

Original Article

Absence of Day 3 Steroid Response Predicts Colitis-Related Complications and Colectomy in Hospitalized Ulcerative Colitis Patients

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Abstract

Background and Aims: Rates and predictors of complications among hospitalized ulcerative colitis (UC) patients requiring high-dose corticosteroids have not been well-characterized, especially in the era of biologics.

Methods: We retrospectively studied consecutive UC admitted for a colitis flare requiring high-dose corticosteroids between April 2006 and December 2016. We evaluated rates and determinants of serious in-hospital complications (colitis-related complications, systemic complications, peri-operative complications and death) and colectomy. We performed multivariable logistic regression analysis to assess the independent association between day 3 steroid response and the risk of incurring in-hospital complications and colectomy.

Results: Of 427 consecutive admissions, serious in-hospital complications occurred in 87 cases (20%), while colitis-related complications occurred in 47 cases (11%). There were significantly fewer colitis-related complications during the 2012 to 2016 period as compared to the 2006 to 2011 period (7% versus 16%, $P < 0.01$), but significantly more systemic complications (16% versus 5%, $P = 0.001$). In-hospital colectomy occurred in 50 hospitalizations (12%). Day 3 steroid response was achieved in 167 hospitalizations (39%). Day 3 steroid nonresponse was significantly associated with colitis-related complications among males (adjusted odds ratio [aOR] 8.22, 95% confidence interval [CI] 1.77 to 38.17), but not among females (aOR 1.39, 95% CI 0.54 to 3.60). Older age, *C. difficile* infection and admission to a non-gastroenterology service were also associated with a higher risk of in-hospital complications. Day 3 steroid nonresponse was significantly associated with in-hospital colectomy (aOR 10.10, 95% CI 3.56 to 28.57).

Conclusion: In our series of UC hospitalizations for a colitis flare, absence of day 3 steroid response was associated with an increased risk of colitis-related complications among males and of in-hospital colectomy. Clinicians should recognize the importance of early steroid response as a marker to guide the need for treatment optimization.

Keywords: Hospitalization; IBD complications; steroid response

Inflammatory bowel disease (IBD) afflicts 0.3% of the North American population and 0.67% of the Canadian population (over 230,000 persons), and is rising in incidence worldwide (1,2). Ulcerative col-

itis (UC), a subtype of IBD, is associated with substantial morbidity, with up to 25% of the patients hospitalized during their disease course due to severe colitis flares (3). Hospitalized patients with

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UC are at high risk of developing serious complications relating to their colitis, including fulminant colitis, toxic megacolon, bowel perforation, abdominal sepsis, massive hemorrhage, venous thromboembolism (VTE) and *Clostridium difficile* infection (CDI) (4–7). These patients may also be at risk for other serious systemic complications such as hypovolemia, acute kidney injury, electrolyte disturbances, malnutrition and cardiovascular complications (8). It is well known that hospitalized UC patients have higher morbidity and mortality than the general hospitalized population (9). The burden of health care costs is also significant in this population, with hospitalizations accounting for 35 to 67% of total health care costs among UC patients (1,10).

Early recognition of hospitalized UC patients facing a high risk of complications could direct early aggressive management to improve outcomes. Yet, no study has adequately described the overall prevalence of serious complications and associated factors among UC patients hospitalized with a flare in the biologic era. In addition to obvious risk factors such as older age and greater co-morbid disease burden, factors such as absence of early steroid response, CDI and admission to a nongastroenterology (GI) service have been previously associated with adverse prognosis in this population and warrant further study as potential risk factors for acute colitis-related complications (11–13).

We evaluated the rates and associated factors of serious in-hospital complications and colectomy among consecutive UC patient hospitalizations for severe disease flares over a 10-year period. Based on its established association with colectomy risk (11), we hypothesized that absence of day 3 corticosteroid response would also be an independent determinant of serious in-hospital complications in this population.

METHODS

Patients and Study Design

We conducted a retrospective cohort study of consecutive patient admissions to The Ottawa Hospital, a tertiary care academic referral centre, with a flare of UC requiring high-dose corticosteroids (≥ 40 mg/day of prednisone or equivalent) between April 2006 and December 2016. Hospitalized patients with UC were identified from our institutional database using International Classification of Diseases and Related Health Problems (ICD)-10 codes. We performed a detailed medical record review to ensure that patients met study eligibility criteria and to record information on pertinent health events and variables. We excluded patient admissions that were shorter than 48 hours or that occurred in postcolectomy patients, as well as elective admissions for expediting surgical management.

Study Definitions

We graded patients as having mild, moderate or severe disease activity based on the endoscopic component of the Mayo

classification system, pertaining to the most recent colonoscopy performed during the disease flare accounting for hospital admission (14). We used physicians' descriptors (i.e., ulcers, friability, etc.) from endoscopy records to grade activity; if these were not available, we used physicians' stated impression of endoscopic activity. We defined all in-hospital medication exposures as receipt of a medication up to and/or during hospitalization. We judged day 3 steroid response as a reduction of ≥ 3 points and $\geq 30\%$ from baseline in the partial Mayo score (the three clinical components of the Mayo score) (15). We defined massive hemorrhage as a hemoglobin drop of ≥ 30 g/L. We defined admission CDI if it was diagnosed within 48 hours of admission; otherwise it was counted as an in-hospital complication. We defined a serious in-hospital complication as any of the following: a colitis-related complication, a major systemic complication indirectly related to colitis, a peri-operative complication, and/or death in hospital. We defined in-hospital colitis-related complication based on having a high likelihood of being directly attributable to the acute colitis flare, including colon perforation, toxic megacolon, intra-abdominal infection, peritonitis, massive hemorrhage, CDI (diagnosed >48 hours into admission) or VTE. We defined a systemic complication as a major systemic insult affecting any of the following organ systems, that is, cardiac, respiratory, renal, hepatobiliary, neurologic or dermatologic. We defined a peri-operative complication as any of wound dehiscence, anastomotic leak or intra-abdominal sepsis.

Study Outcomes

Our main outcome measures were the rates of in-hospital colitis-related complications, all-cause complications and colectomies. Other outcomes included the rates of peri-operative complications and in-hospital death and temporal trends in complication rates. Our primary association of interest was between day 3 steroid response and risk of a colitis-related complication.

Descriptive and Analytical Methods

Categorical variables were reported as frequency and proportions. Continuous variables were reported as medians and interquartile ranges. Univariate analyses were conducted using student's *t*-tests for continuous variables and Chi-square tests for categorical data to assess for temporal differences in patient characteristics and outcomes. We performed multivariable logistic regression analysis to determine factors independently associated with in-hospital colitis-related complications, colectomy, and all-cause complications using the following covariates: day 3 steroid response, endoscopic Mayo activity score, use of a biologic, age, sex, Charlson co-morbidity score, admitting service, disease duration and CDI on admission. Variables demonstrating a *P*-value of < 0.2 were retained in the final models to maximize covariate adjustment, whereas variables with *P*-value of > 0.2 (e.g., endoscopic activity, disease duration) were not retained in the models as they were considered to not be strongly

associated with the outcomes of interest. Day 3 steroid response was retained in all models to assess its independent association with outcome events. We assessed whether the magnitude of effect for our primary associations varied across age and sex groups by testing interaction terms between our primary exposure variable (day 3 steroid response) and each of age and sex in our models. In assessing the independent effects of our primary variable and covariates on outcomes of interest, we define a statistically significant association as $P < 0.05$. All statistical analyses were performed using SAS 9.4 (SAS Institute, 2013).

Ethical Considerations

This study was approved by the Ottawa Health Sciences Network Research Ethics Board.

RESULTS

Study Cohort Baseline Characteristics

We studied 427 consecutive UC hospitalizations for disease flares requiring high-dose corticosteroids. Intravenous sol-medrol (60 mg total daily dose) was administered in 95% of encounters. Baseline characteristics of the study cohort, stratified by day 3 steroid response, are provided in Table 1.

In-Hospital Complication Rates

A serious complication of any type occurred in 87 patients (20%). A colitis-related complication occurred in 47 patients (11%) during hospitalization, including 5 bowel perforations (1.2%), 6 cases of toxic megacolon (1.4%), 6 cases of peritonitis (1.4%), 16 cases of massive hemorrhage (3.7%), 10 cases of hospital-acquired

Table 1. Patient characteristics and outcomes stratified by day 3 steroid response[†]

Variable	Total <i>n</i> = 427	Day 3 steroid response <i>n</i> = 167	No steroid response <i>n</i> = 260	<i>P</i> -value (95% CI)
Age, years (median ± IQR)	34.0 ± 25.7	37.5 ± 25.3	33.2 ± 25.9	0.25
Male sex (<i>n</i> , %)	225 (53)	80 (48)	145 (56)	0.11
Disease Duration (mean ± SD)	2.0 ± 6.9	5.1 ± 7.9	4.0 ± 6.1	0.23
Gastroenterology as admitting service (<i>n</i> , %)	199 (47)	85 (51)	114 (44)	0.16
Charlson Co-Morbidity index ≥ 1 (<i>n</i> , %)	111 (26)	41 (25)	70 (27)	0.59
Endoscopic activity				<0.001
Mayo 1—mild (<i>n</i> , %)	16 (4)	8 (5)	8 (3)	
Mayo 2—moderate (<i>n</i> , %)	108 (25)	54 (32)	54 (21)	
Mayo 3—severe (<i>n</i> , %)	229 (54)	65 (39)	166 (64)	
Positive <i>Clostridium difficile</i> on admission (<i>n</i> , %)	21 (5)	11 (7)	10 (4)	0.13
Received VTE prophylaxis (<i>n</i> , %)	285 (67)	98 (59)	187 (73)	<0.01
Medication exposure [‡]				
Maximum total daily steroid dose (mean ± SD) (mg prednisone equivalent)	75.0 ± 20.8	73.4 ± 10.1	76.0 ± 25.3	0.14
5-ASA agents (<i>n</i> , %)	197 (46)	77 (46)	120 (46)	0.99
AZA/6MP (<i>n</i> , %)	107 (25)	40 (24)	67 (26)	0.68
Biologics (<i>n</i> , %)	207 (48)	42 (25)	165 (63)	<0.001
Length of hospital stay, days (median ± IQR)	8.0 ± 5.0	5.0 ± 3.9	12.0 ± 8.0	<0.001
Serious In-Hospital Complications [§] (<i>n</i> , %)	87 (20)	28 (17)	59 (23)	0.17
Colitis-related complications [‡] (<i>n</i> , %)	47 (11)	12 (7)	35 (13)	0.047
Peri-operative complications ^{**} (<i>n</i> , %)	12 (3)	2 (1)	10 (4)	0.29
Noncolitis-related complications ^{**} (<i>n</i> , %)	49 (11)	19 (11)	30 (12)	0.95
In-hospital death (<i>n</i> , %)	4 (1)	1 (1)	3 (1)	0.95
In-hospital colectomy (<i>n</i> , %)	50 (12)	5 (3)	45 (17)	<0.001

[†]Day 3 steroid response = ≥ 3 points and ≥ 30% improvement in the partial Mayo score in the absence of biologics induction therapy. [‡]Medication exposure = receiving specific medical therapy up to and/or during hospitalization. [§]Serious in-hospital complications = composite of colitis-related complications, peri-operative complications, noncolitis complications, and death in hospital. [‡]Colitis-related complications = perforation, toxic megacolon, intra-abdominal infection, peritonitis, massive hemorrhage, *Clostridium difficile*, venous thromboembolism. ^{**}Peri-operative complications = wound leak, postoperative sepsis, postoperative peritonitis. ^{**}Noncolitis complications = cardiac, respiratory, renal, hepatobiliary, neurologic and dermatologic complications. Bolded values indicate statistically significant association as $P < 0.05$.

5-ASA, 5-aminosalicylate; AZA, Azathioprine, 6MP, 6-mercaptopurine; VTE, Venous thromboembolism.

CDI (2.3%) and 6 cases of venous thromboembolism (1.4%). There were 49 systemic noncolitis complications (11%), of which 12 were renal, 9 were cardiac and 6 were respiratory. There were 50 in-hospital colectomies (12% of hospitalizations), of which 37 (74%) were for medically refractory disease and 9 (18%) were emergent colectomies for fulminant colitis or perforation. Patients who underwent colectomy had a median time to colectomy of 12 days with median hospitalization of 21 days (compared with 7.3 days in patients who did not undergo colectomy). Twelve patients who had colectomies (24%) suffered serious peri-operative complications, of which the majority occurred in colectomies done for medically refractory disease. There were four in-hospital deaths, of which three were attributed to colitis-related complications (1%).

In-Hospital Complication Rates over Time

The rates of in-hospital complications, stratified by admission period (2006 to 2011 versus 2012 to 2016), are presented in Figure 1. The rate of all-cause in-hospital complications did not change between periods. However, in the latter half of the study period, there were significantly fewer colitis-related complications (7% versus 16%, $P < 0.01$) and significantly more noncolitis complications (16% versus 5%, $P = 0.001$). There were no significant differences in the rates of peri-operative complications, colectomy rates or deaths between periods. More patients were admitted to a gastroenterology service (64% versus 24%, $P < 0.001$), diagnosed with CDI on admission (8% versus 1%, $P = 0.001$), prophylaxed against VTE (92% versus 34%, $P < 0.001$) and treated with a biologic agent (53% versus 42%, $P = 0.03$) in the latter half of the study period (Supplementary Table 1).

Day 3 Steroid Response and Factors Associated With In-Hospital Complications

Absence of day 3 response to steroids was significantly associated with risk of incurring a colitis-related complication (unadjusted odds ratio [OR] 2.0, $P = 0.046$) and in-hospital colectomy (OR 6.66, $P < 0.0001$). These associations remained significant in multivariable analysis (aOR 2.59, 95% confidence interval [CI] 1.19 to 5.62 and aOR 10.10, 95% CI 3.56 to 28.57, respectively) (Tables 2 and 3). Sex was a significant modifier of the association between day 3 nonresponse and colitis-related complications (P -value for interaction term = 0.048). When stratified by sex, steroid nonresponse was only associated with colitis-related complications among males (aOR for males 8.22, 95% CI 1.77 to 38.17; aOR for females 1.39, 95% CI 0.54 to 3.60) (Table 2). The risk of colitis-related complications did not vary by age (P -value for interaction term = 0.22). Conversely, age was noted to be a modifier of the association between day 3 steroid response and risk of undergoing in-hospital colectomy in our cohort (P -value for interaction term = 0.057). Having a day 3 steroid response was less protective against in-hospital colectomy with increasing age, although the association remained significant in persons aged 25, 35 and 55 years. Among individuals at the mean age of the cohort (40 years), day 3 steroid nonresponse was associated with an adjusted risk of in-hospital colectomy of 14.77 (95% CI 3.99 to 54.64) (Table 3). The risk of colectomy did not vary by sex (P -value for interaction term = 0.22). Day 3 nonresponse was not associated with all-cause in-hospital complications (aOR 1.45, 95% CI 0.88 to 2.48).

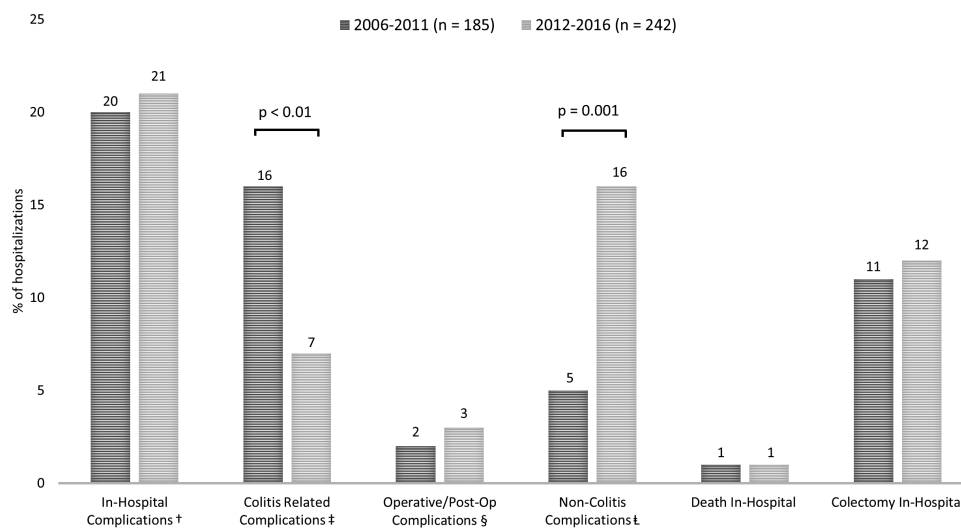


Figure 1. Comparison of in-hospital complications between 2006–2011 and 2012–2016. †In-hospital complications = composite of colitis-related complications, peri-operative complications, noncolitis complications and death in hospital. ‡Colitis-related complications = perforation, toxic megacolon, intra-abdominal infection, peritonitis, massive hemorrhage, Clostridium difficile, venous thromboembolism. §Peri-operative complications = wound leak, postoperative sepsis, postoperative peritonitis. †Noncolitis complications = cardiac, respiratory, renal, hepatobiliary, neurologic and dermatologic complications. 5-ASA, 5-aminosalicylate; AZA, azathioprine; 6MP, 6-mercaptopurine.

In multivariable analysis, development of a colitis-related complication was also significantly associated with older age, admission to a nongastroenterology service and CDI on admission (Table 2), whereas in-hospital colectomy was significantly associated with severe (Mayo 3) endoscopic activity, older age, CDI, Charlson co-morbidity score ≥ 1 , and use of biologics up to and/or during admission (Table 3). Older age (aOR 1.02, 95% CI 1.01 to 1.03) and admission to a non-GI service (aOR 2.59, 95% CI 0.23 to 0.65) were the only factors independently associated with risk of incurring a serious in-hospital complication of any kind (Supplementary Table 2).

Biologics-Naive Versus Biologics-Treated Patient Characteristics and Outcomes

Of 207 patients who were exposed to biologic therapy near the time of hospitalization, 127 patients (61%) were biologics-naive

and received their first dose of biologic during the index hospitalization. In these patients, median disease duration was 2 years (IQR ± 3 years) and median time-to-biologic dose was 6.5 days (IQR ± 3 days) following hospital admission. One hundred and twenty-one patients received infliximab at a 5 mg/kg dose, three patients received infliximab at a 10 mg/kg dose and three patients received a loading dose of adalimumab. Fifteen patients received two or more biologics doses while in hospital. Of 80 patients who were actively receiving treatment with a biologic at the time of hospital admission, 60 patients were treated with infliximab and 20 patients were treated with another biologic agent, including adalimumab, golimumab and vedolizumab. In this group, median disease duration was 4 years (IQR ± 3 years), and median duration of time since initial biologic exposure was 4 months (IQR ± 5 months) at the time of hospital admission. Forty-eight patients received at least one rescue dose of biologic in hospital, with a median time-to-rescue

Table 2. Adjusted odds ratios for factors associated with the development of colitis-related complications in the final multivariable model[†]

Variable	Adjusted odds ratios (aOR) estimates, $n = 427$			
	aOR	95% CI		P-value
Lack of day 3 steroid response [†] (vs. response)	2.59	1.19	5.62	0.02
Nonresponse vs. response in males	8.22	1.77	38.17	0.007
Nonresponse vs. response in females	1.39	0.54	3.60	0.50
Age (per year increase)	1.02	1.01	1.04	0.01
GI admission (vs. non-GI admission)	0.23	0.1	0.53	<0.001
Positive <i>Clostridium difficile</i> on admission (vs. negative)	7.64	2.32	25.14	<0.001
Biologic exposure [§] (vs. no biologic exposure)	0.57	0.27	1.17	0.13

[†]Colitis-related complications = perforation, toxic megacolon, intra-abdominal infection, peritonitis, massive hemorrhage, *Clostridium difficile*, venous thromboembolism. [‡]Day 3 steroid response = ≥ 3 points and $\geq 30\%$ improvement in the partial Mayo score in the absence of biologics induction therapy. [§]Biologic exposure = receipt of biologic therapy (e.g., infliximab, adalimumab) leading up to and/or during hospitalization. Bolded values indicate statistically significant association as $P < 0.05$.

Table 3. Adjusted odds ratios for factors associated with in-hospital colectomy in the final multivariable model

Variable	OR estimates, $n = 427$			
	OR	95% CI		P-value
Lack of day 3 Steroid response [†] (vs. response)	10.10	3.56	28.57	<0.0001
Nonresponse vs. response for mean cohort age (40 years old)	14.77	3.99	54.64	<0.0001
Age (per year increase)	1.03	1.00	1.05	0.04
Charlson score 0 (vs. ≥ 1)	4.44	1.55	12.71	0.01
Disease duration (years)	0.96	0.90	1.02	0.20
Positive <i>Clostridium difficile</i> on admission (vs. negative)	4.80	1.39	16.53	0.01
Endoscopic Mayo score < 3 (vs. 3)	0.29	0.11	0.75	0.01
Biologic exposure [‡] (vs. no biologic exposure)	0.47	0.24	0.94	0.03

[†]Day 3 steroid response = ≥ 3 points and $\geq 30\%$ improvement in the partial Mayo score in the absence of biologics induction therapy. [‡]Biologic exposure = receiving biologic therapy (e.g., infliximab, adalimumab and/or vedolizumab) up to and/or during hospitalization. Bolded values indicate statistically significant association as $P < 0.05$.

biologic dose of 4 days (IQR \pm 2 days). When comparing these two patient groups, there were no significant differences in sex, length of hospital stay, disease duration or overall complication rates, including colectomy or death. There was a significant difference in peri-operative complications and noncolitis-related complications in the pre-exposed group ($P = 0.01$ and $P = 0.04$, respectively).

DISCUSSION

This is the most recent study of UC patient hospitalizations for colitis flares examining complication rates and associated factors in the biologics era. A serious complication from any cause occurred in roughly one in five hospitalizations, while a serious colitis-related complication occurred in approximately one in nine hospitalizations. Twelve per cent of hospitalizations resulted in colectomy, of which one in five colectomies were performed emergently for fulminant colitis or perforation. Absence of clinical response to steroids at day 3 was associated with a 3-fold higher risk of developing a colitis-related complication and a 10-fold higher risk of undergoing colectomy in-hospital. Developing an acute colitis-related complication was also significantly associated with admission to a nongastroenterology service, older age and CDI on admission.

Similar to previous studies, absence of day 3 steroid response was a strong independent predictor of in-hospital colectomy (11,16). For the first time, we show that absence of day 3 steroid response is also associated with a higher risk of developing colitis-related complications in hospital. However, it did not predict the development of systemic complications. This furthers the notion that prompt recognition of steroid nonresponders at day 3 is important in the management of hospitalized UC patients. Patients who fail to respond to steroids by day 3 may typify a more aggressive phenotype of UC with resistant disease. This could explain higher endoscopic severity and biologics exposure in these patients in our study. Early aggressive treatment of those who fail to respond to steroids by day 3, such as administration of rescue biologic therapy or cyclosporine or referral for colectomy, may reduce the risk of life-threatening complications of colitis. Interestingly, although an overall association in the cohort was noted between day 3 steroid response and colitis-related complications, testing for interaction terms demonstrated the effect was restricted to males. We hypothesize that the observed effect of sex may be due to differential acceptance between males and females of undergoing colectomy and possibly avoiding colitis-related complications. This finding should be explored in future prospective studies with other hospitalized UC cohorts. Having a day 3 steroid response was less protective against in-hospital colectomy with increasing age, although the association remained significant across age groups. We hypothesize that the impetus for practitioners

to recommend colectomy may have been greater among older patients, given the potential for a higher risk of serious complications with active colitis (such as venous thromboembolism and sepsis). As well, decreased concern among older individuals about the potential cosmetic and psychosocial effects of colectomy with or without an end ileostomy may have been a factor. With greater importance placed on health, this could have been a contributing factor to this observed trend. However, additional studies are needed to validate this finding and to investigate specific reasons for the changing effect with age.

Surprisingly, our population demonstrated an overall low proportion of patients treated with biologic agents. Of 260 patient encounters with no response to steroids by day 3, 77 (30%) ultimately responded to steroids by day 7, while 165 (63%) were exposed to a biologic agent as rescue therapy. Clinicians may have used other indicators (such as improvement in serum biochemistry or CRP) not captured in the partial Mayo score that suggested patient improvement by day 3. Furthermore, some clinicians may have had less exposure to the practice of early biologic rescue therapy initially, such as general internists and surgeons who do not routinely manage IBD patients. Hence, adopting the practice of early biologic rescue therapy would have gradually become more frequent during the study period.

Direct gastroenterologist involvement in the care of patients hospitalized with UC has been shown previously to be associated with better outcomes (13,17). Similarly, in our cohort, admission to a non-GI service was associated with an increased risk of complications in our cohort. Importantly, this association suggests that patients admitted to non-GI services may require closer in-hospital monitoring and/or aggressive treatment, as they potentially represent a patient population with a poorer prognosis. This finding requires verification in future prospective studies, along with elucidation of causative factors for poorer outcomes in these patients.

We also observed a shift away from colitis-related complications and toward systemic complications with time. Decreased colitis-related complications could suggest improved management of in-patient colitis flares, especially with closer involvement with GI. However, sicker patients with multiple co-morbidities are being admitted to hospital. Notably, patient hospitalizations were significantly more likely to be associated with more co-morbid illnesses in the latter half as compared to the first half of the study period (based on the Charlson index) (18). There could also be other unmeasured factors contributing to these trends, such as resource allocation changes that impacted IBD management or yet undiscovered systemic effects from biologic medications used to treat severe UC in later study years, although this requires verification in other cohorts.

We also observed temporal trends toward more patient admissions to a GI service as opposed to internal medicine or general surgery, increased biologics use in hospital and increased VTE

prophylaxis. The rate of VTE events in our cohort was slightly lower than previously reported rates in hospitalized UC cohorts (5,19), the event rate was similar to rates described in nearby hospital centers in Ontario (20). This difference may reflect improved awareness of the elevated risk of VTE associated with active IBD, as well as the advent of guidelines advocating for VTE prophylaxis in hospitalized IBD patients (19,21–24).

Our study also highlights the impact of *C difficile* infection on hospitalized colitis patients—this infection carried a 7-fold higher risk of developing a colitis-related complication in our study. The rate of in-hospital *C difficile* infections in our cohort was lower than previously documented rates in similar populations (2.3% versus reported rates of 3.7 to 7%) (25,26). Interestingly, the percentage of patients who were positive at admission significantly increased in our study from 1 to 8% in more recent years. Although epidemiological studies also demonstrate an alarming rise in the incidence of *C difficile* among UC patients, it may also reflect increased awareness and more sensitive diagnostic techniques, underscoring the importance of screening and treatment of this infection in all hospitalized UC patients (7).

There are several limitations to our study. The retrospective design could have led to misclassification of some outcome events and predictor variables, unmeasured confounders and missing data. Biopsies were not routinely assessed for cytomegalovirus (CMV) colitis, which could confound the outcomes measured in our study. However, the risk of CMV colitis has been shown to be very low in the hospitalized UC population (1.4%) and likely would not affect our findings (27). As such, it would be important to confirm our study findings in a large prospective study. Second, the assessment of day 3 response was limited to patient-driven clinical response, and may not necessarily correlate with endoscopic disease response. The retrospective nature of our study limited us in terms of using the Travis score/Oxford rule. This tool is commonly used to assess early response to IV steroids in hospitalized severe UC patients as well as predict need for colectomy and escalation in therapy (11). In our study, we looked at day 3 response as a predictor of other adverse outcomes, including but not limited to colectomy. The Mayo score has become widely used in both clinical and research domains to assess disease severity, change in activity over time, and response to treatment. Lewis et al. demonstrated that the partial Mayo score performed as well as the full Mayo score to identify patient perceived clinical response (15). We recognize that this measure has not been validated in the hospitalized UC population; however, current North American guidelines suggest assessing clinical symptoms, objective measures (such as stool frequency) and bloodwork at day 3 to determine whether treatment of a UC flare should be escalated to second-line medical or surgical therapy (28,29).

As such, we used the partial Mayo score (with clinical symptoms, stool frequency and global assessment) as a substitute for the Travis score, reasoning that it would be a suitable and feasible alternative. Furthermore, as we studied UC admissions to a tertiary care referral centre, generalizability of our findings may be limited, particularly to smaller community hospitals. Future studies in this area would ideally be multicentre studies incorporating both academic and community hospitals. We also elected to group complications into specific categories based on our impression of relevance to patients' underlying colitis; however, clinicians may vary in their opinions of these groupings. Future larger studies should aim to assess rates and predictors of each of these complications individually. Notable strengths of our study are the large sample size and focus on hospital admissions in the biologic era, which provides results that are more relevant to current day practice.

CONCLUSION

In conclusion, the complication rates in UC patients hospitalized for disease flares remain high, even in a tertiary care IBD referral centre. However, colitis-related complications have dropped significantly in the last few years, likely as a result of increased use of biologic therapies and updated guidelines on the management of acute severe colitis. Day 3 steroid response may be used to identify patients at higher risk of colectomy and colitis-related complications, allowing for improved patient care through adjusting management strategies and patient education in efforts to minimize risk and improve outcomes.

Supplementary data

Supplementary data are available at *Journal of the Canadian Association of Gastroenterology* online.

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