Factors Associated With Complications of *Clostridium difficile* Infection in a Multicenter Prospective Cohort

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(See the Editorial Commentary by Aronoff on pages 1789–91.)

Background. *Clostridium difficile* infection (CDI) is the most common cause of nosocomial infectious diarrhea and may result in severe complications including death. We conducted a prospective study to identify risk factors for complications of CDI (cCDI).

Methods. Adult inpatients with confirmed CDI in 10 Canadian hospitals were enrolled and followed for 90 days. Potential risk factors were measured within 24 hours of diagnosis. Isolates were typed by polymerase chain reaction ribotyping. cCDI was defined as 1 or more of the following: colonic perforation, toxic megacolon, colectomy, admission to an intensive care unit for cCDI, or if CDI contributed to death within 30 days of enrollment. Risk factors for cCDI were investigated by logistic regression.

Results. A total of 1380 patients were enrolled. cCDI was observed in 8% of patients. The ribotype was identified in 922 patients, of whom 52% were infected with R027. Age ≥80 years, heart rate >90/minute, respiratory rate >20/minute, white cell count $<4 \times 10^9$/L or $\geq 20 \times 10^9$/L, albumin <25 g/L, blood urea nitrogen >7 mmol/L, and C-reactive protein ≥150 mg/L were independently associated with cCDI. A higher frequency of cCDI was observed among R027-infected patients (10.9% vs 7.2%), but the association was not significant in adjusted analysis.

Conclusions. CDI complications were associated with older age, abnormal blood tests, and abnormal vital signs. These factors, which are readily available to clinicians at the time of diagnosis, could be used for outcome prediction and risk stratification to select patients who may need closer monitoring or more aggressive therapy.

Keywords. *Clostridium difficile*; complications; mortality; risk factors; ribotype 027.

Clostridium difficile infection (CDI) is the leading cause of healthcare-associated infectious diarrhea, represents 15%–25% of nosocomial diarrhea caused by antibiotics, and is associated with a high economic burden [1, 2]. In North America, the most dominant strain type isolated since 2002, NAP1/BI/027, has received much attention as it is associated with high incidence rates and increased risk of unfavorable outcomes [3]. However, other strains have also been associated with poor outcomes and increasing incidence, making CDI a persistent challenge in healthcare facilities worldwide [4, 5].

In large cohort studies, patients infected with *C. difficile* had a median risk of developing complications (toxic megacolon, colectomy, shock, perforation) of 11% and a median risk of all-cause 30-day mortality of 13% [4, 6–13]. Mortality and complications (cCDI) have been associated with older age, underlying medical comorbidities, renal failure, and high white blood cell

Received 13 June 2015; accepted 29 July 2015; electronically published 3 September 2015.

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Clinical Infectious Diseases® 2015;61(12):1781–8

DOI: 10.1093/cid/civ749

count (WBC), while hypoalbuminemia and ribotype 027 (R027) have been correlated with mortality alone [14]. Most of these studies were limited by the use of small retrospective cohorts, high heterogeneity regarding their outcomes' and variables' definitions, as well as lack of multivariable analysis. Few studies have measured the association between strain type and unfavorable outcomes.

Oral vancomycin is the recommended treatment for severe CDI, and intravenous metronidazole with high-dose vancomycin is recommended for cCDI [15]. The ability to identify patients at high risk of cCDI early in the course of illness could improve clinical decision-making. Such patients might benefit from closer monitoring, more aggressive rehydration, selection of vancomycin as a first-line agent, adjunctive treatments, or earlier evaluation by surgeons. In this study, we aimed to identify independent risk factors for cCDI in a multicenter prospective cohort study of hospitalized adults with CDI, with an emphasis on strain type.

METHODS

Patients with confirmed CDI, hospitalized in 1 of 10 acute care hospitals in the provinces of Quebec and Ontario, Canada, were enrolled prospectively between June 2005 and October 2008. The participating hospitals are described in Supplementary Methods. The research ethics boards of all participating institutions approved the study.

Inclusion and Exclusion Criteria

Patients with CDI were eligible if they were aged ≥18 years, hospitalized at the time of diagnosis (or, if seen in the emergency or outpatient clinic, hospitalization was planned on the same day), and if the patient or proxy provided written consent to participate. Patients already experiencing 1 of the predefined outcomes at the time of enrollment (colonic perforation, toxic megacolon, septic shock, or indication for emergency colectomy) or receiving palliative care were excluded.

CDI Definition

CDI was defined as having at least 6 unformed stools over 36 hours or having a diagnosis of paralytic ileus, and either positive *C. difficile* toxin detection in a stool sample or pseudomembranous colitis demonstrated by endoscopy. Each participating center performed toxin detection according to local laboratory protocols (see Supplementary Methods). Rapid tests were used to minimize time between collection and results.

Clinical Predictors

Enrollment was performed as soon as possible after a positive *C. difficile* toxin test or endoscopy. At the time of enrollment, we recorded demographics, data on hospital admission, chronic comorbidities, immune status, and surgical procedures or gastrointestinal instrumentation. Information was collected from medical charts and patient interviews about antimicrobial therapy, gastric acid suppression (H2 receptor antagonists, proton pump inhibitors, and antacids), and antiperistaltic agents used within 2 months prior to diagnosis of CDI. Immunosuppression was defined as 1 or more of the following: leukemia, lymphoma, chemotherapy and/or radiation therapy, high-potency glucocorticoids (defined as any intravenous steroids, prednisone ≥20 mg or equivalent, or dexamethasone at any dosage for at least 2 weeks) within 6 months prior to CDI diagnosis, organ transplantation, other immunosuppressive drugs, or human immunodeficiency virus infection. We also collected the following clinical data on characteristics of CDI at enrollment: previous CDI episode, site of acquisition, clinical presentation (including vital signs, abdominal pain, and confusion), and treatment. All laboratory tests were performed at each participating center, except for C-reactive protein (CRP) measurements, which were carried out centrally at the Centre Hospitalier Universitaire de Sherbrooke (see Supplementary Methods). For vital signs and laboratory tests, the most abnormal value within 12 hours before or 24 hours post-enrollment was abstracted.

Clostridium Difficile Culture and Polymerase Chain Reaction Ribotyping

Details of procedures are described in Supplementary Methods. *Clostridium difficile* colonies from stool specimens were grown, and genomic DNA was extracted from a single colony. Amplified products of endpoint polymerase chain reactions (PCRs) were analyzed by automated chip-based microcapillary electrophoresis. Ribotype profiles were determined and analyzed with the GelCompar II software, version 5.1 (Applied Maths NV, Sint-Martens-Latem, Belgium). New ribotype groups were assigned when a group of strains did not match any of the reference strains in our library (electrophoresis profile with Pearson correlation <85% with reference profiles).

Follow-up and Outcomes

Follow-up evaluation was performed until day 90 after enrollment by reviewing medical charts and by directly contacting patients and/or attending physicians. Assessment of outcomes was determined by research assistants who were blinded to the status of the predictor variables. Based on published criteria, cCDI was defined when a patient met any of the following: admission to an intensive care unit (ICU) for complications associated with CDI; colonic perforation, toxic megacolon (defined by a transverse/ascending colon dilation of ≥6 cm on plain X ray and clinical criteria) [16], colectomy, or hemicolectomy; or CDI was the cause or contributed to death within 30 days after enrollment [17]. In a secondary analysis, a less specific definition for complicated CDI (cCDI-2) was used, which included

any reason for admission to an ICU and 30-day all-cause mortality. This second analysis was performed to make our study comparable to several published studies and is provided in Supplementary Results. A patient could experience 1 or more of the listed outcomes.

Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, New York) and SAS 9.4 (SAS Institute Inc., Cary, North Carolina). Frequency of missing data was assessed during data screening. Few variables (mainly laboratory tests) had more than 10% of data missing. Imputation procedures were not considered necessary; missing data were considered as an additional category when relevant. Proportions were compared with 2-tailed χ^2 or Fisher exact tests when appropriate. Logistic regression and Wald tests were used to identify predictors of cCDI and cCDI-2. Multivariable models were built up by selecting variables significant at $P \leq .1$ in univariate analyses manually and by adding them one at a time in order of the lowest P value. Interactions were tested for relevant variables. Models were compared using the likelihood ratio test, and variables significant at $P < .05$ were kept in the final models.

RESULTS

A total of 1380 patients with CDI were enrolled in the 10 participating acute care centers; 65% (n = 894) in Ontario and 35% (n = 486) in Quebec. Patient characteristics are shown in Table 1. Overall, 88% (n = 1207) had at least 1 chronic underlying illness and 63% (n = 866) had 2 or more. The most frequent comorbidities were chronic heart disease (n = 565, 41%), diabetes (n = 364, 27%), chronic lung disease (n = 356, 26%), and cancer (n = 354, 26%). Within the 2 months preceding enrollment, 38% of patients had undergone surgery, 87% had received at least 1 antimicrobial agent, 66% had received at least 1 acid suppression medication, and and 5% had received at least 1 antidiarrheal. One-third of enrolled patients (n = 401) were immunocompromised, with the most frequent cause being receipt of glucocorticoid therapy (n = 221, 16%).

Almost all CDI cases were confirmed with toxin detection (>99%) and a very small number by endoscopy alone (n = 5). Conventional toxin A and B enzyme immunoassay (EIA) was used in all Ontario patients. In Quebec patients, EIA rapid cassette assays were most frequently used (60%) followed by conventional EIA (22%) and/or a combination of tests including cytotoxicity assay (6%). Most patients (95%) were enrolled within 24 hours of a positive toxin test, and the median time between the first symptoms and enrollment was 3 days (interquartile range [IQR], 2–5 days). The majority of CDI cases were classified as healthcare facility–associated (n = 1237, 90%) and corresponded to a first episode in 86% of cases (n = 1180).

Table 1. Characteristics of 1380 Patients With *Clostridium difficile* Infection

Variable	Value or No. (%)
Age	Median 71 y (interquartile range, 58–80)
Sex	
Female	665 (48.2)
Male	715 (51.8)
Charlson comorbidity index	
0–3	747 (54.1)
4–6	399 (28.9)
≥7	234 (17.0)
Antimicrobial exposure[a]	1201 (87.0)
Fluoroquinolones	707 (51.0)
Cephalosporins	694 (50.0)
Carboxy/ureidopenicillins	274 (20.0)
Macrolides/clindamycin	251 (18.0)
Antistaphylococcal/aminopenicillins	225 (16.3)
Acid suppression agents	917 (66.4)
PPI	577 (42.0)
H2-RA	191 (13.8)
PPI + H2-RA	148 (10.7)
CDI diagnosis method	
Conventional toxins A+B EIA	1001 (72.5)
GDH + toxin A detection	239 (17.3)
Cytotoxicity assay	83 (6.0)
Rapid toxins A+B EIA	52 (3.8)
Endoscopy	5 (0.4)
Origin of CDI	
Hospital onset-HCFA	1126 (81.6)
Community onset-HCFA	111 (8.0)
Community acquired	143 (10.4)
CDI treatment	
Metronidazole (PO or IV)	1119 (81.1)
Vancomycin	110 (8.0)
Metronidazole and vancomycin	90 (6.5)
None	61 (4.4)
CDI outcomes (n = 1367)	
30-day all-cause mortality	169 (12.2)
CDI-associated 30-day mortality	54 (4.0)
cCDI[b]	108 (7.9)
cCDI-2[c]	212 (15.5)
At least 1 recurrence[d]	322 (23.6)

Abbreviations: cCDI, complications of CDI; CDI, *Clostridium difficile* infection; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; H2-RA, histamine type-2 receptor antagonists; HCFA, healthcare facility–associated; IV, intravenous; PO, per os; PPI, proton pump inhibitor.

[a] Each patient could have received more than 1 class of antimicrobials within 2 months of enrollment.

[b] cCDI is defined as 1 or more of the following: admission to an intensive care unit (ICU) for complications associated with CDI, colonic perforation, toxic megacolon, colectomy or hemicolectomy, or CDI being the cause or contributed to death within 30 days after enrollment.

[c] cCDI-2 is defined as 1 or more of the following: admission to an ICU for any reason, colonic perforation, toxic megacolon, colectomy or hemicolectomy, or 30-day all-cause mortality.

[d] Recurrence was defined by the presence of diarrhea and *C. difficile* toxin or compatible endoscopy, or prescription of an empiric CDI treatment, at least 48 hours after the completion of the last CDI treatment.

Table 2. Ribotyping and Distribution of Frequent Ribotypes According to the Provinces and Year of Enrollment

	Province			Year of Enrollment			
Ribotypes	Cohort (n = 1380)	Ontario (n = 894)	Quebec (n = 486)	2005 (n = 121)	2006 (n = 410)	2007 (n = 496)	2008 (n = 353)
Stool sample	1054 (76.4)	696 (77.8)	368 (75.7)	98 (81.0)	331 (80.7)	355 (71.6)	270 (76.5)
Positive culture	948 (89.9)	623 (89.5)	325 (88.3)	92 (76.0)	289 (70.5)	326 (65.7)	241 (68.3)
Ribotype obtained	922 (66.8)	614 (68.7)	308 (63.4)	90 (74.4)	285 (69.5)	314 (63.3)	233 (66.0)
R027	483 (52.4)	262 (42.7)	221 (71.7)	35 (28.9)	126 (30.7)	170 (34.3)	152 (43.1)
R001	86 (9.3)	82 (13.3)	4 (1.3)	9 (7.4)	40 (9.8)	30 (6.0)	7 (2.0)
R014	75 (8.1)	59 (9.6)	16 (5.2)	8 (6.6)	27 (6.6)	22 (4.4)	18 (5.1)
Other ribotypes[a]	48 (5.2)	41 (6.7)	9 (2.9)	10 (8.3)	18 (4.4)	14 (2.8)	6 (1.7)
New ribotypes[b]	230 (24.9)	172 (28.0)	58 (18.8)	28 (23.1)	74 (18.0)	78 (15.7)	50 (14.2)

Data is provided in no. (%).

[a] Other ribotypes were R002, R015, R037, and R078.

[b] New ribotypes corresponded to strains whose electrophoresis profile showed a Pearson correlation <85% with reference profiles.

The median duration of hospitalization before CDI onset was 9 days (IQR, 3–21 days). Metronidazole was the most frequent initial treatment (n = 1119, 81%); however, the treatment was changed to oral vancomycin in 16% (n = 177) of patients, mainly due to clinical deterioration.

Strain ribotyping results are shown in Table 2. R027 was the most common strain, particularly in Quebec centers (72% vs 43% in Ontario; $P < .001$), and during years 2007 and 2008 (54% and 65%, respectively; $P < .001$). New ribotypes accounted for 25% of strains, followed by R01 and R014 (9% and 8%, respectively).

Outcomes

Follow-up was completed for 1367 patients. Toxic megacolon occurred in 15 patients and an intestinal perforation in 2. Hemi- or total colectomy was performed in 16 patients. In 42 patients, ICU admission was needed for CDI management. Overall, 12% of patients died within 30 days (n = 169; median time to death, 10 days; IQR, 5–18 days), while 22% died within 90 days (n = 296). At 30 days, CDI was identified as the direct cause of death in 1% of cases (n = 15) and was associated with death in 3% (n = 39). Consequently, cCDI was observed in 8% of patients (n = 108). When considering all-cause ICU admission and mortality, cCDI-2 was observed in 16% (n = 212) of patients, of which 81% died within 30 days and 21% were admitted to an ICU.

Risk Factors for cCDI

Factors associated with cCDI in univariable analyses are shown in Table 3. The odds of developing cCDI were higher in patients with WBC $\geq 20 \times 10^9$/L, serum albumin <25 g/L, CRP ≥150 mg/L, blood urea nitrogen (BUN) ≥7 mmol/L, or serum creatinine ≥200 µmol/L. Age greater than 80 years; chronic heart, lung, or kidney disease; dementia; recent elective surgery; tachycardia; leukopenia (WBC $< 4 \times 10^9$/L); tachypnea; fever (>38°C); or hypothermia (<36°C) were also significantly associated with cCDI in univariable analysis but to a lesser extent. No statistically significant association was found between cCDI and gender, site of CDI acquisition, province, diabetes mellitus, cancer, immunosuppression, antimicrobial use, proton pump inhibitors, anti-peristaltic agents, confusion, and platelet count. In bivariable analysis, BUN was associated with cCDI (7–10 mmol/L: odds ratio [OR], 2.8; 95% confidence interval [CI], 1.4–5.6; ≥11 mmol/L: OR, 6.1; 95% CI, 3.2–11.8) but not serum creatinine (100–199 µmol/L: OR, 1.1; 95% CI, .6–1.9; ≥200 µmol/L: OR, 1.4; 95% CI, .7–2.6).

The multivariable logistic regression model identified the following 7 independent correlates of cCDI (Table 4): age ≥80 years (OR, 2.2; 95% CI, 1.2–4.0), increased heart rate (>90/min; OR, 2.1; 95% CI, 1.4–3.3) and tachypnea (respiratory rate >20/min; OR, 1.7; 95% CI, 1.1–2.8), abnormal WBC ($< 4 \times 10^9$/L [OR, 2.6; 95% CI, 1.3–5.5] and/or $\geq 20 \times 10^9$/L [OR, 2.2; 95% CI, 1.2–4.0]), serum albumin <25 g/L (OR, 3.1; 95% CI, 1.0–9.3), BUN ≥11 mmol/L (OR, 4.9; 95% CI, 2.8–8.5), and CRP ≥150 mg/L (OR, 3.6; 95% CI, 1.8–7.2).

Although a higher frequency of cCDI was observed among R027 strains (10.9% vs 7.2%; $P = .008$), the association with R027 did not reach statistical significance after multivariable adjustment (OR, 1.6; 95% CI, .96–2.7). None of the other ribotypes were associated with cCDI.

Risk Factors for cCDI-2

In univariable analyses, in addition to all the risk factors associated with cCDI, we also found significant associations between chemotherapy, fluoroquinolones use in the prior 2 months, confusion, and cCDI-2 (Supplementary Table 1). No association between a specific ribotype and cCDI-2 was identified. The final multivariable logistic regression model contained 4 additional independent correlates of cCDI-2, for a total of 11.

Table 3. Variables Associated With Complicated *Clostridium difficile* Infection in Univariable Analysis

Variable	No. Complicated *Clostridium difficile* Infections/ Total (%)	Odds Ratio (95% Confidence Interval)	*P* Value
Age (y)			
18–64	27/511 (5.3)	. . .	
65–79	39/504 (7.7)	1.50 (.94–2.50)	.12
≥80	42/342 (12.3)	2.51 (1.52–4.16)	<.001
Comorbidities			
Dementia			
No	95/1264 (7.5)	. . .	
Yes	13/93 (14.0)	2.00 (1.07–3.73)	.03
Heart disease			
No	46/803 (5.7)	. . .	
Yes	62/554 (11.2)	2.07 (1.39–3.09)	<.001
Lung disease			
No	71/1011 (7.0)	. . .	
Yes	37/346 (10.7)	1.58 (1.04–2.41)	.03
Kidney disease			
No	73/1061 (6.9)	. . .	
Yes	35/296 (11.8)	1.82 (1.19–2.78)	.01
Surgery (≤2 mo)			
None	75/835 (9.0)	. . .	
Emergency	14/169 (8.3)	0.92 (.50–1.66)	.77
Elective	19/353 (5.4)	0.58 (.34–.97)	.04
Strain ribotype			
Other	31/430 (7.2)	. . .	
R027	52/475 (10.9)	1.58 (.99–2.52)	.05
Unavailable	25/452 (5.5)	0.75 (.44–1.29)	.31
Heart rate			
≤90/min	43/866 (5.0)	. . .	
>90/min	65/484 (13.4)	2.97 (1.98–4.44)	<.001
Respiratory rate			
≤20/min	43/866 (5.0)	. . .	
>20/min	65/484 (13.4)	2.97 (1.98–4.44)	<.001
Fever (°C)			
36–38	86/1188 (7.2)	. . .	
<36 or >38	19/155 (12.3)	1.79 (1.06–3.04)	.03
White blood cell count (10^9/L)			
<4	14/121 (11.6)	2.57 (1.34–4.94)	.01
4–11.9	35/723 (4.8)	. . .	
12–19.9	30/345 (8.7)	1.87 (1.13–3.10)	.02
≥20	28/144 (19.4)	4.75 (2.78–8.10)	<.001
Serum albumin (g/L)			
<25	52/364 (14.3)	8.58 (3.06–24.10)	<.001
26–34.9	37/600 (6.2)	3.38 (1.19–9.61)	.02
≥35	4/210 (1.9)	. . .	
Missing	15/183 (8.2)	4.60 (1.50–14.11)	.01
C-reactive protein (mg/L)			
<50	20/487 (4.1)	. . .	
50–149.9	27/413 (6.5)	1.63 (.90–2.96)	.11
≥150	32/122 (26.2)	8.30 (4.55–15.17)	<.001
Creatinine (μmol/L)			
0–99	44/868 (5.1)	. . .	
100–199	35/301 (11.6)	2.46 (1.55–3.92)	<.001
≥200	25/133 (18.8)	4.33 (2.55–7.37)	<.001
Dialysis	3/34 (8.8)	1.81 (.53–6.16)	.34
Blood urea nitrogen (mmol/L)			
<7	22/716 (3.1)	. . .	
7–10.9	18/207 (8.7)	3.00 (1.58–5.72)	.01
≥11	54/292 (18.5)	7.16 (4.27–12.00)	<.001
Dialysis	3/35 (8.6)	2.96 (.84–10.40)	.09
Missing	11/107 (10.3)	3.62 (1.70–7.69)	.01

Univariable analysis was performed on 1357 patients.

These variables were comorbidities (dementia and chronic heart disease), recent chemotherapy, and recent elective surgery, the latter as a protective factor (Supplementary Table 2).

DISCUSSION

In this large multicenter prospective cohort with CDI followed for 90 days after enrollment, 8% developed a cCDI. This is consistent with other studies using a similar definition for *C. difficile* complication [6, 9, 10]. The population was mainly hospitalized elderly patients with numerous comorbidities, frequent exposure to antimicrobials, acid suppression, and infected predominantly with the R027 strain. Independent predictors of cCDI were older age, increased heart and respiratory rates, leukocytosis, leukopenia, azotemia, high CRP, and hypoalbuminemia. In several studies, older age, increased WBC, and increased serum creatinine and/or BUN have been repeatedly reported as independent predictors of cCDI; other risk factors were only reported occasionally [6, 14, 18]. Systemic inflammatory response criteria (tachycardia, tachypnea, abnormal WBC) and high CRP likely reflect the severity of colonic inflammation. Elevated BUN may indicate severe diarrhea with subsequent dehydration resulting in inadequate renal perfusion and prerenal azotemia. Urea is the primary metabolite derived from dietary proteins and tissue protein turnover; hence, unlike creatinine, it is also affected by catabolic factors such as fever and sepsis [19]. While guidelines and previous investigations have considered elevation in serum creatinine (≥1.5 × baseline value) as a marker of severity [15], BUN appeared as a strong confounding factor for creatinine in our study, such that the association of creatinine with both outcomes was no longer significant after

Table 4. Independent Risk Factors for Complicated *Clostridium difficile* Infection on Multivariable Logistic Regression

Variable	Adjusted Odds Ratio (95% Confidence Interval)	*P* Value
Age (y)		
18–64	. . .	
65–79	1.13 (.64–1.99)	.67
≥80	2.20 (1.22–3.96)	.009
Heart rate		
≤90/min	. . .	
>90/min	2.13 (1.35–3.34)	.001
Respiratory rate		
≤20/min	. . .	
>20/min	1.75 (1.08–2.84)	.023
White blood cell count (10^9/L)		
<4	2.61 (1.25–5.45)	.011
4–11.9	. . .	
12–19.9	1.42 (.82–2.44)	.21
≥20	2.20 (1.20–4.03)	.011
Serum albumin (g/L)		
<25	3.11 (1.04–9.31)	.043
26–34.9	2.05 (.69–6.07)	.19
≥35	. . .	
Missing	2.33 (.69–7.78)	.17
C-reactive protein (mg/L)		
<50	. . .	
50–149.9	1.18 (.63–2.23)	.61
≥150	3.61 (1.81–7.20)	<.001
Missing	1.44 (.75–2.77)	.28
Blood urea nitrogen (mmol/L)		
<7	. . .	
7–10.9	2.61 (1.32–5.17)	.006
≥11	4.88 (2.81–8.48)	<.001
Dialysis	4.03 (1.02–15.90)	.046
Missing	3.70 (1.59–8.60)	.002

Multivariable analysis was performed on 1333 patients.

adjustment for BUN. Finally, hypoalbuminemia results from protein losses through inflamed colonic mucosa and from increased catabolism due to sepsis [20].

In addition to the recommended definition of cCDI [17], we tested a less specific but frequently used definition (cCDI-2, Supplementary Results). In addition to the other predictors found with the first model, cCDI-2 was independently associated with dementia, chronic heart disease, recent chemotherapy, and elective surgery (the latter being protective). The first 3 factors identify a subgroup of patients with chronic and severe preexisting medical conditions with a higher likelihood of mortality for which CDI may have played a minor role or none at all. On the other hand, a recent elective surgery may reflect better underlying health status. The use of a less specific definition of cCDI by previous researchers may have led to the identification of risk factors related to mortality in general, and thus may be less useful for patient management.

R027 accounted for half of the strains identified in our patients. We found a trend toward an association between R027 and cCDI, nearly reaching the level of significance ($P = .053$). When cCDI-2 was used as the outcome, no association was demonstrated. Thus, the selection of a less specific outcome definition might, in part, explain why several studies were unable to demonstrate a significant association between the epidemic strain and the risk of an unfavorable outcome [21–23]. Furthermore, despite the advanced PCR ribotyping that was used [24, 25], more discriminatory techniques are suggested to clarify the relation of R027 subtypes with the outcomes [26–28]. Genetic changes have been observed in the pathogenicity locus of *C. difficile*, but observational studies are inconsistent concerning their impact on CDI outcomes [21, 23, 29–31]. These studies varied substantially in CDI incidence rates across centers, definitions of outcomes, and typing techniques [14]. Associations with cCDI have been found for R018 and R056 [4, 32], but the limited number of these strains among our patients precluded us to verify these findings.

This study had some limitations. Stool samples were unavailable for subsequent testing in almost 25% of included patients and 10% of the specimens were negative in culture. Consequently, we managed to type bacterial strains in only 67% of patients. Some patients might have had false-positive tests for toxin, since the reported specificities of EIAs range from 95% to 99% and the testing was performed before commercial PCR assays became available [33]. Missing values for clinically important variables were inevitable despite the prospective enrollment, particularly when additional blood samples needed to be drawn. For some categorical variables with missing data, we performed dummy variable adjustment instead of dropping them to avoid reducing the sample size and generating differentially distorted associations [34] and to reach an acceptable event per variable ratio [35]. Establishing causal links between death, admission to an ICU, and CDI is challenging [36–38], particularly in patients with multiple comorbidities. However, since this assessment was made prospectively, we believe it was reliable. Finally, patients in this cohort were enrolled from 2005 to 2008; the currently circulating strains might differ from the ones collected during that period.

The study also had several strengths. This multicenter prospective cohort was assembled specifically to identify predictors of cCDI at the time of diagnosis based on methodologically accepted criteria [39]. Diagnosis was based on toxin identification plus clinical symptoms compatible with CDI. We preselected variables that are routinely available at the time of diagnosis, and these variables were measured as close as possible to the time of diagnosis. Outcomes were evaluated by assistants blinded to the data collected at enrollment.

CONCLUSIONS

Through a large multicenter prospective cohort, we identified age ≥80 years, increased respiratory (>20/min) and heart rate (>90/min), WBC <4 and ≥20 × 10^9 /L, elevated CRP (≥150 mg/L), hypoalbuminemia (serum albumin <25 g/L), and elevated BUN (≥7 mmol/L) as independent risk factors for CDI complications. These predictors, which were readily available at the time of diagnosis, could serve to develop and validate a score that can be used to identify patients who could benefit from more aggressive treatment and closer monitoring. Ultimately, the usefulness of prediction scores will need to be evaluated by examining the fate of patients treated with either metronidazole or vancomycin whose "at-risk" status differs whether a given score or the current Infectious Diseases Society of America criteria are used.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. We thank all the project research assistants for their efforts.

Author contributions. L. V., A. M., A.-C. L., A. E. S., W. L. G., M. P. M., S. M. C., and J. P. conceived and designed the study. L. V., A. M., A.-C. L., A. E. S., W. L. G., M. P. M., K. K., and J. P. obtained data. C. N. A. C., J. P., L. V., J. R. G., and L.-C. F. performed the analyses and interpretation. C. N. A. C. drafted the article. All authors reviewed and approved the final version.

Financial support. This work was supported by the Canadian Institutes of Health Research (MOP-74514). C. N. A. C. is a recipient of a scholarship for doctoral training from the Fonds de recherche du Québec-Santé. L. V. is a member of the Fonds de recherche du Québec-Santé–funded Centre de Recherche du Centre Hospitalier Universitaire de Sherbrooke.

Potential conflicts of interests. A. M. was a member of an advisory board for Optimer Pharmaceuticals (now Merck & Co., Inc.). She has received grants for phase 3 clinical trial from Merck & Co. Inc. and from GlaxoSmithKline Inc. for an observational study. A. E. S. received an honorarium for consultancy on advisory boards for Merck Canada Inc. and Cubist Pharmaceuticals Inc. L. V. was a consultant to Pfizer and Optimer Pharmaceuticals; has received research grants from Pfizer, Optimer Pharmaceuticals, Merck, and Sanofi Pasteur; and has received honorary for lectures from Optimer Pharmaceuticals. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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