Second-Look Endoscopy in Hospitalized Severe Ulcerative Colitis: A Retrospective Cohort Study

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Background: Acute severe ulcerative colitis (ASUC) is a serious complication of ulcerative colitis (UC). Management of partial responders to steroids or rescue therapy remains challenging. Whether there is a role for re-look sigmoidoscopic evaluation in disease management is unknown.

Methods: Our study cohort consisted of patients who underwent 2 sigmoidoscopic procedures during the same index hospitalization for ASUC at our center. Reasons for repeat endoscopic evaluation and endoscopic and histologic severity of inflammation during both procedures were noted. Multivariable regression models were performed to identify predictors of improvement at the second endoscopic assessment and to determine the independent effect of such an improvement on in-hospital colectomy and at 3, 6, and 12 months.

Results: Our study included 49 patients (mean age, 42 years; 52% women). Just under one-third of patients (30%) were noted to have improved endoscopic appearance at the second sigmoidoscopy, at a median of 9 days after initial exam. None of the patients who had improvement on the second endoscopy underwent in-hospital colectomy, compared with 46% of those with worsening or persistent disease ($P = 0.002$). Similar differences in the improved group persisted at 3 months ($P = 0.007$) and 6 months ($P = 0.027$). Histologic severity at the first endoscopy was associated with increased risk of colectomy in-hospital (odds ratio, 3.8; 95% confidence interval, 1.02–14.21) and at 3 and 6 months.

Conclusions: After a median interval of 9 days, endoscopic improvement was noted in 30% of patients with ASUC undergoing a second sigmoidoscopy, which predicted lower rates of colectomy in-hospital and at 3 and 6 months.

Key Words: ulcerative colitis, endoscopy, hospitalization, colectomy

INTRODUCTION

Acute severe ulcerative colitis (ASUC) is a serious complication of ulcerative colitis (UC) associated with significant morbidity. Initial treatment for ASUC consists of intravenous steroids. The ~60% of patients who respond to intravenous steroids with resolution of symptoms are discharged home with optimization of maintenance regimen.^{1,2} Up to one-third of patients may be steroid refractory, with no improvement in clinical or biochemical markers with 3–7 days of intravenous steroids. Such patients usually receive either medical rescue therapy with infliximab or cyclosporine or undergo surgery. However, many patients demonstrate an incomplete symptomatic and biochemical response to either steroids or

medical rescue therapy. The management of such patients is challenging for both the provider and the patients themselves as options exist to accelerate medical rescue therapy such as higher doses of infliximab, trying a salvage rescue strategy, or undergoing colectomy. The imperfect correlation between symptoms, circulating biochemical markers such as C-reactive protein, and endoscopic severity further contribute to the challenges of decision-making in this setting.

In clinical practice, a sigmoidoscopy is commonly performed in most ASUC patients at admission to evaluate for severity of inflammation and to rule out complications such as cytomegalovirus (CMV) infection. Endoscopic severity at initial presentation has been shown to correlate with failure of medical therapy and need for colectomy.^{3,4} Whether there is a benefit to a second endoscopic assessment during hospitalization in patients with partial symptomatic response is not known. We hypothesized that a second-look endoscopic evaluation during the index hospitalization in this population would be valuable in identifying those with partial endoscopic response who may benefit from continued medical rescue therapy, while also defining complete nonresponders who will require colectomy. Consequently, we performed this retrospective study with the following aims: (1) to identify the proportion of ASUC patients undergoing a repeat sigmoidoscopic evaluation during the index hospitalization for ASUC and (2) to define the short- and long-term prognosis of patients who demonstrate endoscopic improvement on this second evaluation.

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METHODS

Study Population

In this retrospective study, we reviewed our experience with ASUC patients hospitalized during 2005–2017 at Massachusetts General Hospital (MGH), a tertiary referral center serving the greater Boston area and the rest of New England. Our primary cohort consisted of those who underwent 2 sigmoidoscopic procedures during the same index hospitalization for ulcerative colitis. Potential subjects were identified using the Research Practice Data Registry. As described in prior studies from our center, this is a comprehensive data warehouse of all inpatient and outpatient contacts at MGH and other Partners Healthcare–affiliated hospitals.^{5,6} It is continually populated with data from office visits, in-patients stays, discharge summaries, surgical procedures, endoscopy, radiology, pathology reports, and electronic prescriptions. First, a preliminary screen identified all patients with a diagnosis of UC (*International Classification of Diseases*, 9th edition, Clinical Modification [ICD-9-CM] 556.x; 10th edition [ICD-10] K51.x) who were hospitalized during the study period and underwent a flexible sigmoidoscopy. Manual chart review of each subject was performed to confirm inflammatory bowel disease (IBD) diagnosis, to identify hospitalizations related to acute exacerbations of UC, and to determine those who underwent 2 endoscopic procedures during the same admission. Patients were excluded if they were younger than age 18 years, were admitted for non-IBD-related indications, had a J-pouch or stoma, or were admitted for an elective surgery. Our primary intent was to define the impact of the second-look endoscopic evaluation on subsequent management and patient outcomes. Secondarily, we compared the outcomes of patients who underwent a repeat sigmoidoscopic evaluation compared with those who only had the index sigmoidoscopic evaluation upon admission. This comparison was achieved by selecting a random 1:1 unmatched control UC patient from among all patients who were hospitalized for management of severe ulcerative colitis during that same period.

Covariates and Outcomes

Further review of the electronic medical records was performed to collect additional data of included patients. Covariates obtained included age, gender, disease extent according to the Montreal classification, smoking history, and disease duration. Information was also extracted regarding medical and surgical history for their IBD at the time of admission. Baseline laboratory results were obtained of hemoglobin, albumin, white blood cell count, platelet count, C-reactive protein, and erythrocyte sedimentation rate where available. Additionally, reasons for repeat endoscopic evaluation and endoscopic and histologic severity of inflammation during both procedures were noted. Subjects were stratified into those patients with improved endoscopic appearance at the second sigmoidoscopy and those with worsening or persistent disease, based on the impression of the endoscopist.

Not all endoscopists routinely used validated scoring systems to define severity. Histologic severity was determined by the pathologist based on overall impression of the histologic findings.

The primary outcomes of interest were need for in-hospital colectomy and colectomy at 3 months and 6 months after discharge. Secondary outcomes were initiation of biologic or cyclosporine therapy during hospitalization, readmission within 90 days, and colectomy at 1 year after discharge (long-term morbidity).

Statistical Analyses

Statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX, USA). Continuous variables were summarized using means and standard deviations and compared using the *t* test, whereas categorical variables were expressed as proportions and compared using the chi-square test; the Fisher exact test was used when necessary. Regression models were performed to identify predictors of improvement at the second endoscopic assessment and to determine the independent effect of such improvement on in-hospital, short-term (3- and 6-month), and long-term (12-month) morbidity. We first performed univariate analysis to identify predictors of each of our primary outcomes. Significant variables ($P < 0.05$) or variables previously described in the literature to be important were used in a multivariable regression model to identify independent statistically significant variables with a 2-sided P value < 0.05 . Approval for this study was obtained from the Institutional Review Board of the Partners Healthcare Human Subjects Research Committee.

RESULTS

Study Cohort

Our primary study cohort included 49 patients hospitalized for ulcerative colitis who underwent 2 sigmoidoscopic evaluations during the index hospitalization. The median interval between the 2 sigmoidoscopies (interquartile range) was 9 (3–16) days. The mean age of included patients was 42 years, and just over half were women (52%). A majority of the patients were on oral steroids at the time of admission (74%). Fewer than one-fifth (18%) were current or past users of biologic therapy at hospitalization. The mean admission C-reactive protein (CRP) and albumin were 55.7 mg/L and 3.2 g/dL, respectively. Endoscopic severity at the first endoscopy was noted to be mild in 12%, moderate in 33%, and severe in 55%. Just under half (41%) were noted to have severe inflammation at histology, 37% had moderate inflammation, and 10% had mild inflammation. Among all these patients, 7 (14%) were diagnosed with CMV colitis during hospitalization. The indication for the second endoscopic evaluation was persistent symptoms or worsening of symptoms in 32 patients (76%) despite either intravenous steroid and/or medical rescue therapy, and only partial improvement in symptoms in 10 patients (24%).

Endoscopic Findings

Fourteen patients (30%) were noted to have improved endoscopic appearance by the second sigmoidoscopy. Table 1 compares several demographic, disease, and admission characteristics between patients with improved endoscopic findings and worsened endoscopic findings on the second sigmoidoscopy. Patients with improved inflammation were similar to those with worsening or persistent disease in prehospitalization medications, admission CRP ($P = 0.61$) and albumin levels ($P = 0.42$), and receiving anti-tumor necrosis factor (TNF) biologic medical rescue therapy during hospitalization ($P = 0.59$).

Outcomes in Patients With Endoscopic Improvement

None of the patients who had improvement on the second endoscopy underwent in-hospital colectomy, compared with 46% of those with worsening or persistent disease ($P = 0.002$). Among those who underwent in-hospital colectomy, 3 patients (19%) received oral steroid therapy before hospital admission ($P = 0.390$) and 1 patient (6%) received immunomodulator therapy ($P = 0.524$). In total, 5 patients (10%) failed biological

therapy before hospital admission, but only 1 of those patients underwent in-hospital colectomy ($P = 0.962$).

On multivariable analysis, adjusting for smoking CRP, albumin, and anti-TNF biologic medical rescue therapy, severe endoscopic findings on the first sigmoidoscopy were not independently associated with in-hospital colectomy (odds ratio [OR], 2.34; 95% confidence interval [CI], 0.66–8.23) or colectomy at 3 months (OR, 2.13; 95% CI, 0.64–7.13) or 6 months (OR, 2.48; 95% CI, 0.74–8.26). In contrast, persistent severe endoscopic findings on the second sigmoidoscopy were associated with in-hospital colectomy (OR, 26.25; 95% CI, 3.07–224.21; $P = 0.003$) and colectomy at 3 months (OR, 7.92; 95% CI, 1.89–33.24) and at 6 months (OR, 5.63; 95% CI, 1.50–21.10). Of the 15 patients who underwent in-hospital colectomy, 13 patients (87%) were experiencing persistent/worsening symptoms between the first and second endoscopic procedures, and 2 patients experienced only a partial improvement in symptoms. However, none of the patients who demonstrated an improvement in endoscopic appearance between the first and second sigmoidoscopies underwent colectomy, compared with 15 (46%) patients with persistent or worsening endoscopic appearance ($P = 0.002$). Similar differences with lower rates of

TABLE 1. Baseline Characteristics on Hospital Admission

Characteristic	Improved Endoscopic Findings (n = 14)	Persistent/Worsened Endoscopic Findings (n = 33)	P
Mean (SD) age, y	49.7 (5.8)	39.6 (3.4)	0.124
Female, No. (%)	8 (57.1)	17 (51.5)	0.724
Mean (SD) duration of IBD, y	5.2 (4.4)	4.4 (9.0)	0.743
Smoking status			0.133
Never smoking, No. (%)	7 (50.0)	24 (72.7)	
Ever smoking, No. (%)	7 (50.0)	9 (27.3)	
Mean (SD) number of bowel movements at admission over 24 h	15.5 (6.7)	15.3 (9.1)	0.961
UC extent			0.242
Limited colitis, No. (%)	3 (21.4)	7 (21.9)	
Pancolitis, No. (%)	11 (78.6)	25 (78.1)	
Prior hospitalization in past 3 mo, No. (%)	2 (14.3)	9 (27.3)	0.336
Medication at admission			
Oral steroids, No. (%)	10 (71.4)	24 (72.7)	0.927
Immunomodulator, No. (%)	2 (14.3)	2 (6.1)	0.355
Anti-TNF, No. (%)	4 (28.6)	4 (12.1)	0.170
Laboratory results at admission			
Mean CRP (SD), mg/dL	62.8 (61.7)	52.7 (45.9)	0.606
Mean white blood cell count (SD), /mm ³	10.3 (3.0)	12.4 (5.6)	0.203
Mean albumin (SD), g/L	3.3 (0.8)	3.1 (0.8)	0.422
CMV colitis at hospitalization, No. (%)	1 (7.1)	5 (15.2)	0.452
<i>Clostridium difficile</i> infection during admission, No. (%)	1 (7.1)	2 (6.1)	0.890
Anti-TNF rescue therapy during admission, No. (%)	6 (42.9)	17 (51.5)	0.587
Severe endoscopic findings at index sigmoidoscopy, No. (%)	7 (50.0)	18 (54.6)	0.775
Severe histologic inflammation at index sigmoidoscopy, No. (%)	5 (41.7)	15 (48.4)	0.692

colectomy in the improved group persisted at 3 months (7% vs 48%; $P = 0.007$) and 6 months (14% vs 48%; $P = 0.027$) (Fig. 1), though the differences were somewhat less striking at 12 months (Supplementary Table 1). Additional variables associated with in-hospital colectomy were low serum albumin ($P = 0.047$) and ever smoking ($P = 0.049$).

Histology

Table 2 presents a comparison of the histologic findings of the 2 endoscopic procedures. Histologic severity at the first endoscopy was associated with increased risk of colectomy in-hospital (OR, 3.8; 95% CI, 1.02–14.21), at 3 months (OR, 5.7; 95% CI, 1.51–21.57), and at 6 months (OR, 5.7; 95% CI, 1.51–21.57) when compared with those with nonsevere histologic disease. In contrast, histologic severity at the second endoscopic procedure was not independently associated with colectomy in-hospital ($P = 0.556$), at 3 months ($P = 0.218$), or at 6 months ($P = 0.123$).

Comparison With Patients Undergoing a Single Sigmoidoscopy

The control patients who underwent a single sigmoidoscopy were similar in age, gender, age at diagnosis, disease duration, and smoking status but were more likely to have limited UC extent ($P < 0.001$) and a shorter duration of hospital admission (8 vs 23 days; $P < 0.001$). Both groups were similar in severe disease on endoscopy (27% vs 24%; $P = 0.54$) and histology (20% vs 22%; $P = 0.96$). Among the hospitalized UC patients who underwent a single endoscopic procedure, 5 (10%) underwent in-hospital colectomy compared with 16 (33%) who underwent 2 endoscopic procedures, confirming that patients who underwent 2 procedures were a high-risk population of partial or nonresponders ($P = 0.014$). A longer time interval until in-hospital colectomy was noted in those who underwent 2 endoscopic procedures compared with those who underwent a single endoscopic procedure (24 vs 11 days; $P = 0.013$). However, there were no differences in long-term colectomy rates at 3 months ($P = 0.52$), 6 months ($P = 0.40$), and 1 year after discharge ($P = 0.21$).

Pooled Analysis of Cases and Controls: Endoscopic and Histologic Outcomes

To robustly examine the predictive value of endoscopic and histologic severity from the index colonoscopy, we pooled together both the cases and controls ($n = 98$). Among the entire cohort, histologic severity at the index sigmoidoscopic evaluation remained a significant predictor for in-hospital colectomy ($P = 0.012$) and colectomy at 3 months ($P = 0.004$), 6 months ($P = 0.004$), and 12 months ($P = 0.008$). Similarly, endoscopic severity showed a trend toward increased rates of colectomy at 6 months ($P = 0.067$) and 12 months ($P = 0.074$).

FIGURE 1. Likelihood of colectomy, stratified by change in endoscopic severity between index and second-look sigmoidoscopy.

DISCUSSION

The management of acute severe ulcerative colitis is complex. In particular, accurately predicting which patients are failing to respond to intravenous corticosteroids or medical rescue therapy and would need a colectomy is challenging. Although many predictive models have been developed,^{7–10} few have incorporated dynamic changes in objective disease severity, and those relying on biochemical changes (such as improvement in CRP) are only of moderate value.

In this retrospective study, we demonstrated that up to one-third of patients with partial or no improvement in symptoms who underwent a second sigmoidoscopic assessment at a median of 9 days after the first evaluation demonstrated endoscopic improvement, and that such patients had lower risk for

TABLE 2. Association Between Endoscopic and Histologic Severity at Index and Second-Look Sigmoidoscopy and Colectomy in Hospitalized Ulcerative Colitis Patients

	Odds Ratio (95% CI)	P
Colectomy during hospitalization		
Severe histology 1st endoscopy	3.80 (1.02–14.21)	0.047
Severe histology 2nd endoscopy	1.53 (0.37–6.25)	0.556
Colectomy at 3 mo		
Severe histology 1st endoscopy	5.70 (1.51–21.57)	0.010
Severe histology 2nd endoscopy	2.40 (0.60–9.67)	0.218
Colectomy at 6 mo		
Severe histology 1st endoscopy	5.70 (1.51–21.57)	0.010
Severe histology 2nd endoscopy	3.00 (0.74–12.13)	0.123

in-hospital colectomy and lower risk for colectomy up until 1 year; this is in comparison with those who demonstrated continued endoscopically severe inflammation, who were at a nearly 50% risk for colectomy within 6 months. These findings suggest that there may be value to repeat endoscopic assessment in the hospitalized UC population. Although a “second-look” endoscopy is not part of routine clinical care of hospitalized patients with ASUC, it has been extensively studied in upper gastrointestinal bleeding, particularly related to peptic ulcer.^{11–14} The effect of second-look endoscopy performed within 24–48 hours after therapeutic endoscopy has been shown to be useful in identifying patients who are at a lower risk of re-bleeding.^{15,16} Adding to the literature, our findings suggest that a second-look endoscopy may have value in a subset of patients with ASUC, identifying those who demonstrate early endoscopic improvement even in the setting of nonimprovement of symptoms. Such patients may be at a lower short- and medium-term risk of colectomy and could potentially benefit from escalation of medical therapy.

Our study also adds to the literature evaluating predictive value of endoscopic or histologic assessment at admission in the management of hospitalized patients with acute severe ulcerative colitis. Studies have evaluated the predictive value of endoscopic severity on initial sigmoidoscopic evaluation and subsequent disease outcomes. Jarnerot et al. found no significant association between endoscopic severity and response to infliximab therapy,¹⁷ whereas Monterubbianesi et al. identified that the presence of severe endoscopic lesions at admission, such as deep ulcerations or spontaneous bleeding, was an independent indicator for colectomy after infliximab salvage therapy.¹⁸ A French group reported that endoscopic findings at baseline did not change therapeutic decision-making, but they found a significant difference in colectomy rates between the patients with severe endoscopic lesions (71%) compared with patients without severe endoscopic findings (17%; $P < 0.001$).¹⁹ On multivariate analysis, the presence of at least 1 severe endoscopic lesion was an independent predictor of colectomy after cyclosporine salvage therapy (hazard ratio, 2.38; 95% CI, 1.80–3.14). Objective endoscopic scoring systems such as the Mayo Endoscopic Score (MES) and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) have been evaluated for their predictive value of the need for colectomy in ASUC.^{3, 20, 21} A retrospective study from China found that 80% of ASUC patients with a UCEIS score of ≥ 7 subsequently needed colectomy, regardless of medical rescue therapy.³ Also, the UCEIS score (sensitivity, 60.3%; specificity, 85.5%; cutoff value, 7 points) had a better prognostic accuracy in comparison with the MES (sensitivity, 89.2%; specificity, 43.6%; cutoff value, 3 points) in ASUC patients. Our findings are broadly consistent with this literature and add to the role of endoscopic evaluation by suggesting that endoscopic improvement, even within 2 weeks of the initial index endoscopic evaluation, was a predictor of better long-term outcomes and reduced need for colectomy.

There are few studies demonstrating an association between histologic severity in ASUC and its ability to predict colectomy. A small retrospective pediatric study reported that the presence of histologic ulceration ($P = 0.024$) and increased lymphoplasmacytic infiltrate ($P = 0.038$) was associated with need for colectomy.²² A prospective cohort study followed UC patients in endoscopic remission over time (median, 72 months) and found that histological remission better predicts lower rates of corticosteroid use and ASUC requiring hospitalization, whereas endoscopic mucosal healing did not.²³ These findings suggest that histologic findings outperformed endoscopic findings as a predictor for severe ulcerative colitis. Consistent with this is our observation that histological severity at the first endoscopy was the most robust predictor of in-hospital colectomy and rates of surgery up to 1 year after index hospitalization.

There are a few implications of our findings. We demonstrate that in a subset of patients with ASUC who underwent a second-look sigmoidoscopy due to persistent or partial symptom improvement, early endoscopic improvement may identify patients who are at a lower risk for colectomy. However, this does not suggest that all patients with ASUC should routinely undergo repeated sigmoidoscopic evaluations. Those who demonstrate consistent clinical and biochemical improvement may have a good outcome with continued medical therapy, whereas those with deteriorating clinical and biochemical markers may benefit from early colectomy. However, in others, where there is suspicion that clinical improvement (or lack thereof) is discordant with biochemical improvement, or where improvement is only partial, a second-look sigmoidoscopic evaluation may be helpful to identify patients who have already demonstrated an improvement and consequently are at lower risk for colectomy. As noninvasive tests like fecal calprotectin are incorporated more routinely in clinical care, it is likely that they will supplant the need for early re-look sigmoidoscopy. However, the dynamics and predictive value of day-to-day changes in fecal calprotectin in ASUC are still unknown, and further research is needed on this topic.

We readily acknowledge several limitations to our study. Our study was a single-center retrospective cohort study, and the number of patients was low and may have limited statistical power. Second, endoscopic and histologic findings were not objectively measured using standardized disease activity scores such as the UCEIS and MES. Future studies are needed to objectively examine endoscopic findings to systematically quantify improvement. Third, we did not have data on change in disease activity scores or inflammatory laboratory results as these were not systematically obtained at the same time points as the endoscopic evaluation and were available in only a small subset of patients, which precluded meaningful analysis. Fourth, the patients who underwent a second-look sigmoidoscopy were a selected subgroup of patients for whom the treating gastroenterologist determined that partial or nonimprovement in symptoms challenged the decision for colectomy. And last, due to

the retrospective study design, unmeasured confounders and the impact of missing data could have influenced our results.

In conclusion, our retrospective cohort study suggests that in a subset of patients, there may be a role for a second-look sigmoidoscopy in hospitalized patients with severe ulcerative colitis with partial clinical or biochemical response to steroids or medical rescue therapy. There is a need to systematically study which patients may benefit from such evaluation and may be able to avoid colectomy.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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