Clostridium difficile infection worsens the prognosis of ulcerative colitis

Negrón, María E; Barkema, Herman W; Rioux, Kevin; De Buck, Jeroen; Checkley, Sylvia; Proulx, Marie-Claude; Frolkis, Alexandra; Beck, Paul L; Dieleman, Levinus A; Panaccione, Remo; Ghosh, Subrata; Kaplan, Gilaad G

DOI:
10.1155/2014/914303

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Negrón, ME, Barkema, HW, Rioux, K, De Buck, J, Checkley, S, Proulx, M-C, Frolkis, A, Beck, PL, Dieleman, LA, Panaccione, R, Ghosh, S & Kaplan, GG 2014, 'Clostridium difficile infection worsens the prognosis of ulcerative colitis', *Canadian Journal of Gastroenterology and Hepatology*, vol. 28, no. 7, 914303, pp. 373-80. https://doi.org/10.1155/2014/914303

Clostridium difficile infection worsens the prognosis of ulcerative colitis

María E Negrón DVM MS[1,2], Herman W Barkema DVM PhD[1,2,3], Kevin Rioux MD PhD FRCPC[1,4], Jeroen De Buck PhD[1,2], Sylvia Checkley DVM PhD[5], Marie-Claude Proulx MSc[4], Alexandra Frolkis PhD[1,3], Paul L Beck MD PhD[1,4], Levinus A Dieleman MD PhD[1,6], Remo Panaccione MD FRCPC[1,4], Subrata Ghosh MD FRCPC FRCCPE[1,4], Gilaad G Kaplan MD MPH FRCPC[1,3,4]

ME Negrón, HW Barkema, K Rioux, et al. *Clostridium difficile* infection worsens the prognosis of ulcerative colitis. Can J Gastroenterol Hepatol 2014;28(7):373-380.

BACKGROUND: The impact of *Clostridium difficile* infections among ulcerative colitis (UC) patients is well characterized. However, there is little knowledge regarding the association between C *difficile* infections and postoperative complications among UC patients.
OBJECTIVE: To determine whether C *difficile* infection is associated with undergoing an emergent colectomy and experiencing postoperative complications.
METHODS: The present population-based case-control study identified UC patients admitted to Calgary Health Zone hospitals for a flare between 2000 and 2009. C *difficile* toxin tests ordered in hospital or 90 days before hospital admission were provided by Calgary Laboratory Services (Calgary, Alberta). Hospital records were reviewed to confirm diagnoses and to extract clinical data. Multivariate logistic regression analyses were performed among individuals tested for C *difficile* to examine the association between C *difficile* infection and emergent colectomy and diagnosis of any postoperative complications and, secondarily, an infectious postoperative complication. Estimates were presented as adjusted ORs with 95% CIs.
RESULTS: C *difficile* was tested in 278 (58%) UC patients and 6.1% were positive. C *difficile* infection was associated with an increased risk for emergent colectomy (adjusted OR 3.39 [95% CI 1.02 to 11.23]). Additionally, a preoperative diagnosis of C *difficile* was significantly associated with the development of postoperative infectious complications (OR 4.76 [95% CI 1.10 to 20.63]).
CONCLUSION: C *difficile* diagnosis worsened the prognosis of UC by increasing the risk of colectomy and postoperative infectious complications following colectomy. Future studies are needed to explore whether early detection and aggressive management of C *difficile* infection will improve UC outcomes.

Key Words: Clostridium difficile; *Colectomy; Postoperative complications; Ulcerative colitis*

L'infection à *Clostridium difficile* aggrave le pronostic de colite ulcéreuse

HISTORIQUE : Les répercussions des infections à *Clostridium difficile* sont bien caractérisées chez les patients atteints d'une colite ulcéreuse (CU). Cependant, on ne sait pas grand-chose de l'association entre ces infections et les complications postopératoires chez les patients atteints de CU.
OBJECTIF : Déterminer si l'infection à C *difficile* s'associe à une colectomie d'urgence et à des complications postopératoires.
MÉTHODOLOGIE : Dans le cadre de la présente étude cas-témoins en population, les chercheurs ont repéré les patients atteints de CU qui avaient été admis aux hôpitaux de la *Calgary Health Zone* entre 2000 et 2009. Les *Calgary Laboratory Services* de Calgary, en Alberta, ont fourni les résultats des tests de toxine du C *difficile* demandés à l'hôpital ou 90 jours avant l'hospitalisation. Les chercheurs ont examiné les dossiers hospitaliers pour confirmer les diagnostics et en extraire les données cliniques. Ils ont effectué des analyses de régression logistique multivariée auprès des personnes qui avaient subi un test de C *difficile* pour examiner l'association entre cette infection, d'une part, et la colectomie d'urgence et le diagnostic de complications postopératoires, puis une complication infectieuse postopératoire, d'autre part. Ils ont présenté les évaluations sous forme de rapports de risque aux indices de confiance de 95 %.
RÉSULTATS : Un test de C *difficile* a été effectué chez 278 patients atteints de CU (58 %); 6,1 % étaient positifs. L'infection à C *difficile* s'associait à un risque accru de colectomie d'urgence (RR rajusté 3,39 [95 % IC 1,02 à 11,23]). De plus, un diagnostic préopératoire de C *difficile* s'associait de manière significative à l'apparition de complications infectieuses postopératoires (RR 4,76 [95 % IC 1,10 à 20,63]).
CONCLUSION : Le diagnostic de C *difficile* aggrave le pronostic de CU, car il accroît le risque de colectomie et les complications infectieuses postopératoires après une colectomie. D'autres études s'imposent pour explorer si le dépistage précoce et la prise en charge dynamique de l'infection à C *difficile* amélioreront les résultats cliniques de la CU.

Ulcerative colitis (UC) is characterized by periods of remission followed by periods of disease activity that decrease quality of life. In Western nations, the prevalence of UC has been as high as 500 per 100,000 persons (1), and approximately 15% of UC patients undergo surgical resection of the colon within the first 10 years of diagnosis (2,3). Furthermore, UC patients who undergo colectomy are at increased risk for postoperative morbidity and mortality (4,5).

The increased incidence and severity of *Clostridium difficile* infections during the past decade (6,7), along with outbreaks of more virulent strains (8), have increased public and practitioner awareness of the importance of this pathogen. While antibiotic exposure is the primary risk factor for C *difficile* infection, UC has become recognized as an independent risk factor (9,10). C *difficile* infection risk among UC patients has increased over time, with C *difficile* prevalence doubling from 26.6 to 51.2 per 1000 discharges from 1998 to 2004 (11). C *difficile* infection may worsen the prognosis of UC because the infection has been associated with higher morbidity and increased risk for surgery up to one year after diagnosis of infection (11-13). Consequently, C *difficile* diagnosis is associated with higher hospital costs among inflammatory bowel disease patients (11). These studies assessed only inpatient C *difficile* test results and, thus, missed the impact of C *difficile* infections diagnosed before hospital admission (11,14).

We studied whether C *difficile* diagnosis in hospital or 90 days before hospital admission among UC patients was associated with an emergent colectomy and, furthermore, the development of postoperative complications.

[1]*Alberta Inflammatory Bowel Disease Consortium;* [2]*Department of Production Animal Health, Faculty of Veterinary Medicine;* [3]*Department of Community Health Sciences;* [4]*Department of Medicine, Faculty of Medicine;* [5]*Department of Ecosystem and Public Health, Faculty of Veterinary Medicine, University of Calgary, Calgary;* [6]*Department of Medicine, Faculty of Medicine, University of Alberta, Edmonton, Alberta*
Correspondence: Dr Gilaad Kaplan, Teaching Research and Wellness Centre, 6D56, 3280 Hospital Drive Northwest, Calgary, Alberta T2N 4N1. Telephone 403-592-5015, fax 403-592-5090, e-mail ggkaplan@ucalgary.ca
Received for publication September 6, 2013. Accepted May 26, 2014

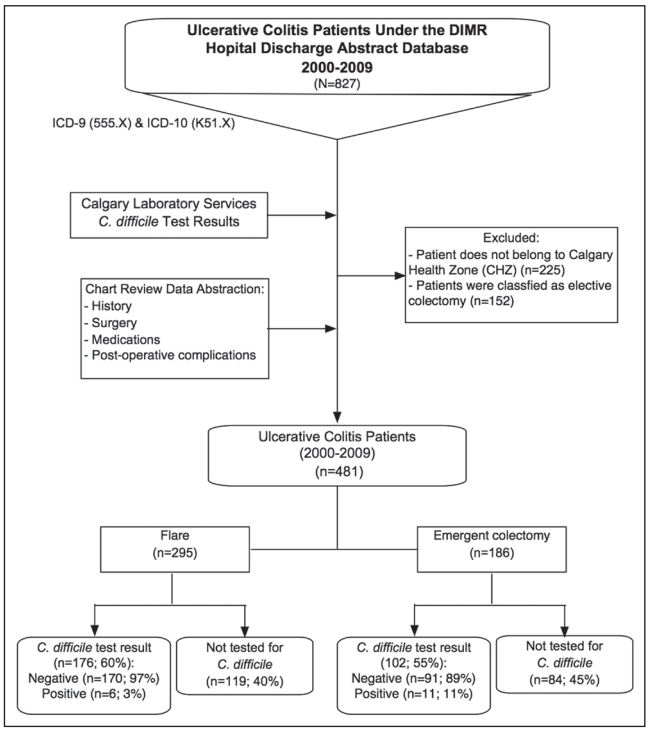

Figure 1) *Flow diagram illustrating the inclusion and exclusion criteria for identifying patients admitted with a flare for ulcerative colitis and tested* Clostridium difficile (C. difficile) *infection in hospital and up to 90 days before admission. DIMR Data Integration, Measurement and Reporting;* ICD International Classification of Diseases, Ninth and 10th Revisions

METHODS

Data sources

The Data Integration, Measurement and Reporting Hospital Discharge Abstract database was used to capture hospitalizations of UC patients in the Calgary Health Zone (CHZ) in Alberta. The CHZ is a population-based health authority that provides health care to Calgary residents and >20 nearby cities under a public, single-payer system (15). This database includes patients' demographic data, admission and discharge date, and 42 diagnostic and 25 procedural coding fields using the *International Classification of Diseases, Ninth and 10th Revisions*, Clinical Modification (ICD-9-CM and ICD-10-CM) and the Canadian Classification of Health Intervention (CCI) (4,16).

The population-based Calgary Laboratory Services database was used to identify UC patients who underwent stool testing for C *difficile*. Calgary Laboratory Services confirmed the C *difficile* infection using a two-step approach: an enzyme immunosorbent assay (EIA) for toxins A and B (TechLab C. *difficile* TOX A/B II, TechLab Enteric Diagnostics, USA) was used as a screening method; and the stool sample was tested using a second EIA (Triage *Clostridium difficile* panel, Biosite Diagnostics, USA) if the results of the first EIA were positive. A sample was considered to be C *difficile* positive if both tests were positive.

Study population

The study population consisted of adults (≥18 years of age) admitted emergently to a CHZ hospital between January 1, 2000 and December 31, 2009 for a UC flare. The approach of identifying the study population was previously validated (16). First, the Data Integration, Measurement and Reporting Hospital Discharge Abstract database was used to identify patients admitted to hospital with a diagnosis of UC (ICD-9-CM 556.X or ICD-10-CA K51.X) in any diagnostic position and a procedural code for colectomy (ICD-9-CM 45.7, 45.8 or CCI 1.NM.87, 1.NM.89, 1.NM.91, 1.NQ.89, 1.NQ.90). The colectomy admission was recorded as the index date. Second, from the remaining discharge abstracts, UC patients admitted to hospital for a flare were identified from admissions with a UC code in the primary diagnostic position. Among patients with UC who were admitted to hospital for a flare, but did not undergo a colectomy, all hospital admissions that occurred within the study period (2000 to 2009) were recorded and one admission was randomly selected as the index date (16). Patients who were not tested for C *difficile* in hospital or within 90 days of hospitalization were not included in the study population. Figure 1 illustrates the inclusion and exclusion criteria that defined the study population. Medical charts of all UC patients identified were reviewed to confirm that the UC patients were admitted to hospital emergently for a UC flare and to collect patients' surgical and medical history relevant to the index admission.

Selection of cases and controls

The primary case definition was undergoing an emergent colectomy during the index admission. Colectomy was defined as emergent if the decision to perform colectomy was made during the admission and after failing to respond to medical management, or because the patient experienced a complication. Controls were the remaining UC patients discharged from hospital without a colectomy after responding to medical management.

The secondary case definition was the development of any postoperative complication and, specifically, an infectious postoperative complication among UC patients who underwent an emergent colectomy. Postoperative complications were defined as an unexpected medical event that occurred between the start of the operation and discharge from the hospital. These complications were classified into seven complication categories including postoperative infection (Appendix 1). Complications were stratified according to severity using the Clavien classification of surgical complications (17). The development of postoperative complications was recorded if the patient experienced at least one complication described under any of the categories graded as Clavien II or higher (ie, requiring medical or surgical intervention or leading to death). C *difficile* infection was not considered to be a postoperative complication (4). The definition of postoperative complication has been previously validated for UC (16).

Exposure

The primary exposure was a diagnosis of C *difficile* infection in hospital or 90 days before the index admission. Ninety days before hospital admission was defined a priori to ensure that patients defined as negative for C *difficile* were not treated for a C *difficile* infection before hospital admission. A patient was classified as diagnosed with C *difficile* if at least one test result was positive during the predetermined period. The date of the first positive test was recorded as the index date of infection. C *difficile* diagnosis was confirmed by medical chart review. Patients were classified as C *difficile* negative if all test results during the predetermined period were negative.

Covariates

Additional demographic and clinical data extracted from chart review included: age (stratified as 18 to 32, 33 to 47 and ≥48 years, based on the tercile of the cohort); sex; disease extent (left-sided versus pancolitis); disease duration (defined as the interval between UC diagnosis and admission date), length of flare (<2, 2 to 8, >8 weeks); and smoking status (current, ex-smoker, never). Inflammatory bowel disease medications (5-aminosalicylic acid or sulfasalazine, azathioprine, corticosteroids and infliximab) taken at time of admission and/or administered in-hospital were recorded. Patients were classified as having comorbidities (ie, health conditions occurring before hospitalization) if they had at least one of the comorbidities listed in Appendix 2. The definition of comorbidity has been previously validated for UC (16).

Statistical analysis

The associations between the outcome and categorical variables were tested using the Fisher's exact test or the χ^2 test. Continuous variables were expressed as median with interquartile range and compared using the Wilcoxon rank-sum test. Multivariate logistic regression analysis

TABLE 1
Characteristics of ulcerative colitis (UC) patients admitted to hospital stratified according to flare (medically responsive) and emergent colectomy. Emergent colectomy patients were further stratified into development of any postoperative complication and development of infectious complications

	All UC patients (n=278)			Emergent colectomy patients (n=102)					
	Emergent colectomy			Any complication			Infectious complication		
Characteristics	No (n=176)	Yes (n=102)	P	No (n=71)	Yes (n=31)	P	No (n=81)	Yes (n=21)	P
Sex									
Male	52.3 (92)	62.8 (64)		54.9 (39)	80.6 (25)		56.8 (46)	85.7 (18)	
Female	47.7 (84)	37.2 (38)	0.090	45.1 (32)	19.4 (6)	0.015	43.2 (35)	14.3 (3)	0.021
Age at admission, years									
25th percentile	27.0	31.0		30.0	43.0		31.0	46.0	
Median	36.0	47.0		40.0	50.0		43.0	50.0	
75th percentile	47.0	58.0	<0.001	55.0	65.0	0.028	55.0	72.4	0.022
Clostridium difficile infection									
No	96.6 (170)	89.2 (91)		93.0 (66)	80.7 (25)		92.6 (75)	76.2 (16)	
Yes	3.4 (6)	10.8 (11)	0.013	7.0 (5)	10.3 (6)	0.085	7.4 (6)	23.8 (5)	0.046
Disease duration, years									
25th percentile	0	0		0	0		0	0	
Median	1.0	2.0		2	1		2	1	
75th percentile	6.0	6.0	0.401	7	4.5	0.474	7	4	0.549
Missing data	n=5	n=3			n=3			n=3	
Smoking									
Current	10.8 (18)	9.8 (10)		11.3 (8)	6.4 (2)		9.9 (8)	9.5 (2)	
Ex-smoker	28.9 (48)	35.3 (36)		33.8 (24)	38.7 (12)		33.3 (27)	42.9 (9)	
Never	60.3 (100)	54.9 (56)	0.550	54.9 (39)	54.8 (17)	0.814	56.8 (46)	47.6 (10)	0.721
Missing data	n=10								
Flare duration, weeks									
<2	18.3 (32)	25.5 (26)		25.4 (18)	25.8 (8)		25.9 (21)	23.8 (5)	
2–8	49.1 (86)	47.1 (48)		50.7 (36)	38.7 (12)		49.4 (40)	38.1 (8)	
>8	32.6 (57)	27.4 (28)	0.332	23.9 (17)	35.5 (11)	0.426	24.7 (20)	38.1 (8)	0.456
Missing data	n=1	n=1							
Disease extent									
Left-sided	46.4 (71)	17.7 (17)		15.4 (10)	22.3 (7)		17.3 (13)	19.1 (4)	
Pancolitis	53.6 (82)	82.3 (79)	<0.001	84.6 (55)	77.4 (24)	0.403	82.7 (62)	80.9 (17)	1.0
Missing data	n=23	n=6			n=6		n=6		
Comorbidity									
No	68.8 (121)	60.8 (62)		64.8 (46)	51.6 (16)		64.2 (52)	47.6 (10)	
Yes	31.2 (55)	39.2 (40)	0.191	35.2 (25)	48.4 (15)	0.210	35.8 (29)	52.4 (11)	0.166
Prednisone at admission									
No	47.3 (84)	20.6 (21)		23.9 (17)	12.9 (4)		23.5 (19)	9.5 (2)	
Yes	52.3 (92)	79.4 (81)	<0.001	76.1 (54)	87.1 (27)	0.205	76.5 (62)	90.5 (19)	0.229
5-aminosalicylic acid*									
No	31.8 (56)	30.4 (31)		28.2 (20)	35.5 (11)		28.4 (23)	28.1 (8)	
Yes	68.2 (120)	69.6 (71)	0.805	71.8 (51)	64.5 (20)	0.460	71.6 (58)	69.9 (13)	0.389
Azathioprine*									
No	67.0 (118)	69.6 (71)		70.4 (50)	67.7 (21)		70.4 (57)	66.7 (14)	
Yes	33.0 (58)	30.4 (31)	0.659	29.6 (21)	32.6 (10)	0.787	29.6 (24)	33.3 (7)	0.742
Infliximab*									
No	81.3 (143)	86.3 (88)		88.7 (63)	80.7 (25)		86.4 (70)	85.7 (18)	
Yes	18.7 (33)	13.7 (14)	0.281	11.3 (8)	19.3 (6)	0.275	13.6 (11)	14.3 (3)	1.0
Intravenous steroids in hospital									
No	12.5 (22)	1.0 (1)		0 (0)	3.2 (1)		1.2 (1)	0 (0)	
Yes	87.5 (154)	99.0 (101)	<0.001	100 (71)	96.7 (30)	0.304	98.8 (80)	100 (21)	1.0

*Data presented as % (n) unless otherwise indicated. *Medication taken at admission or in hospital*

was performed to determine the association between the need for an emergent colectomy and diagnosis of *C difficile* (defined a priori) after adjusting for other covariates. Age was a priori forced into the regression model. For the other covariates, a backward elimination approach was used to examine independent effects of additional variables on the need for emergent surgery with an entry P value <0.20. Variables were kept in the model if: the two-sided P value was <0.05; or there was evidence of confounding because their removal resulted in a 30% change in the estimate of the primary exposure. The variance inflation factor was used to measure multicollinearity among the independent variables. Multicollinearity was considered to be negligible if the variance inflation factor was <10. Interactions

TABLE 2
Logistic regression results of all ulcerative colitis patients (n=278) who underwent emergent colectomy with *Clostridium difficile* diagnosis as primary exposure

	Adjusted OR (95% CI)
C difficile diagnosis	
No	1.00 (Reference)
Yes	3.39 (1.02–11.23)
Age, years	
18–32	1.00 (Reference)
33–47	1.21 (0.06–2.44)
≥48	5.05 (2.44–10.47)
Disease distribution	
Left-side/undetermined	1.00 (Reference)
Pancolitis	4.41 (2.33–8.33)
Prednisone at admission	
No	1.00 (Reference)
Yes	2.75 (1.45–5.20)
Intravenous steroids in hospital	
No	1.00 (Reference)
Yes	15.61 (1.77–137.18)

between *C difficile* positivity and variables that were indepedently associated with colectomy were tested and included in the model if the likelihood ratio test was statistically significant (ie, P<0.05). Point estimates were presented as adjusted ORs with 95% CIs.

The association between *C difficile* infection and the development of postoperative complications was also evaluated. Multivariate logistic regression was performed to examine the association between postoperative complications (and then postoperative infection separately) and *C difficile* diagnosis (defined a priori) after adjusting for other covariates. A backward elimination approach was used to examine the independent effects of variables on the development of postoperative complications (and postoperative infection) using the same procedure as described above.

A sensitivity analysis was performed to determine whether the timing of *C difficile* diagnosis affected the association with the outcomes. For this, logistic regression models were recalculated with *C difficile* diagnosis defined as having at least one positive test result in hospital or 14 days before the index admission. Patients who were not tested for *C difficile* in hospital or 90 days before admission were included in a second sensitivity analysis. Logistic regression models were recalculated for all three outcomes: emergent colectomy, any postoperative complication and infectious complication.

All analyses were performed using STATA version 11 (STATA Corp, USA). The study was approved by the Conjoint Health Research Ethics Board at the University of Calgary (Calgary, Alberta). The present study was conducted in accordance with the strengthening of the reporting of observational studies in epidemiology (STROBE) statement (18).

RESULTS

A total of 278 UC patients met the inclusion criteria. Table 1 summarizes the baseline characteristics of the study population. The indications for an emergent colectomy were bowel complication (n=9), cancer/dysplasia (n=1) and failed medical management in hospital (n=92). *C difficile* diagnosis was recorded in 11 (11%) UC patients who underwent an emergent colectomy compared with six (3%) patients who responded to medical management (P=0.01). Patients diagnosed with an infection in hospital or up to 90 days before hospitalization had higher odds of undergoing emergent surgery when admitted to hospital (adjusted OR 3.39 [95% CI 1.02 to 11.23]) (Table 2).

TABLE 3
Logistic regression results for emergent colectomy patients (n=102) experiencing any postoperative complication and infectious postoperative complications with *Clostridium difficile* diagnosis as primary exposure

	Complication(s)	
	Any	Infectious
C difficile diagnosis		
No	1.00 (Reference)	1.00 (Reference)
Yes	3.70 (0.89–15.3)	4.76 (1.10–20.63)
Age, years		
18–32	1.00 (Reference)	1.00 (Reference)
33-47	1.35 (0.24–5.30)	1.56 (0.31–7.93)
≥48	2.77 (0.77–9.96)	3.43 (0.8–14.68)
Sex		
Male	1.00 (Reference)	1.00 (Reference)
Female	0.28 (0.09–0.82)	0.23 (0.6–0.88)
Comorbidity		
No	1.00 (Reference)	NS
Yes	1.52 (0.53–4.35)	

Data presented as adjusted OR (95% CI). NS Not significant (was not significant on final model)

Table 1 summarizes the characteristics of the 102 patients who underwent an emergent colectomy and were preoperatively tested for *C difficile*. The median time from *C difficile* diagnosis to surgery was 12 days (interquartile range 14 days). At least one postoperative complication was recorded in 30% of UC patients and 20% developed an infectious postoperative complication. Infectious postoperative complications experienced among UC patients with *C difficile* included: sepsis (n=3), abscess (n=2), urinary tract infection (n=1), pneumonia (n=3) and infected central line (n=1) (Appendix 3). *C difficile* was diagnosed preoperatively in 24% of patients who experienced an infectious postoperative complication, compared with 7% of UC patients who did not develop an infectious postoperative complication (P=0.046) (Table 1).

Preoperative diagnosis of *C difficile* was not significantly associated with developing any postoperative complication (adjusted OR 3.16 [95% CI 0.89 to 11.23]) (Table 3). However, individuals diagnosed with *C difficile* preoperatively had higher odds of developing a new infectious postoperative complication (adjusted OR 4.76 [95% CI 1.10 to 20.63]) (Table 3).

The sensitivity analysis that restricted the exposure definition to only patients tested for *C difficile* in hospital or 14 days before admission resulted in similar associations between *C difficile* infection and emergent colectomy (adjusted OR 3.70 [95% CI 1.06 to 12.89]) (Appendix 4), whereas the associations were strengthened for any complication (adjusted OR 6.11 [95% CI 1.32 to 28.21]) and infectious complications (adjusted OR 7.93 [95% CI 1.54 to 40.75) (Appendix 5).

The sensitivity analysis that included patients not tested for *C difficile* resulted in a nonsignificant association between *C difficile* infection and emergent colectomy (OR 2.80 [95% CI 0.86 to 9.11]) (Appendix 6). However, individuals not tested for *C difficile* had higher odds of undergoing an emergent surgery compared with those with a negative *C difficile* test result (OR 1.69 [95% CI 1.09 to 2.63]) (Appendix 6). Individuals diagnosed with *C difficile* preoperatively had higher odds of developing a new infectious postoperative complication (OR 4.67 [95% CI 1.17 to 18.47]) (Appendix 7). Similar to the authors' primary analysis, a preoperative diagnosis of *C difficile* was not significantly associated with developing any postoperative complication (adjusted OR 3.55 [95% CI 0.95 to 13.21) (Appendix 7). Patients with an unknown preoperative *C difficile* status were not at increased risk for developing any complication (OR 1.56 [95% CI 0.80 to 3.07) or a new infectious postoperative complication (OR 1.49 [95% CI 0.67 to 3.29]) (Appendix 7).

DISCUSSION

UC patients diagnosed with C *difficile* in hospital or 90 days before admission were more likely to undergo an emergent colectomy after controlling for factors such as age, disease extent and corticosteroid use. Additionally, a preoperative diagnosis of C *difficile* increased the risk for developing an infectious postoperative complication. Consequently, C *difficile* infection is an important clinical outcome for UC patients admitted to hospital with a flare.

UC patients have higher mortality and surgery risk at one and five years following a C *difficile* diagnosis compared with UC patients without C *difficile* (19,20). However, reports describing the impact of C *difficile* diagnosis on in-hospital and short-term risk of colectomy are inconsistent. Two single-centre studies (21,22) failed to find an association between C *difficile* and the need for colectomy at index admission or three months following C *difficile* diagnosis. In addition, a large, nationwide study using in-hospital data reported a negative association between C *difficile* diagnosis and colectomy, even after taking into consideration patients who were admitted electively (11). The conflicting results between these previous studies and our study may be attributed to methodological differences from our study. Previous studies were potentially limited because of selection bias arising from data collected from tertiary care centres and/or misclassification bias from using administrative databases (23). In contrast, our study was population-based, and used chart reviews to confirm exposures and outcomes. Moreover, previous studies did not account for C *difficile* testing that occurred before admission to hospital. Furthermore, surgery thresholds may differ among centres (24). Also, different C *difficile* ribotypes (8,25) and lack of consensus on the treatment of C *difficile* infections among UC patients may have influenced infection outcomes (26,27). Finally, over time, better surveillance and diagnostic tests along with more aggressive treatment of C *difficile* infections may account for the differences observed (26-30).

Several factors may explain the increased risk for postoperative infection among patients with a C *difficile* infection. First, patients with a C *difficile* infection may have greater UC disease severity, immunosuppression or systemic toxicity (28). Second, antibiotic exposure before surgery may have increased susceptibility for acquisition of antibiotic-resistant nosocomial infections (29). Finally, C *difficile* toxin worsens gut permeability (30,31) and promotes bacterial migration, which may have increased the risk for septic complications (32). Our sensitivity analysis that restricted the study population to individuals tested within 14 days of hospital admission or during hospital admission suggested that the timing of C *difficile* infection influenced postoperative morbidity.

We studied a large population-based cohort of UC patients (16). The diagnosis of UC was confirmed in all cases, which improved the accuracy of our data. Administrative databases may misclassify the diagnosis of UC, colectomy and postoperative complications, thereby influencing the magnitude of risk estimates and the precision of CIs (16). Additionally, we were able to determine the reason for admission (flare versus elective colectomy) and only included individuals admitted as a flare in our analysis. Also, C *difficile* test results were obtained from a population-based laboratory database that records both in-hospital and outpatient testing. Thus, we captured all tests performed on these patients during the study period. Using a centralized laboratory database that captures all C *difficile* testing is essential because administrative coding of C *difficile* includes a misclassification error and could miss C *difficile* diagnosis before admission. Finally, patients were tested for C *difficile* using a sequential testing approach, which optimized the positive predictive value of detecting diseases with low prevalence.

Several limitations to the present study should be considered. First, we excluded UC patients who were not tested for C *difficile* in hospital or within 90 days of index admission. Consequently, some UC patients may have been C *difficile* positive but were never detected. This gives rise to a possible differential misclassification bias in which patients with a more severe form of colitis were more likely to be tested for C *difficile*, reflecting a population with a more severe form of UC. Second, we were unable to report C *difficile* incidence rates among UC patients (33). Third, patient information was obtained by reviewing patients' charts, relying on various clinicians for their completeness and accuracy. Due to the retrospective nature of the data, we were not able to control for disease severity by calculating a Mayo score. Additionally, C-reactive protein levels were not reliably measured in all patients during the early study years. Fourth, we were unable to study other patient-related factors, such as antibiotic administration and response, because they were not reliably recorded in the patients' charts. Antibiotic treatment of C *difficile* (eg, timing and first-line agent) may have influenced disease course. Fifth, approximately 42% of the patients were not tested for C *difficile*, which may have introduced a selection bias. Previous studies using administrative databases have assumed that a negative code for C *difficile* is a negative test for C *difficile* (11). However, our sensitivity analysis demonstrated that individuals not tested for C *difficile* were also at increased odds for colectomy compared with those who tested negative. Finally, the number of patients with UC who tested positive for C *difficile* was small, reducing the precision of our findings. Furthermore, the small number of outcomes in the postoperative complications analysis may affect the generalizability of our results. Consequently, our findings should be independently replicated.

C *difficile* diagnosis was associated with undergoing an emergent colectomy and developing postoperative infectious complications. These findings have important clinical implications. First, physicians should carefully assess for C *difficile* infection among all UC patients presenting with a flare of disease activity. Second, UC patients with a C *difficile* infection who undergo a colectomy should be monitored closely and precautions should be taken to prevent infections. Third, increased surveillance for C *difficile* infections with early identification and aggressive treatment provides potential avenues for improving outcomes among UC patients. Future studies are necessary to assess interventions that may reduce the morbidity of C *difficile* infections among UC patients, and to determine whether timing of colectomy for UC patients with C *difficile* infection should be adjusted to minimize postoperative infectious complications. At minimum, these patients require careful surveillance for infections postoperatively.

ACKNOWLEDGEMENTS: The authors acknowledge the DIMR department for providing data from the CHZ. Dr Kaplan is supported through a New Investigator Award from the Canadian Institute of Health Research and a Population Health Investigator Award from Alberta Innovates – Health Solutions.

FUNDING: This project was funded by the Alberta Inflammatory Bowel Disease Consortium, which is funded by an AHFMR Interdisciplinary Team Grant. AHFMR is now Alberta Innovates – Health Solutions.

CONTRIBUTIONS: Study concept and design: MEN, HWB, GGK. Data acquisition: MEN, MCP, GGK. Analysis and interpretation of the data: MEN, HWB, AF, PLB, LD, RP, SG, GGK. Statistical analysis: MEN. Drafting of the manuscript: MEN, HWB, GGK. Critical revision of the manuscript for important intellectual content: MEN, HWB, KR, JDB, SC, MCP, AF, PLB, LD, RP, SG, GGK. Administrative, technical or material support: HWB, MCP, AF, GGK. Final approval of the manuscript: MEN, HWB, KR, JDB, SC, MCP, AF, PLB, LD, RP, SG, GGK.

DISCLOSURES: Gilaad Kaplan: Gilaad Kaplan has served as a speaker for Janssen, Merck, Schering-Plough, Abbott and UCB Pharma. He has participated in advisory board meetings for Jansen, Abbott, Merck, Schering-Plough, Shire and UCB Pharma. Dr Kaplan has received research support from Abbott and Shire. Marie-Claude Proulx: Ms. Proulx has no relevant conflicts of interest. Maria Negron: Dr Negron has no relevant conflicts of interest. Remo Panaccione: Dr Panaccione has served as a speaker, a consultant and an advisory board member for Abbott Laboratories, Merck, Schering-Plough, Shire, Centocor, Elan Pharmaceuticals, and Procter & Gamble. He has served as a consultant and

speaker for AstraZeneca. He has served as a consultant and an advisory board member for Ferring and UCB Pharma. He has served as a consultant for Glaxo-Smith Kline and Bristol-Meyers Squibb. He has served as a speaker for Byk Solvay, Axcan, Janssen and Prometheus. He has received research funding from Merck, Schering-Plough, Abbott Laboratories, Elan Pharmaceuticals, Procter & Gamble, Bristol-Meyers Squibb, and Millennium Pharmaceuticals. He has received educational support from Merck, Schering-Plough, Ferring, Axcan and Janssen. Subrata Ghosh: Dr Ghosh has served as a speaker for Merck, Schering-Plough, Centocor, Abbvie, UCB Pharma, Pfizer, Ferring, and Procter & Gamble. He has participated in ad hoc advisory board meetings for Centocor, Abbott, Merck, Schering-Plough, Proctor & Gamble, Shire, UCB Pharma, Pfizer and Millennium. He received research funding from Procter and Gamble, Merck and Schering-Plough. Herman Barkema: Dr Barkema has served as a speaker for Merck, Pfizer and Schering-Plough. Kevin Rioux: Dr Rioux has received research support from Shire and Janssen. Jeroen De Buck: Dr De Buck has no relevant conflicts of interest. Sylvia Checkley: Dr Checkley has no relevant conflicts of interest. Alexandra Frolkis: Ms Frolkis has no relevant conflicts of interest. Paul Beck: Dr Beck has no relevant conflicts of interest. Levinus A Dieleman: Dr Dieleman has served as a speaker and consultant for AbbVie and Janssen.

APPENDIX 1
Postoperative complications classification

Category	Complications
Gastrointestinal	Small bowel obstruction, pouch leak or pouch failure, bowel perforation, ileus, ischemic bowel and gastrointestinal bleeding
Wound	Fistula, hematoma or seroma, wound dehiscence and delayed wound healing and iatrogenic injuries including foreign body accidentally left during procedure
Infectious	Sepsis and bacteremia, abscess, wound infection, urinary tract infection, pneumonia and empyema
Renal and endocrine	Acute renal failure, fluid and electrolyte disorders (eg, hypokalemia) and adrenal disorders
Cardiovascular	Thrombosis or embolism, myocardial infarction, cardiac arrest, hypotension or shock, cardiac arrhythmias and congestive heart failure
Pulmonary	Acute respiratory failure, hypoxemia, pleural effusion and pulmonary edema, pneumothorax and atelectasis, asthma and chronic obstructive pulmonary disease exacerbation
Neurological	Neurological disease, cerebrovascular disease, psychoses, delirium, seizures and neuropathies

APPENDIX 2
Comorbidity classifications

Category	Comorbidity
Coronary artery disease	Coronary artery disease, ischemic heart disease, myocardial infarction, peripheral vascular disease
Cancer	Lymphoma, metastatic tumour, solid tumour without metastases
Other cardiovascular	Cardiac arrhythmia, valvular disorder
Congestive heart failure	Congestive heart failure
Diabetes	Diabetes with complications, diabetes without complications
Venous thromboembolism	Deep vein thrombosis
Gastrointestinal	Cytomegalovirus infection, pancreatitis, peptic ulcer disease
Hematological	Blood loss anemia, coagulopathy, cyclical neutropenia, deficiency anemia
Hypertension	Hypertension
Liver	Fatty liver, primary sclerosing cholangitis, liver disease
Neurological	Cerebrovascular disease, hemiplegia and paraplegia
Pulmonary	Asthma, chronic obstructive pulmonary disease, sarcoidosis
Renal	Renal failure (acute or chronic)
Rheumatoid	Ankylosing spondylitis, episcleritis, uveitis and iritis, gout, sacroiliitis, rheumatoid arthritis

APPENDIX 3
Postoperative complications observed among patients tested for *Clostridium difficile*

	C difficile	
Complication categories*	**Negative**	**Positive**
Gastrointestinal		
No complications	82	8
At least one complication	9	3
Pouch leak	2	0
Bowel perforation	1	0
Ileus	4	0
Ischemic bowel	0	1
Gastrointestinal bleed	3	2
Wound		
No complications	87	10
At least one complication	10	1
Hematoma/seroma	0	1
Dehiscence	2	1
Infectious		
No complications	75	6
At least one complication	16	5
Sepsis	7	3
Abscess	6	2
Wound infection	3	0
Urinary tract infection	2	1
Pneumonia	4	3
Infected central line	0	1
Perianal infection	1	0
Renal and endocrine		
No complications	87	9
At least one complication	4	2
Acute renal failure	1	2
Fluid/electrolyte disorders	2	1
Adrenal	1	0
Cardiovascular		
No complications	83	8
At least one complication	8	3
Thrombosis	5	2
Myocardial infarction	3	1
Cardiac arrest	1	0
Hypotension/shock	3	1
Cardiac arrhythmia	5	0
Pulmonary		
No complications	84	7
At least one complication	9	2
Acute respiratory failure	4	2
Hypoxia	2	1
Pleural effusion/pulmonary edema	4	1
Pneumothorax and atelectasis	1	0
Neurological		
No complications	91	11
At least one complication	0	0

*Data presented as n. *Patients may have had ≥1 postoperative complication*

APPENDIX 4
Sensitivity analyses: Logistic regression results for all ulcerative colitis patients (n=278) who underwent emergent colectomy with *Clostridium difficile* diagnosis in hospital or 14 days before admission as primary exposure

	Adjusted OR (95% CI)
C difficile diagnosis	
No	1.00 (Reference)
Yes	3.70 (1.06–12.89)
Age, years	
18–32	1.00 (Reference)
33–47	1.14 (0.56–2.34)
≥48	5.06 (2.39–10.74)
Disease distribution	
Left-sided/undetermined	1.00 (Reference)
Pancolitis	5.04 (2.39–10.74)
Prednisone at admission	
No	1.00 (Reference)
Yes	2.54 (1.32–4.85)
Intravenous steroids in hospital	
No	1.00 (Reference)
Yes	11.51 (1.36–97.46)

APPENDIX 5
Sensitivity analyses: Logistic regression results among emergent colectomy patients (n=102) who experienced any postoperative complication and infectious postoperative complication with *Clostridium difficile* diagnosis in hospital or 14 days before admission as primary exposure

	Complication(s)	
	Any	Infectious
C difficile diagnosis		
No	1.00 (Reference)	1.00 (Reference)
Yes	6.11 (1.32–28.21)	7.93 (1.54–40.75)
Age, years		
18–32	1.00 (Reference)	1.00 (Reference)
33–47	1.86 (0.42–8.29)	2.98 (0.43–20.60)
≥48	3.61 (0.88–14.96)	5.18 (0.8–33.77)
Sex		
Male	1.00 (Reference)	1.00 (Reference)
Female	0.29 (0.1–0.89)	0.21 (0.57–0.86)
Comorbidity		
No	1.00 (Reference)	1.00 (Reference)
Yes	1.75 (0.58–5.26)	2.05 (0.57–7.45)

Data presented as adjusted OR (95% CI)

APPENDIX 6
Sensitivity analyses: Logistic regression results among ulcerative colitis patients (n=481) who underwent emergent colectomy, including those not tested for *Clostridium difficile*

	Adjusted OR (95% CI)
C difficile diagnosis	
No	1.00 (Reference)
Yes	2.80 (0.86–9.11)
Not tested	1.69 (1.09–2.63)
Age, years	
18–32	1.00 (Reference)
33–47	1.27 (0.75–2.15)
≥48	3.52 (2.05–6.04)
Disease distribution	
Left-sided/undetermined	1.00 (Reference)
Pancolitis	4.51 (2.83–6.04)
Prednisone at admission	
No	1.00 (Reference)
Yes	3.11 (1.95–4.99)
Intravenous steroids in hospital	
No	1.00 (Reference)
Yes	6.21 (2.33–16.53)

APPENDIX 7
Sensitivity analyses: Logistic regression results among emergent colectomy patients (n=186) who experienced any postoperative complication and infectious postoperative complication, including those not tested for *Clostridium difficile*

	Complication(s)	
	Any	Infectious
C difficile diagnosis		
No	1.00 (Reference)	1.00 (Reference)
Yes	3.55 (0.95–13.21)	4.67 (1.17–18.47)
Not tested	1.56 (0.80–3.07)	1.49 (0.67–3.29)
Age, years		
18–32	1.00 (Reference)	1.00 (Reference)
33–47	1.16 (0.47–2.89)	1.03 (0.32–3.37)
≥48	2.81 (1.24–6.41)	3.61 (2.04–9.81)

Data presented as adjusted OR (95% CI)

REFERENCES

1. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterol 2012;142:46-54.
2. Kaplan GG, Seow CH, Ghosh S, et al. Decreasing colectomy rates for ulcerative colitis: A population-based time trend study. Am J Gastroenterol 2012;12:1879-87.
3. Frolkis AD, Dykeman J, Negron ME, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: A systematic review and meta-analysis of population-based studies. Gastroenterol 2013;145:996-1006.
4. de Silva S, Ma C, Proulx MC, et al. Postoperative complications and mortality following colectomy for ulcerative colitis. Clin Gastroenterol Hepatol 2011;11:972-80.
5. Soon IS, Wrobel I, deBruyn JC, et al. Postoperative complications following colectomy for ulcerative colitis in children. J Pediatr Gastroenterol Nutr 2012;54:763-8.
6. Ricciardi R, Ogilvie JW, Roberts PL, Marcello PW, Concannon TW, Baxter NN. Epidemiology of *Clostridium difficile* colitis in hospitalized patients with inflammatory bowel diseases. Dis Colon Rectum 2009;52:40-5.
7. Chandler RE, Hedberg K, Cieslak PR. *Clostridium difficile* associated disease in Oregon: Increasing incidence and hospital-level risk factors. Infect Control Hosp Epidemiol 2007;28:116-22.
8. Hubert B, Loo VG, Bourgault AM, et al. A portrait of the geographic dissemination of the *Clostridium difficile* North American pulsed-field type 1 strain and the epidemiology of *C. difficile*-associated disease in Quebec. Clin Infect Dis 2007;44:238-44.
9. Ananthakrishnan AN. *Clostridium difficile* infection: Epidemiology, risk factors and management. Nat Rev Gastroenterol Hepatol 2011;8:17-26.
10. Berg AM, Kelly CP, Farraye FA. *Clostridium difficile* infection in the inflammatory bowel disease patient. Inflamm Bowel Dis 2013;19:194-204.
11. Nguyen GC, Kaplan GG, Harris ML, Brant SR. A national survey of the prevalence and impact of *Clostridium difficile* infection among hospitalized inflammatory bowel disease patients. Am J Gastroenterol 2008;103:1443-50.

12. Issa M, Vijayapal A, Graham MB, et al. Impact of *Clostridium difficile* on inflammatory bowel disease. Clin Gastroenterol Hepatol 2007;5:345-51.
13. Ananthakrishnan AN, McGinley EL, Saeian K, Binion DG. Temporal trends in disease outcomes related to *Clostridium difficile* infection in patients with inflammatory bowel disease. Inflamm Bowel Dis 2011;17:976-83.
14. Ananthakrishnan AN, McGinley EL, Binion DG. Excess hospitalisation burden associated with *Clostridium difficile* in patients with inflammatory bowel disease. Gut 2008;57:205-10.
15. Alberta Health Services. Alberta Health Services Annual Report, April 1, 2009-March 31, 2010. <www.albertahealthservices.ca/Publications/ahs-pub-annual-rpt.pdf> (Accessed November 1, 2012).
16. Ma C, Crespin M, Proulx MC, et al. Postoperative complications following colectomy for ulcerative colitis: A validation study. BMC Gastroenterol 2012;12:39.
17. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications. Ann Surg 2004;240:205-13.
18. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): Explanation and elaboration. PLoS Med 2007;4:e297.
19. Murthy SK, Steinhart AH, Tinmouth J, et al. Impact of *Clostridium difficile* colitis on 5-year health outcomes in patients with ulcerative colitis. Aliment Pharmacol Ther 2012;36:1032-9.
20. Navaneethan U, Mukewar S, Venkatesh PG, et al. *Clostridium difficile* infection is associated with worse long term outcome in patients with ulcerative colitis. J Crohns Colitis 2012;6:330-6.
21. Kariv R, Navaneethan U, Venkatesh PG, Lopez R, Shen B. Impact of *Clostridium difficile* infection in patients with ulcerative colitis. J Crohns Colitis 2011;5:34-40.
22. Kaneko T, Matsuda R, Taguri M, et al. *Clostridium difficile* infection in patients with ulcerative colitis: Investigations of risk factors and efficacy of antibiotics for steroid refractory patients. Clin Res Hepatol Gastroenterol 2011;35:315-20.
23. Molodecky NA, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Challenges associated with identifying the environmental determinants of the inflammatory bowel diseases. Inflamm Bowel Dis 2011;17:1792-9.
24. Kaplan GG, McCarthy EP, Ayanian JZ, Korzenik J, Hodin R, Sands BE. Impact of hospital volume on postoperative morbidity and mortality following a colectomy for ulcerative colitis. Gastroenterol 2008;134:680-7.
25. Sundram F, Guyot A, Carboo I, Green S, Lilaonitkul M, Scourfield A. *Clostridium difficile* ribotypes 027 and 106: Clinical outcomes and risk factors. J Hospl Infect 2009;72:111-8.
26. Goodhand JR, Alazawi W, Rampton DS. Systematic review: *Clostridium difficile* and inflammatory bowel disease. Aliment Pharmacol Ther 2011;33:428-41.
27. Yanai H, Nguyen GC, Yun L, et al. Practice of gastroenterologists in treating flaring inflammatory bowel disease patients with *Clostridium difficile*: Antibiotics alone or combined antibiotics/immunomodulators? Inflamm Bowel Dis 2011;17:1540-6.
28. Kaplan GG, Hubbard J, Panaccione R, et al. Risk of comorbidities on postoperative outcomes in patients with inflammatory bowel disease. Arch Surg 2011;146:959-64.
29. Tacconelli E, De Angelis G, Cataldo MA, et al. Antibiotic usage and risk of colonization and infection with antibiotic-resistant bacteria: A hospital population-based study. Antimicrob Agents Chemother 2009;53:4264-9.
30. Moore R, Pothoulakis C, LaMont JT, Carlson S, Madara JL. *C. difficile* toxin A increases intestinal permeability and induces Cl^- secretion. Am J Physiol Gastrointest Liver Physiol 1990;259:G165-G72.
31. Hetch G, Charalabos P, LaMont JT, Madara JL. *Clostridium difficile* toxin A perturbs cytoskeletal structure and tight junction permeability of cultured human intestinal epithelial monolayers. J Clin Invest 1988;82:1516-24.
32. Feltis BA, Kim AS, Kinneberg KM, et al. *Clostridium difficile* toxins may augment bacterial penetration of intestinal epithelium. Arch Surg 1999;134:1235-42.
33. Schulz KF, Grimes DA. Case-control studies: Research in reverse. Lancet 2002;359:431-4.