 complication (i.e., shock, need for colectomy, megacolon, perforation, or death within 30 days) during the first recurrence. Older age, a high leukocyte count, and renal failure at first recurrence were strongly associated with a complicated CDAD.

Conclusions. Metronidazole is not inferior to vancomycin for treatment of patients with a first recurrence of CDAD, but the risk of complications with any treatment of CDAD may be higher than has previously been documented.

Since the identification of *Clostridium difficile* as the etiological agent of pseudomembranous colitis [1], frequent recurrences have been noted in patients treated with either metronidazole or vancomycin, with up to 35% of patients experiencing at least a second episode [2–10]. These recurrences can correspond to either a relapse of the original infection or a reinfection with a different strain [11, 12]. After the 1995 recommendations by the Centers for Disease Control and Prevention to avoid the use of vancomycin to prevent the emergence of drug-resistant organisms [13], metronidazole became the standard first-line treatment for *Clostridium difficile*–associated disease (CDAD).

In the context of a large epidemic of health care–associated CDAD in the province of Quebec, Canada, associated with a high case-fatality rate, we performed an observational study that documented that patients with CDAD who were initially treated with oral vancomycin were less likely to develop complications or to die within 1 month after the initial diagnosis than were their counterparts who were treated with metronidazole [14]. Subsequently, we showed that, compared with patients treated with metronidazole in 1991–2002, those treated with metronidazole in 2003–2004 were more likely to have their regimen switched to vancomycin because of a perception of treatment failure and were twice as likely to experience at least 1 recurrence of CDAD [15]. The epidemic in Quebec is caused by a toxinotype III, North American PFGE type 1/PCR-ribotype 027 (NAP1/027) strain of *C. difficile* that is a

Received 22 August 2005; accepted 16 November 2005; electronically published 7 February 2006.

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Clinical Infectious Diseases 2006; 42:758–64

1058-4838/2006/4206-0004$15.00

hyperproducer of toxins A and B; it emerged in the middle of 2002 and has also been found in several American states, the United Kingdom, and The Netherlands [16–19]. In our hospital, this strain represented 67% of isolates from patients with health care–associated CDAD in 2004–2005 [18]. Another report from Texas documented a high frequency of treatment failures with metronidazole, prompting a reassessment of current therapeutic strategies [20, 21].

Most authorities recommend that patients who experience a recurrence of CDAD should be treated with the same drug as was used during their first episode [5–7, 10, 22–24]. To determine whether such an approach remained appropriate in light of recent changes in the epidemiology and virulence of *C. difficile,* we reviewed the outcomes for patients found to have a first recurrence of CDAD in our institution since 1991.

METHODS

We previously reported on the risk factors for a first recurrence of CDAD among all patients who had CDAD diagnosed at our institution between 1991 and mid-2004 [15]. This database has been expanded up to mid-2005 and will now be used to examine the outcomes of patients who experienced at least 1 recurrence. In brief, we reviewed cases of CDAD diagnosed during the period from January 1991 through June 2005 at the Centre Hospitalier Universitaire de Sherbrooke (CHUS), a tertiary care hospital. Its clinical microbiology laboratory is the sole laboratory to perform the *C. difficile* toxin assay in the Estrie region of Quebec. The same *C. difficile* toxin B cytotoxin assay was used throughout that period. Patients with a positive toxin assay result were identified through computerized medical records. Additionally, for inpatients, cases of pseudomembranous colitis, antibiotic-associated colitis, or *C. difficile* colitis were identified through the hospital discharge database. Patients with CDAD were defined as patients who met at least 1 of the following criteria: (1) a positive *C. difficile* cytotoxin assay result, (2) endoscopic evidence of pseudomembranous colitis, or (3) evidence of pseudomembranous colitis from histopathologic examination of an endoscopic biopsy specimen or a specimen obtained during colectomy or autopsy. CDAD was considered to have been hospital acquired if the patient had been hospitalized when the inciting antibiotics were administered. Medical records were reviewed to extract demographic, clinical, and laboratory data. Patients treated with metronidazole received 250 mg of the drug 4 times per day or 500 mg 3 times per day for 10–14 days. Most patients treated with oral vancomycin received 125 mg 4 times per day for 10–14 days; a minority of patients received 250–500 mg of oral vancomycin 4 times per day.

Two episodes of CDAD in the same patient were considered to be distinct events if they occurred >2 months apart; an episode that occurred within 2 months of a prior episode was considered to be a recurrence of the initial one. A recurrence could correspond either to a relapse with the same strain or to a reinfection with a different strain. It is not possible in clinical practice to differentiate between these 2 mechanisms, and the term "recurrence" was used as a designation for both. A patient was considered to have had a first recurrence if, within 60 days after the initial diagnosis, (1) there was recurrence of diarrhea, and (2) an additional specimen tested positive for *C. difficile* toxin or the attending physician ordered a second course of treatment against *C. difficile* without asking for an additional assay to be performed. The same definition was used for a second recurrence within a time frame of 60 days after diagnosis of the first recurrence. As a proxy for reexposure to *C. difficile,* we measured the number of days that each patient was hospitalized within the 60 days that followed the diagnosis of the first recurrence.

The analyses were limited to patients who lived in the Estrie region (for whom toxin assays requested by attending physicians suspecting a recurrence would normally have been sent to CHUS) and who had experienced a first recurrence of CDAD. Kaplan-Meier analyses were used to measure the probability of a second recurrence after treatment of the first one. For patients who did not experience a second recurrence, data were censored either when the patient died or 60 days after the diagnosis of the first recurrence. Cox proportional hazards modeling was used to calculate unadjusted and adjusted hazard ratios (HRs) and their 95% CIs. For multivariate analysis, models were built up sequentially, starting with the variable most strongly associated with the outcome and continuing until no other variable reached significance. When the final model was reached, each variable was dropped in turn to assess its effect. Different models were compared using the likelihood ratio test, and variables significant at the $P \leqslant .05$ level were kept in the final model. The proportional hazards assumption was verified by comparing the Kaplan-Meier curve to the Cox predicted curve for a given variable.

RESULTS

A total of 463 patients fulfilled the case definition, of which 154 (33.3%) had a second recurrence (127 [82.5%] of these were confirmed by an additional toxin assay). Ninety-eight second recurrences (63.6%) occurred within 30 days after diagnosis of the first recurrence, and 56 occurred 31–60 days after that date. Age and duration of hospitalization were strongly associated with a higher risk of a second recurrence (table 1). As shown in the Kaplan-Meier plots (figure 1), the 60-day probabilities of a second recurrence were 22.6%, 25.4%, and 41.8% among patients aged 0–17, 18–64, and ⩾65 years, respectively ($P = .004$, by log rank test). The 60-day probability of a second recurrence was 29.2% among patients who did not stay a single day in hospital after their first recurrence, whereas

Table 1. Risk factors for a second recurrence of *Clostridium difficile*–associated disease (CDAD).

Characteristic	No. of second recurrences/total no. of patients (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Age, years			
0–17	7/31 (22.6)	0.88 (0.38–2.02)	0.91 (0.39–2.10)
18–64	26/107 (24.3)	1.00	1.00
⩾65	121/325 (37.2)	1.83 (1.19–2.79)[a]	1.75 (1.14–2.70)[a]
Sex			
Female	83/259 (32.0)	1.00	NS
Male	71/204 (34.8)	1.11 (0.81–1.53)	…
Place of CDAD acquisition			
Community	40/127 (31.5)	1.00	NS
Other hospital	6/16 (37.5)	1.08 (0.46–2.56)	…
CHUS	108/320 (33.8)	1.22 (0.85–1.76)	…
Period of diagnosis			
1991–2002	48/166 (28.9)	1.00	NS
2003–2005	106/297 (35.7)	1.30 (0.93–1.83)	…
Immunosuppression			
No	121/367 (33.0)	1.00	NS
Yes	20/67 (29.9)	0.94 (0.59–1.51)	…
Duration of hospitalization within 60 days after first recurrence, days			
0	49/173 (28.3)	1.00	1.00
1–15	52/155 (33.5)	1.42 (0.96–2.10)	1.32 (0.89–1.96)
⩾16	52/126 (41.3)	1.63 (1.10–2.41)[a]	1.39 (0.93–2.08)
Peak leukocyte count, $\times 10^9$ cells/L[b]			
<10.0	32/102 (31.4)	1.00	NS
10.0–19.9	45/123 (36.6)	1.21 (0.77–1.90)	…
⩾20.0	16/54 (29.6)	1.39 (0.76–2.54)	…
NA	61/184 (33.2)	1.08 (0.70–1.66)	…
Peak creatinine level, μmol/L[b]			
<100	46/134 (34.3)	1.00	NS
100–199	32/90 (35.6)	1.18 (0.75–1.86)	…
⩾200	10/40 (25.0)	0.92 (0.46–1.82)[a]	…
NA	66/199 (33.2)	0.95 (0.65–1.38)	…
Treatment administered for first recurrence of CDAD			
Metronidazole only	42/115 (36.5)	1.00	NS
Vancomycin only	68/171 (39.8)	0.97 (0.66–1.43)	…
Metronidazole and vancomycin sequentially	8/20 (40.0)	0.98 (0.46–2.09)	…
Metronidazole plus vancomycin at once	4/16 (25.0)	0.80 (0.29–2.23)	…
Other treatment	3/8 (37.5)	0.96 (0.30–3.09)	…

NOTE. CHUS, Centre Hospitalier Universitaire de Sherbrooke; HR, hazard ratio; NA, not available; NS, not significant.

[a] $P < .05$.

[b] Peak values within 1 week after diagnosis of the first recurrence of CDAD.

it was 39.4% and 46.2% among those who stayed 1–15 and ⩾16 days in the hospital, respectively ($P = .04$, by log rank test). Diagnosis in 2003–2005 tended to be associated with a higher risk of a second recurrence, but not significantly so ($P = .13$). Risk of a second recurrence did not vary according to the sex of the patient, the patient's immune status, or peak creatinine level and peak leukocyte count at the time of first recurrence (as markers of severity). The risk of a second recurrence was the same regardless of whether the first recurrence had been treated with vancomycin, metronidazole, or a combination of both drugs (information on treatment of the first recurrence was available only for 330 patients). In multivariate Cox regression modeling, only age (HR for each additional year of age, 1.013; 95% CI, 1.004–1.021; $P = .004$) and duration of hospitalization (HR for each additional day of hospitalization, 1.010; 95% CI, 1.001–1.019; $P = .03$) significantly increased

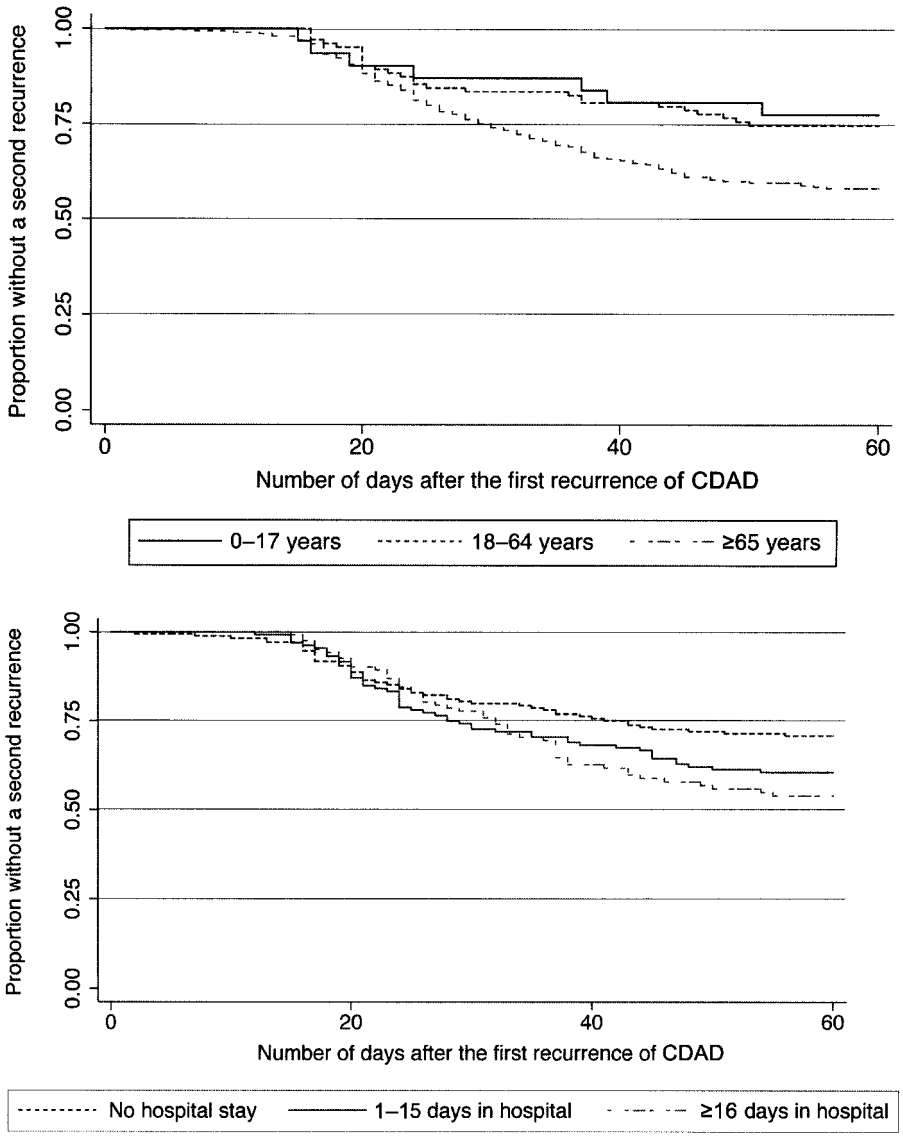

Figure 1. Kaplan-Meier plot of the 60-day probability of a second recurrence of *Clostridium difficile*–associated disease (CDAD) according to age group *(top)* and duration of hospital stay after first recurrence *(bottom),* 1991–2005.

the fit of the model. These are presented as categorical variables in table 1 for the sake of simplification.

The nonsignificant trend for a somewhat higher frequency of second recurrence in 2003–2005 versus 1991–2002 was similar when examining only patients whose first recurrence had been treated with metronidazole (HR, 1.34; 95% CI, 0.82–2.17; $P = .24$) or vancomycin (HR, 1.27; 95% CI, 0.80–2.02; $P = .31$). When analysis was restricted to cases diagnosed in 2003–2005 (a period during which the NAP1/027 strain was present), use of vancomycin as treatment of the first recurrence was not associated with a lower risk of a second recurrence, compared with use of metronidazole (HR, 0.83; 95% CI, 0.50–1.37; $P = .47$). If analysis for the entire study period was restricted to patients who received metronidazole as treatment for the initial episode, use of vancomycin as the treatment of the first recurrence was not associated with a lower risk of a second recurrence, compared with use of metronidazole a second time (HR, 1.16; 95% CI, 0.74–1.82; $P = .52$); conversely, among patients who received only vancomycin for treatment of the initial episode, vancomycin treatment of the first recurrence did not perform significantly better than metronidazole (HR, 0.68; 95% CI, 0.32–1.46; $P = .32$). A similar finding emerged when we examined patients who, during the initial episode, had received metronidazole followed by vancomycin because of suboptimal response (HR for vancomycin vs. metronidazole as treatment of the first recurrence, 1.18; 95% CI, 0.40–3.60; $P = .77$).

We then examined the frequency of the development of com-

Table 2. Factors associated with complicated *Clostridium difficile*–associated disease (CDAD) during first recurrence.

Characteristic	No. of patients with complicated CDAD/ total no. of patients (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Age (years)	…	1.037 (1.014–1.061)[a,b]	1.039 (1.001–1.079)[a,c]
Sex			
Female	28/259 (10.8)	1.00	NS
Male	23/204 (11.3)	1.05 (0.58–1.88)	…
Place of CDAD acquisition			
Community	6/127 (4.7)	1.00	NS
Other hospital	0/16 (0.0)	0.00	…
CHUS	45/320 (14.1)	3.30 (1.37–7.94)[c]	…
Period of diagnosis			
1991–2002	15/166 (9.0)	1.00	NS
2003–2005	36/297 (12.1)	1.39 (0.74–2.62)	…
Immunosuppression			
No	41/367 (11.2)	1.00	NS
Yes	10/67 (14.9)	1.39 (0.66–2.94)	…
Peak leukocyte count, $\times 10^9$ cells/L[d]			
<10.0	8/102 (7.8)	1.00	1.00
10.0–19.9	13/123 (10.6)	1.39 (0.55–3.49)	0.84 (0.27–2.61)
⩾20.0	21/54 (38.9)	7.48 (3.02–18.50)[b]	4.44 (1.41–13.98)[c]
NA	9/184 (4.9)	0.60 (0.23–1.62)	1.57 (0.16–15.80)
Peak creatinine level, μmol/L[d]			
<100	10/134 (7.5)	1.00	1.00
100–199	19/90 (21.1)	3.32 (1.46–7.53)[c]	3.77 (1.35–10.51)[c]
⩾200	14/40 (35.0)	6.68 (2.67–16.67)[b]	4.73 (1.48–15.16)[c]
NA	8/199 (4.0)	0.52 (0.20–1.35)	0.43 (0.04–4.31)
Treatment administered for first recurrence of CDAD			
Metronidazole only	15/115 (13.0)	1.00	1.00
Vancomycin only	12/171 (7.0)	0.50 (0.23–1.12)	0.49 (0.20–1.20)[e]
Metronidazole and vancomycin sequentially	2/20 (10.0)	0.74 (0.16–3.52)	0.69 (0.13–3.78)[e]
Metronidazole plus vancomycin at once	7/16 (43.8)	5.19 (1.68–16.00)[c]	3.56 (0.85–14.95)[e]
Other treatment	2/8 (25.0)	2.22 (0.41–12.04)	0.60 (0.09–4.16)[e]

NOTE. Information on treatment of the first recurrence was available for only 330 patients. Complicated CDAD was defined as any combination of megacolon, perforation, need for a colectomy, shock, and death (all causes) within 30 days after diagnosis of first recurrence. CHUS, Centre Hospitalier Universitaire de Sherbrooke; NS, not significant.

[a] The crude and adjusted ORs are for each additional year of age.
[b] $P \leqslant .001$.
[c] $P < .05$.
[d] Peak values within 1 week after diagnosis of the first recurrence of CDAD.
[e] Adjusted for age, peak leukocyte count, and peak creatinine level.

plicated CDAD during the first recurrence using the same definition as during the initial episode (i.e., megacolon, perforation, need for a colectomy, shock requiring vasopressors, or death [all causes] within 30 days after the diagnosis of the first recurrence, or any combination thereof) [14]. Of 463 patients, 51 (11.0%) developed at least 1 of these complications (shock in 10, need for colectomy in 3, megacolon in 2, and death within 30 days in 43). Age was strongly associated with a higher risk of developing complicated CDAD, as was having a high leukocyte count or renal failure, even after allowing for confounding factors. Age is presented as a continuous variable in table 2; when categorized, 0 (0%) of 31 children aged <18 years developed complicated CDAD, compared with 8 (7.5%) of 107 adults aged 18–64 years and 43 (13.2%) of 325 patients aged ⩾65 years ($P = .03$). Compared with patients whose first recurrence had been treated with metronidazole, those then treated with vancomycin tended to be less likely to develop complicated CDAD, but this finding was not statistically significant ($P = .09$ in univariate analysis; $P = .12$ in multivariate analysis). Recent surgery and tube feeding were not associated with a higher risk of developing a complicated outcome during the first recurrence (data not shown).

DISCUSSION

Previous studies identified the following risk factors for a first recurrence among patients with CDAD: age >65 years, a poor immune response against toxin A, markers of severe CDAD,

the use of additional antibiotics following the initial episode of CDAD, chronic renal failure, and a high leukocyte count [15, 25–28]. The few studies that specifically examined risk factors for an additional recurrence (i.e., age, lower quality of health index, number of previous episodes, and administration of additional antibiotics) among patients who had experienced at least 1 recurrence documented a higher frequency of additional recurrences (42%–65% of patients) than we did [29–31], but those studies enrolled patients who had experienced multiple recurrences; on average, they had already experienced 3 prior episodes.

In contrast to what we documented among patients receiving treatment for an initial episode of CDAD, patients given metronidazole as treatment of a first recurrence of CDAD in 2003–2005 did not experience significantly more-frequent second recurrences than their counterparts of earlier years, nor did they experience second recurrences more frequently than did patients treated with vancomycin. Additionally, the risk of a second recurrence was associated with the number of days spent in hospital following the first recurrence, suggesting that a sizeable fraction of these patients were having reinfections rather than true relapses. This contrasts with our findings when examining first recurrences, which were not associated with a longer hospital stay after adjusting for confounding factors [15]. Previous studies that used molecular methods have shown that between one-tenth and one-half of recurrent episodes are reinfections rather than relapses of infection with the original strain [11, 12]. The association between a second recurrence and age is in line with our previous findings for patients receiving their initial treatment for CDAD [15]. Older individuals may have a less effective immune response against *C. difficile* or its toxins that predisposes them to genuine relapses; at the same time, those who stay longer in hospital are more exposed to possible reinfections.

The probability of a further recurrence is not the only important factor to be considered when selecting a treatment for the first recurrence; one also wants the patient to avoid developing complications or dying as a result of this first recurrence. Our results suggest that treatment with vancomycin tended to be associated with a lower probability of developing complications of this first recurrence, compared with use of metronidazole, but this finding was not statistically significant.

Our study has 2 important limitations. First, because of its observational nature, there may be some residual confounding; patients treated with, for example, vancomycin may have differed from those treated with metronidazole for factors themselves related to the risk of developing complications or of experiencing a second recurrence. Second, even if our study population was much larger than that of previous studies of patients with recurrent CDAD [29–31], the sample size was smaller than the sample used to examine initial episodes of CDAD [15], and our measurements were less precise. These limitations must be kept in mind when examining secular changes in the frequency of post–metronidazole therapy recurrences of CDAD and the effect of various treatments on the risk of complicated CDAD.

Our findings suggest that, when used to treat a first recurrence, metronidazole and vancomycin are associated with the same frequency of a second recurrence, regardless of which of the 2 agents had been used to treat the initial episode. Given that metronidazole is much cheaper than vancomycin, and to avoid promoting the emergence of vancomycin-resistant cocci, we recommend that metronidazole should be used for most patients with a first recurrence of CDAD. The decision to administer vancomycin as treatment for the first recurrence should be based on the presence of markers of severe disease at the time of first recurrence, rather than on previous drug exposure, but vancomycin's superiority over metronidazole in that situation remains unproven. Whether metronidazole will remain as effective in the future needs to be monitored. The role of other therapeutic modalities, such as use of immunoglobulins [32], administration of *C. difficile* toxoid vaccine [33], administration of probiotics [34] and administration of fecal material [35], remains to be determined.

Acknowledgments

We are indebted to the staff of the medical records department of the CHUS for their patience.

Financial support. I.B. received a scholarship from a joint program between the Université de Sherbrooke and the Fonds de Recherche en Santé du Québec.

Potential conflicts of interest. J.P. has worked as a consultant for Viropharma and has received speaking fees from Aventis. All other authors: no conflicts.

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