The effect of pre-admission immunosuppression on colectomy rates in acute severe ulcerative colitis

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Abstract

Background: Patients on immunosuppression at the time of acute severe ulcerative colitis have been suggested to be at a higher risk of colectomy than those who are treatment-naïve. The aim of this study was to examine the effect of immunosuppressive therapy on the risk of colectomy.

Method: We conducted a retrospective observational cohort study using prospective data examining the 30 day and 1 year colectomy rates of 200 consecutive patients with an index episode of acute severe ulcerative colitis as defined by the Truelove and Witts criteria.

Results: Immunosuppression on admission was shown not to increase colectomy rate at 30 days post-admission (immunomodulator: $p = 0.422$, oral steroids: $p = 0.555$). A total of 24 patients underwent colectomy between 30 days and 1 year. A three-fold higher risk of colectomy at 1 year was seen in those requiring an immunomodulator prior to the index admission compared with those started *de novo* during the index admission [41% *versus* 14% odds ratio (OR): 2.93 (1.19–7.24 $p = 0.016$)]. Factors most predictive of colectomy at 30 days were abdominal radiographic colonic dilation ≥5.5 cm, first presentation of ulcerative colitis, C-reactive protein ≥ 45 mg/l on day 3 of therapy and bowel frequency ≥8 on day 3.

Conclusion: The need for an immunomodulator prior to admission with acute severe ulcerative colitis increases the medium-term colectomy rate by three-fold at 1 year. Prospective studies are needed to confirm these findings and develop strategies to reduce the high risk in this subgroup of patients.

Keywords: immunosuppression, inflammatory bowel disease, outcomes research, ulcerative colitis

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Introduction

Acute severe ulcerative colitis (ASUC) is common, occurring in one in five patients with ulcerative colitis (UC) during their disease course and accounting for 75% of hospitalizations.[1] Of these patients 19–40% will come to colectomy after failing medical therapy.[2–4]

Over half the patients admitted with ASUC are on immunosuppressive therapy at the time of admission.[1,2] Respected authors in this field have suggested that patients on immunosuppressive therapy at the time of ASUC may be at higher risk for colectomy than immunosuppression-naïve patients but this has not been clearly demonstrated in the literature.[5,6] This study explores the question: is the outcome of a patient on oral steroids or an immunomodulator at the time of admission with ASUC comparable with patients naïve to these agents?

There is discordance in the literature regarding the effect of immunosuppression on ASUC on outcome. There are data to show that oral steroid

use prior to admission is associated with a higher colectomy rate but these are limited to a few studies and key confounders were not accounted for.[7,8] Immunomodulator treatment at the time of admission has not been demonstrated to significantly increase the colectomy rate in the majority of studies.[9–12] There is a single large retrospective study demonstrating a 24% higher 1-year colectomy rate in patients presenting with ASUC established on an immunomodulator compared with immunomodulator-naïve patients receiving ciclosporin rescue therapy.[13]

To address the discordance in outcome from previous studies we conducted a retrospective observational cohort study using prospective data to determine the colectomy rate at 30 days after admission in immunosuppressed *versus* non-immunosuppressed patients with ASUC. Those who avoided colectomy at 30 days were followed out to 1 year after admission to examine the medium-term effect of immunosuppression on outcome.

Methods

A retrospective observational cohort study was performed. The conduct of this study was approved by the Royal Brisbane and Women's Hospital (RBWH) Ethics Committee (HREC Reference number: HREC/14/QRBW/323). All patients provided written informed consent for this study. Data were collected prospectively on consecutive patients with their index ASUC episode managed at the RBWH (Brisbane, Australia), a metropolitan hospital providing secondary and tertiary care to the population of north Brisbane, and to surrounding regional areas from January 2000 to May 2014. All patients were followed by clinical outpatient review until 30 days after admission. Outcomes were analyzed at this point. By this time, patients had either undergone a colectomy or were censored. Patients who avoided colectomy at 30 days were followed out to 1 year to examine the effect of immunomodulators or oral steroids on medium-term colectomy rates.

Definitions

Immunosuppressive treatment prior to hospitalization
Immunomodulator therapy was defined as being on a stable dose of an immunomodulator for at least 4 months prior to admission. Oral steroid treatment was defined as oral prednisolone use of 40 mg for at least 5 days prior to admission.

Treatment response
Patients with a bowel frequency of <3 per day without blood on day 4 of intravenous steroids were considered to have a good response to steroids and completed a 5 day course. Patients with a bowel frequency of ≥8 bowel actions per day with or without blood or a bowel frequency of 3–8 per day with or without blood and C-reactive protein (CRP) > 45 ml/l assessed on day 4 of treatment were considered to have a suboptimal response and offered rescue therapy with infliximab or ciclosporin.

Case selection
Hospitalized patients aged ≥18 years old with an index episode of ASUC meeting Truelove and Witts criteria on admission with at least 1 year of follow up were included. The disease extent was defined as maximal endoscopic or radiographic extent of disease at the time of admission.[14] In addition all patients in this real-life cohort had to demonstrate a Mayo endoscopic score of ≥2 on their admission flexible sigmoidoscopy regardless of topical rectal therapy use. Abdominal radiographic colonic dilation was defined as a maximal transverse colon diameter ≥5.5 cm demonstrated on plain abdominal radiograph during the first 3 days of admission.[15,16] Patients who had received prior therapy with either infliximab or ciclosporin were excluded from the study. Patients with concomitant enteric infection were excluded from this study by stool analysis including *Clostridium difficile* toxin assay and immunohistochemistry for cytomegalovirus.

Inpatient management
Patients were treated with our department's standard protocol for management of ASUC including intravenous hydrocortisone 100 mg four times daily for 3–5 days with prophylactic heparin and close monitoring and replacement of electrolytes.[17] Patients with a suboptimal intravenous steroid response on day 4 of treatment were offered rescue therapy with ciclosporin infusion at 4 mg/kg (2000–2003) or 2 mg/kg (2003–2014) or a single infusion of infliximab at 5 mg/kg (2001–2014). Additional doses of infliximab were not administered within the 30 day period as was the evidence-based practice at the time of study.

The choice of rescue therapy was based on informed patient consent after a presentation of the best available evidence regarding the potential risks and benefits of both therapies at the time of admission. Patients not on an immunomodulator at the time of admission were commenced on azathioprine or mercaptopurine during the admission with dosing guided by therapeutic drug monitoring. Patient on an immunomodulator on admission were continued on the same drug throughout the study period. Patients who failed rescue therapy or developed complications of severe colitis (perforation, toxic megacolon, haemorrhage or multiple organ dysfunction) at any stage during their admission were referred for emergent colectomy.

Data collection and selection of laboratory parameter cutoffs

All data were prospectively collected and entered into our secure inflammatory bowel disease database. Clinical and laboratory parameters were assessed in a binary manner, using previously published thresholds in comparable cohorts of ASUC patients, with 0 referring to low risk, and 1 referring to high risk. The abdominal radiographic colonic diameter was defined as abnormal in this study as $\geqslant 5.5\,$cm, since this has been demonstrated in prior studies to correlate with medical therapy failure and colectomy.[2,18] A CRP level on day 3 of $\geqslant 45\,$mg/l was chosen as a cutoff as it is the key component of both the Oxford and Swedish indices predicting colectomy.[7,19,20] The same cutoff was used in evaluating CRP on day 1 in this study for consistency.

The number of bowel actions $\geqslant 8$ on day 3 has been strongly correlated with medical therapy failure and colectomy in multiple adult studies and a paediatric study.[7,19,20] Cutoffs for haemoglobin on admission ($<105\,$g/l) and erythrocyte sedimentation rate (ESR) on admission ($\geqslant 31\,$mm/h) were chosen as they are components of the Truelove and Witts criteria and have been shown to increase the colectomy rate if present on admission.[3] The cutoff for albumin on admission was chosen as $<30\,$g/l as it has been associated with intravenous steroid failure in previous studies.[2,18]

Data analysis

Demographic and clinical parameters of the cohort were compared between those who either had or did not have a colectomy at the 30-day and 1 year endpoints. Age at the time of admission was compared using the independent samples t test, disease duration was compared using the Mann–Whitney U test, all other parameters were compared using the Chi-square test. Odds ratios (ORs) and 95% confidence intervals (95% CIs) are presented to define effect sizes and estimated errors for each parameter to predict outcomes. Multivariate analyses were conducted using the stepAIC function with the Generalized Linear Model (binomial GLM) to ascertain the optimum combination of parameters associated with colectomy. Bonferroni correction was applied to the comparative alpha value, such that p-values were compared with an adjusted alpha [$\alpha = 0.05/K$ (K = number of characteristics tested), $0.05/18 = 0.00278$].

Assessing all possible parameters (demographic, clinical, radiographic and laboratory) in the multivariate setting using the stepAIC function (the stepAIC function reduces the model parameter space sequentially *via* optimal Akaike information criterion assessment), parameters were chosen linearly associated with colectomy (Table 1). While not all parameters have p-values less than the multivariate level of significance, each contribute to the likelihood of having a colectomy by the 30-day endpoint. Due to the low sample size of current smokers, those who were current smokers were combined with ex-smokers for this analysis. A total of 24 patients who had not undergone colectomy by day 30 were analyzed separately (Table 2). There were no significant associations between the parameters studied on admission with ASUC and colectomy at 1 year. Due to the low number of colectomies, further multivariate analysis was not performed. All statistical analyses were conducted using the R statistical software environment, version 3.2.3[21]

Results

Patient cohort

A total of 225 index admissions for ASUC were identified from January 2000 to May 2014. A comprehensive review of the cases resulted in 200 patients who met the inclusion criteria (89% of the cohort). Overall, 62 patients failed medical therapy and went on to colectomy within 30 days of admission (31%). A total of 22 patients

Table 1. Baseline demographics and univariate analysis. Outcome at 30 days.

Characteristic	No colectomy	Colectomy	OR (95% CI)	*p*-value
n	138	62		
Age				
Mean ± SD	36.24 (16.56)	40.45 (16.17)		0.093
Sex				
Male	74	23	Ref (1.0)	
Female	64	39	1.95 (1.06–3.65)	0.0306
Smoking status				
No	88	28	Ref (1.0)	
Previous	42	28	2.10 (1.10–3.97)	
Current	8	6	2.36 (0.74–7.38)	0.132
Disease duration (years)				
Median (IQR)	2 (7.3)	1 (3.5)		0.108
Disease extent				
E1/E2	52	12	Ref (1.0)	
E3	85	50	2.52 (1.25–5.38)	0.0093
Abdominal radiograph colonic diameter				
<5.5 cm	129	47	Ref (1.0)	
≥5.5 cm	9	15	4.51 (1.86–11.52)	0.0004
First presentation of UC				
No	112	37	Ref (1.0)	
Yes	26	25	2.89 (1.49–5.66)	0.0013
5-ASA on admission				
No	76	43	Ref (1.0)	
Yes	61	19	0.55 (0.29–1.04)	0.0644
Oral steroid on admission				
No	73	30	Ref (1.0)	
Yes	65	32	1.2 (0.65–2.19)	0.555
Immunomodulator on admission				
No	97	47	Ref (1.0)	
Yes	41	15	0.76 (0.37–1.49)	0.422
Bowel actions on Day 1				
6–7	31	8	Ref (1.0)	
≥8	107	54	1.93 (0.86–4.8)	0.1145
Bowel actions on Day 3				
<8	102	31	Ref (1.0)	
≥8	33	30	2.97 (1.57–5.67)	0.0006
CRP on Day 1				
<45 mg/l	63	21	Ref (1.0)	
≥45 mg/l	73	40	1.64 (0.88–3.11)	0.1185

Table 1. (continued)

Characteristic	No colectomy	Colectomy	OR (95% CI)	*p*-value
CRP on Day 3				
<45 mg/l	109	35	Ref (1.0)	
≥45 mg/l	28	26	2.87 (1.49–5.58)	0.0012
ESR on Day 1				
<31 mm/h	30	6	Ref (1.0)	
≥31 mm/h	73	40	2.68 (1.08–7.73)	0.0341
Albumin Day 1				
≥30 g/l	86	29	Ref (1.0)	
<30 g/l	52	33	1.87 (1.02–3.46)	0.0397
Haemoglobin on Day 1				
≥105 g/l	101	45	Ref (1.0)	
<105 g/l	37	17	0.97 (0.49–1.90)	0.9666

5-ASA, aminosalicylates; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; OR, odds ratio; SD, standard deviation; UC, ulcerative colitis.

Table 2. Patients that avoided colectomy at 30 days. Outcome at 1 year.

Characteristic	All	No colectomy	Colectomy	OR (95% CI)	*p*-value
n	138	114	24		
Age					
Mean ± SD	36.2 (16.6)	36.03 (16.79)	37.25 (15.68)		0.734
Sex					
Male	74	63	11	Ref (1.0)	
Female	64	51	13	1.45 (0.59–3.61)	0.3998
Smoking status					
No	88	71	17	Ref (1.0)	
Previous	42	35	7	0.97 (0.44–2.15)	
Current	8	8	0	–	0.382
Disease duration (years)					
Median (IQR)	2 (7.3)	2 (8.02)	2.08 (3.62)		0.298
Disease extent					
E1/E2	52	44	8	Ref (1.0)	
E3	85	69	16	1.26 (0.51–3.39)	0.6073
Radiographic colonic dilation					
<5.5 cm	129	109	20	Ref (1.0)	
≥5.5 cm	9	5	4	4.32 (0.95–18.41)	0.0268
First presentation of UC					
No	112	93	19	Ref (1.0)	
Yes	26	21	5	1.18 (0.35–3.39)	0.7836

(Continued)

Table 2. (continued)

Characteristic	All	No colectomy	Colectomy	OR (95% CI)	*p*-value
5-ASA on admission					
No	76	60	16	Ref (1.0)	
Yes	61	53	8	0.57 (0.21–1.43)	0.2245
Oral steroid on admission					
No	73	64	9	Ref (1.0)	
Yes	65	50	15	2.13 (0.86–5.28)	0.151
Immunomodulator status					
Started during admission	97	85	12	Ref (1.0)	
Started prior to admission	41	29	12	2.93 (1.19–7.24)	0.0167
Bowel actions on Day 1					
6–7	31	26	5	Ref (1.0)	
≥8	107	88	19	1.1 (0.39–3.66)	0.8332
Bowel actions on Day 3					
<8	102	87	15	Ref (1.0)	
≥8	33	25	8	1.86 (0.67–4.86)	0.2053
CRP on Day 1					
<45 mg/l	63	49	14	Ref (1.0)	
≥45 mg/l	73	64	9	0.5 (0.19–1.24)	0.1248
CRP on Day 3					
<45 mg/l	109	89	20	Ref (1.0)	
≥45 mg/l	28	24	4	0.76 (0.2–2.29)	0.6139
ESR on Day 1					
<31 mm/h	30	21	9	Ref (1.0)	
≥31 mm/h	73	64	9	0.33 (0.11–0.97)	0.0319
Albumin Day 1					
≥30 g/l	86	69	17	Ref (1.0)	
<30 g/l	52	45	7	0.64 (0.23–1.63)	0.8212
Haemoglobin on Day 1					
≥105 g/l	101	82	19	Ref (1.0)	
<105 g/l	37	32	5	1.14 (0.38–3.43)	0.8212

5-ASA, aminosalicylates; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; OR, odds ratio; SD, standard deviation; UC, ulcerative colitis.

proceeded directly to colectomy after failing intravenous steroids due to complications from colitis. Rescue therapy was administered to 110 patients who failed intravenous steroids during the initial severe episode and was successful in avoiding colectomy in 72 patients (65.4%) at 30 days. A total of 46 patients received ciclosporin (41%) and 64 received infliximab (59%).

Impact of immunosuppressive therapy on colectomy rate at 30 days and at 1 year

At the time of admission 56 patients were on an immunomodulator: mercaptopurine (*n* = 18), azathioprine (*n* = 26), oral methotrexate, (*n* = 6), mycophenolate (*n* = 5), and thioguanine (*n* = 1). Those who were on an immunomodulator or oral steroid at the time of admission with ASUC

were at no increased risk for colectomy at 30 days (immunomodulator: $p = 0.422$, and oral steroids: $p = 0.555$). Excluding first presentations of UC which may be more treatment-responsive there was still no significant increased risk for colectomy in immunomodulator-treated or oral steroid-treated patients at 30 days ($p = 0.40$ and $p = 0.16$ respectively).

Of the 138 patients who avoided colectomy at 30 days after admission, 24 subsequently came to colectomy between 30 days and 1 year. A three-fold higher risk of colectomy was seen in patients requiring an immunomodulator prior to the index admission compared with those started *de novo* during the index admission [41% *versus* 14% OR: 2.93 (1.19–7.24) $p = 0.016$]. No significant effect for the need for oral steroids prior to admission was seen on the colectomy rate at 1 year ($p = 0.151$) as shown in Table 1.

Impact of immunosuppressive therapy on colectomy rate in the subgroup of patients requiring rescue therapy

There was no increased risk of short-term colectomy at 30 days when patients who were established on an immunomodulator at admission were given rescue therapy with infliximab compared with those given ciclosporin ($p = 0.56$). Patients established on an immunomodulator at the time of admission requiring rescue therapy with ciclosporin or infliximab showed no additional risk for colectomy at 1 year compared with patients naïve to an immunomodulator on presentation. [ciclosporin: OR 1.63 (95% CI: 0.41–6.51 $p = 0.49$) and infliximab: OR 0.26 (95% CI: 0.05–1.30 $p = 0.09$)]. In addition, patients who required rescue therapy during the index admission but avoided colectomy at 30 days were stratified by immunomodulator status prior to admission and rescue therapy type. No significant association was found between immunomodulator status or rescue therapy type (infliximab or ciclosporin) and the 1 year colectomy rate in this subgroup (ciclosporin $p = 0.058$ and infliximab $p = 0.05$).

Univariate and multivariate analysis of clinical, radiographic and laboratory parameters

Results from the univariate analyses are shown in Table 2. There was no significant difference in the mean age or median disease duration for those patients who had a colectomy as compared with those that did not ($p = 0.093$ and 0.108 respectively). There were slightly more females in the colectomy group ($p = 0.031$).

In relation to predictors of colectomy at 30 days of the laboratory parameters only CRP ≥ 45 mg/l on day 3 ($p = 0.01$) remained significant after adjustment for multiple comparisons. ESR > 31 mm/h ($p = 0.03$) and albumin < 30 g/l on day 1 ($p = 0.04$) though not significant after adjustment for multiple comparisons, were still moderately associated with colectomy at the nominal significance level (see Table 2).

The four parameters found on univariate analysis predicting colectomy at 30 days were retained in the multivariate model (Table 3). Of these, abdominal radiograph colonic diameter ≥5.5 cm and first presentation of UC were the strongest [OR 4.56 (95% CI: 1.76–11.85), and OR 2.75 (95% CI: 1.34–5.67) respectively]. No parameters on admission were predictive of colectomy at 1 year.

Discussion

In our study we assessed the effect of immunosuppression status at the time of hospitalization on the outcome of ASUC in the largest cohort of patients to date examined in this regard. In following 200 consecutive ASUC patients admitted over a 14-year period we have demonstrated that immunosuppressive use prior to admission does not significantly increase the short-term risk of colectomy at 30 days but immunomodulator status does affect the medium-term colectomy rate. Patients requiring an immunomodulator prior to admission were three times more likely to come to colectomy at 1 year compared with those started *de novo* during the admission with ASUC. In addition, we found that patients requiring an immunomodulator prior to admission and needing rescue therapy with infliximab or ciclosporin were at no additional risk for colectomy compared with patients naïve to treatment with an immunomodulator.

A single retrospective study reported that in patients with moderate to severe steroid-refractory UC, prior oral steroid use existed in 70% of patients undergoing colectomy compared with 42% who avoided colectomy.[7] Consistent with our findings when further analysis was performed in that study, oral steroid use prior to admission was not a predictor of colectomy, whereas the number of bowel actions and the CRP level on day 3 were predictive of colectomy at 30 days.[7]

Table 3. Multivariate analysis of variables associated with colectomy at 30 days.

Characteristic	OR (95% CI)	*p*-value
Abdominal radiograph colonic diameter		
<5.5 cm	Ref (1.0)	
≥5.5 cm	4.56 (1.76–11.85)	0.002
First presentation of UC		
No	Ref (1.0)	
Yes	2.75 (1.34–5.67)	0.006
CRP on Day 3		
<45 mg/l	Ref (1.0)	
≥45 mg/l	2.43 (1.19–4.97)	0.015
Bowel actions Day 3		
<8	Ref (1.0)	
≥8	2.11 (1.06–4.18)	0.033
Smoker		
No	Ref (1.0)	0.041
Yes (previous and current)	2.01 (1.03–3.93)	

CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; UC, ulcerative colitis.

There is a paucity of published data examining the effect of immunomodulator therapy on the ASUC population overall. This is likely due to the small numbers of patients on this treatment (8%) who subsequently develop ASUC and is a testament to its protective effects.[2] Multiple studies including two controlled trials have shown that treatment with these agents can reduce or eliminate steroid use over time and maintain long-term steroid-free remission in UC.[22–26] The immunomodulator, azathioprine, used in combination with infliximab therapy in moderate to severe UC outpatients has also been demonstrated to increase clinical remission, clinical response and mucosal healing when compared with infliximab or azathioprine monotherapy.[27]

No studies however, have looked at the outcomes of an entire cohort of ASUC established on immunosuppressive treatment at the time of admission. Studies have investigated the effect of prior immunomodulator use on the outcome of intravenous steroid-refractory patients receiving rescue therapy. In these studies, subanalysis with small numbers all showed no significant increase in colectomy rate when infliximab was used as a rescue therapy.[10–12] When looking at ciclosporin-treated patients, two subanalyses, including one study with prospective data, showed no significant increase in colectomy rate in patients already established on an immunomodulator (azathioprine) compared with immunomodulator-naïve patients.[9,10]

There is a single study demonstrating a higher colectomy rate in patients established on immunomodulator therapy prior to an ASUC episode requiring rescue therapy. This large retrospective study by Moskovitz and colleagues, found patients receiving ciclosporin rescue therapy demonstrated a higher 1-year colectomy rate if already on the immunomodulator azathioprine prior to admission (59%) compared with those starting azathioprine *de novo* at the time of rescue therapy

(35%).[13] In our study we found agreement in the higher risk for colectomy at 1 year in those patients established on an immunomodulator prior to admission *versus* those started *de novo* during admission (43% *versus* 14%). However, we differed with respect to outcomes in those requiring rescue therapies. Our cohort shows no difference in colectomy rates in patients requiring either ciclosporin or infliximab rescue and when comparing those who are established on an immunomodulator with those who are started on the immunomodulator during the admission.

This Moskovitz and colleagues paper looked exclusively at ciclosporin rescue and immunomodulator use and concluded that this combination was responsible for the higher colectomy rate. From our data, the higher colectomy rate is related to a more medically refractory subgroup of patients rather than that in which a combination of an immunomodulator and biologic therapy is selected.

In our study, results from multiple logistic regression analysis confirmed some of the key parameters which can assist stratify a patient as high risk for colectomy at 30 days after admission. Abdominal radiographic colonic dilation ≥ 5.5 cm, first presentation of UC, CRP ≥ 45 mg/l on day 3 and bowel frequency ≥ 8 on day 3 of treatment predicted the need for colectomy after the initial ASUC episode.[2,7,18,19]

We identified the first presentation of UC as a risk factor for colectomy in our cohort. The first presentation of UC with ASUC was seen in 25% of our cohort, which is marginally lower than the 34–48% described in similarly defined cohorts[2,3,20] There are limited published data that include this variable in the risk factors for colectomy after ASUC. Ho and colleagues (2004) included this variable but found no significant increase in the colectomy rate ($p = 0.13$).[1] Factors that may be implicated in explaining this risk factor include any delays in diagnosis and in the introduction of appropriate medical therapy.

There are limitations to this study. Firstly, although prospective data are used, this is a real-life study and the data analysis is retrospective, which is a limitation. The results should ideally be confirmed in a prospective manner but given the difficulty in performing this sort of study with a large sample size, this is unlikely to occur. Further to this point, due to the real-life nature of this cohort, no formal matching was attempted between the naïve and treated patient groups, introducing the possibility of selection bias in this cohort of patients, which is a limitation of observational studies. Rescue therapy with infliximab was limited to a single infusion during the study period which is less intensive when compared with current infliximab rescue regimens. Despite this, only 17% of patients requiring rescue therapy during their admission went on to colectomy between discharge and 12 months.

Sample size is often a potential issue when investigating subgroups of patients based on treatment received. However, this is one of the largest ASUC studies to date and is a consecutive series of cases that provides extensive real-life data.

An additional finding in our study is that patients established on an immunomodulator show no increased risk of colectomy when given ciclosporin rescue therapy compared with immunomodulator-naïve patients, and if clinically indicated, this option should not be avoided for that reason.

Patients with the following key parameters: abdominal radiographic colonic dilation ≥ 5.5 cm, first presentation of UC, CRP ≥ 45 mg/l on day 3 or a bowel frequency ≥ 8 per day on day 3, should be considered high risk for short-term colectomy and have rescue therapy discussed and given early along with a stomal therapist and colorectal surgery consultation.

The results of this study have implications for clinical practice. Immunosuppressive therapy prior to admission with ASUC does not increase the short-term risk of colectomy and cannot reliably identify patients at higher risk for medical therapy failure; this is best predicted by patient-related factors identified in this and previous similar studies. With regard to medium-term outcomes however, the need for an immunomodulator prior to ASUC identifies a subgroup of patients as more refractory to medical therapy with a three-fold higher risk of colectomy at 1 year. This fact should be discussed with patients to manage realistic expectations. Prospective studies in this area to confirm these findings and develop strategies to reduce the colectomy rate in this higher risk subgroup of patients are needed.

Conflict of interest statement
The authors declare that there is no conflict of interest.

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