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Effect of pre-admission immunosuppressive therapy and regional transfer versus metropolitan hospital presentation on colectomy rates in acute severe ulcerative colitis

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Abstract

Ulcerative colitis is a chronic idiopathic inflammatory disorder of the colon with a relapsing remitting course. It affects 40,000 Australian patients currently.[1] During their disease course 1 in 5 of these patients develop a severe episode of colitis requiring hospital admission and a significant proportion of them 19-40 % require resection of the colon to remain healthy.[2] The colectomy rate of acute severe ulcerative colitis (ASUC) continues to remain high despite significant advances in medical therapy over the last three decades. Risk stratification and optimal treatment strategy remain clinical challenges. It has been suggested by some authors that patients established on immunosuppressive therapy at the time of severe ulcerative colitis are a higher risk for colectomy than those not on treatment.[3] Over half the patients admitted for this condition are on treatment at the time of admission but the outcomes of these patients have not been well studied. In addition many patients are transferred to large tertiary metropolitan hospitals from smaller regional hospitals which lack inflammatory bowel disease or gastroenterology specialty input. The initial management of these patients is therefore undertaken in these regional hospitals and the effect of this on colectomy rates not currently known.

This thesis firstly aimed to identify whether being on immunosuppressive treatment at the time of admission with ASUC increases the risk of colectomy. Secondly this thesis aimed to compare the colectomy rates of ASUC patients presenting initially to regional with those presenting directly to a metropolitan tertiary hospital. We aimed to identify the driving factors for any inequality to allow development of strategies to improve the outcome of regional patients with this condition.

Our findings show that immunosuppressive therapy prior to admission with ASUC does not significantly increase the colectomy rate. Predictors of colectomy confirmed were colonic dilation $\geq$ 5.5cm, transfer from a regional hospital, CRP level $\geq$ 45 mg/ml on day 3 of admission, first presentation of ulcerative colitis and bowel action frequency $\geq$ 8 on day 3 of treatment. Knowledge of these key parameters allows the clinician to select high risk patients for early and aggressive rescue therapy, stomal therapist and colorectal surgeon review.

In regards to our second aim we found that regional transfer patients were three times as likely to undergo colectomy as patients presenting directly to our metropolitan hospital at 30 days post admission. The primary factor identified was poor response to intravenous steroids. Predictors of colectomy in regional transfer patients identified were bowel frequency $\geq$ 8 on day 3 and CRP $\geq$ 45 mg/L on day 3 of therapy.

Declaration by the Author

This thesis is composed of my original work and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole including statistical assistance, study design, data analysis, significant technical procedures, professional editorial advice and any other original research used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to quality for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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Publications during candidature

No publications

Publications included in this thesis

No publications included

Contributions by others to this thesis

This thesis is based on a large body of work which precedes it. The data is drawn from a prospective inflammatory bowel disease database set up by Associate Professor Graham Radford-Smith in 1996 and has been added to over the years by members of the inflammatory bowel disease team. Without these members adding prospective data the current observations about severe ulcerative colitis could not have been made. I would also like to acknowledge Associate Professor Graham Radford-Smith as my mentor for developing this projects study design and direction and for supervision and ongoing input into the evolution of the project for without this its completion would not have been possible.

Statement of parts of the thesis submitted to qualify for the award of another degree

None

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Keywords

Corticosteroids ; immunomodulator ; Ulcerative colitis ; Colectomy ; Regional

Australia and New Zealand Standard Research Classifications

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Fields of research (FoR) classification

FoR code:1103 Clinical sciences, 100%

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Abbreviations

5-ASA : 5-Aminosalicylic acid

ASUC: Acute severe ulcerative colitis

COPD : Chronic obstructive pulmonary disease

CRP : C-Reactive protein

ESR : Erythrocyte sedimentation rate

UC : Ulcerative colitis

Introduction

Acute severe ulcerative colitis (ASUC) is a life and colon threatening inflammatory condition with a high colectomy rate of 19-40 % stable over the last 30 years despite significant advances in medical management.[4] Intensive medical management in the modern era has reduced the mortality to 1-2 % in specialist centres but mortality can be significantly higher in non-specialist centres as evidenced by a review of a British district hospitals severe colitis patients in 2001 demonstrating six deaths in a six year period with a mortality of 24 %. [5 6]

ASUC occurs in 1 in 5 patients with ulcerative colitis (UC) during their disease course and accounts for 70 % of hospitalizations. [6, 7] In these patients 55 % are on treatment with oral corticosteroids or an immunomodulator at the time of admission.[6] Little data is available on the effect of treatment immediately prior to hospitalization on colectomy rate and none examining it using prospectively collected data. The first aim of this project examines the association between immunosuppression prior to admission and colectomy rate.

This issue is of key importance in the risk stratification process of patients being admitted with severe ulcerative colitis. A number of predictors of colectomy have been identified but the ability to predict the outcomes of individual patients still remains challenging. In 25 % of patients it is not possible to predict the outcome of the severe attack of colitis. Respected authors in this field have suggested that patients already receiving treatment at the time of a severe episode of ulcerative colitis may be at higher risk than patients not receiving treatment and thus could be treated more aggressively.[3] There are little data published on this and this was selected as the primary research question for the first aim of this project.

The second aim of this project looks at outcomes for patients with ASUC presenting first to a regional hospital and then being transferred to a metropolitan tertiary hospital part way through their care. As our geographical area of Queensland has a high land mass compared to population density there are significant barriers to optimal care including geographic isolation from medical specialists, patient and physician perception of illness severity and delayed patient presentation.[8] It would therefore be important to evaluate outcomes of these patients and if there is a significant difference in outcome to try and identify modifiable factors which could ensure better outcomes for regional patients with ASUC.

Colectomy rate in ASUC

The colectomy rate in comparable cohorts of acute severe ulcerative colitis patients defined by Truelove and Witt criteria is reported at 19 – 40 %. [9] [10, 11]

Effect of oral corticosteroids on colectomy rate

Oral corticosteroids are commonly prescribed to induce remission in active ulcerative colitis prior to admission as evidenced by the United Kingdom national clinical audit of inpatient care showing 33 % are on this treatment at time of admission. [6] Oral corticosteroid therapy although effective for induction of remission in mild-moderate cases of active ulcerative colitis is not particularly effective in inducing remission in severe ulcerative colitis. This was demonstrated by Kjeldsen at el in their 1993 review of 89 severe ulcerative colitis patients treated with oral prednisolone showing a remission rate of 47 % and colectomy rate 24 % at 2 years. This compares with mild-moderate patients in the same cohort which had high remission rates of > 80 % with oral steroids and lower colectomy rates of 3-13 % [12]

In a Korean study of moderate ulcerative colitis patients (less severe than our study population) who had failed oral corticosteroid therapy and went on to have intravenous steroid therapy 46 % of patients were in remission at 1 year and 42 % of patients could not achieve steroid free remission and steroid dependant with 9 % refractory to treatment at 1 year with no steroid response. Oral corticosteroid use > 14 days and Haemoglobin < 110 g/dl were identified as poor prognostic factors in this patient cohort. [13]

A large population based cohort study over 10 years following incident cases of ulcerative colitis found that patients requiring oral corticosteroid use soon after diagnosis were 2.9 times more likely to have a colectomy and 4.9 times more likely to be steroid dependant within 5 years than those who did not. [14]

No studies have looked directly at use of oral corticosteroids prior to admission with ASUC and colectomy rates after standard treatment with intravenous steroid and rescue therapy with infliximab or ciclosporin in case of intravenous steroid failure.

Effect of immunomodulators on colectomy rate

No studies have looked specifically at the effect of immunomodulator therapy on the colectomy rate of the ASUC patient population overall. Immunomodulators most notably the thiopurines (Azathioprine, Mercaptopurine and thioguanine) are effective agents in maintaining clinical and biochemical remission in patients who have had an episode of moderate-severe ulcerative colitis.[15] They are slow to act and therefore not useful in inducing remission in ASUC but appear to be effective in preventing relapse and maintain steroid free remission. Multiple prior studies including two controlled trials have shown that treatment with a thiopurine can reduce or eliminate steroid use over time and maintain long term steroid free remission. [16-20] In the landmark study by Pannacione et al thiopurine use in combination with infliximab therapy was demonstrated to increase clinical remission, clinical response and mucosal healing when compared with Infliximab or thiopurine monotherapy.[21]

No studies have looked at an overall cohort of ASUC patients to determine the effect of prior immunomodulator treatment. Multiple studies have however looked at the effect of prior immunomodulator use on the outcome of ASUC in intravenous steroid refractory ulcerative colitis receiving rescue therapy. In these studies sub-analysis with very small numbers showed no significant increase in colectomy rate when infliximab was used as rescue therapy. [22-24] A single large retrospective study looking at patients receiving cyclosporine rescue therapy by Moskowitz et al demonstrated a higher 1 year colectomy rate of 59 % in patients already on azathioprine compared to 35 % for those started azathioprine de novo at the time of rescue therapy with cyclosporine. [25]

Effect of regional versus metropolitan mode of presentation on colectomy rate

It is estimated that in Australia 1 in 10 inflammatory bowel disease patients lives in an outer regional or remote location which makes access to specialist healthcare challenging especially in a complex condition such as ulcerative colitis.[26] Queensland has a particular issue due to large land mass with 39 % of the total number of inflammatory bowel disease patients living in regional or remote Queensland. [26]

Poorer outcomes have been demonstrated in a number of chronic diseases in Australian rural and regional patients including asthma, COPD, post myocardial infarction and cancer related deaths of all causes.[27-29] It is likely that regional and rural inflammatory bowel disease patients may have similarly worse outcomes due to geographic isolation and lack of specialist care. In addition regional and rural patients may have their condition diagnosed later than metropolitan patients and may have optimal treatment delayed affected outcome.

An epidemiological study from the United Kingdom looking at patients admitted to a regional hospital with ASUC found a mortality of 9.2 % at 1 year and 20 % at 5 years. [30] There was no significant link between mortality and social deprivation, distance to hospital, urban/rural residence and geographic location. [30] The mortality in this study however is significantly higher than published mortality rates in specialist tertiary hospitals in the United Kingdom who have a 1-2 % mortality rate but consistent with other reports from United Kingdom regional hospitals. [6 5] There is other data showing that post-operative mortality is lowest in centres that perform a high volume of operations which also has relevance to the regional versus metropolitan issue in regard to ulcerative colitis and colectomy. [31]

There is epidemiological data from the United States examining over 20,000 ulcerative colitis patient admissions to hospital demonstrating that colectomy rates vary by race and geographic location. Hispanic and African American patients were more likely to undergo colectomy and have a longer delay between admission and colectomy compared to Caucasian patients. Colectomy rates varied by geographic location as well with patients in the west and Midwest undergoing colectomy 3 times more than patients in the Northeast.[32] In addition patients were more likely to undergo colectomy if admitted to an urban hospital rather than a rural, a larger hospital compared to a smaller hospital and a teaching hospital versus a non-teaching hospital. [32]

There are no direct studies looking at colectomy rates in regional versus metropolitan presenting patients with ASUC which this study hopes to address.

Hypotheses generation

From the review of literature it became apparent that there is a paucity of published data to guide clinical management of patients on immunosuppressive therapy presenting with acute severe ulcerative colitis. A large single center retrospective study even concluded that it could be harmful to administer rescue therapy with ciclosporin to patients failing intravenous steroids established on an immunomodulator, demonstrating a significantly worse outcome in terms of colectomy rates.[25] This has led many treatment algorithms to suggest avoiding ciclosporin rescue therapy in these patients. The rest of the evidence suggests no significant worsening in outcome which leaves clinicians in doubt when faced with such a patient.

In addition anecdotally when managing these patients there is the impression that they may be more difficult to treat than patients not on an immunosuppressant at the time of admission. This can lead to incorrect risk stratification and is based on clinical dogma rather than objective evidence of a poor outcome. Our hypothesis was that patients established on an immunosuppressive medication (either an immunomodulator or oral steroid) would be more difficult to treat and thus be more likely to fail medical therapy and come to colectomy.

In regards to outcomes of regional patients with severe ulcerative colitis the literature again is sparse. There is a single small cohort study from a British regional hospital demonstrating significantly increased peri-operative mortality in patients managed regionally compared to in large tertiary centers but there is no data in regards to colectomy rates. This issue has significance as many of our patients are transferred from regional hospitals over a vast area with the effect on their outcome unknown.

Statement of hypotheses

1. Patients on treatment with an immunomodulator or oral corticosteroid at the time of admission would be more refractory to treatment and more likely to fail medical therapy and come to colectomy than those naïve to immunosuppression.

2. Patients presenting to a regional hospital requiring transfer compared to those presenting to a metropolitan tertiary centre would have a higher colectomy rate at 30 days due to failure of initial intravenous steroid therapy

Projects aims

1. To determine using prospective data if immunosuppressive therapy prior to admission with severe colitis affects the colectomy rate at 30 days
2. To evaluate the effect of regional hospital transfer versus tertiary metropolitan hospital initial presentation on 30 day colectomy rate in patients with severe ulcerative colitis and identify any causative factors for any difference

Methodology

Data collection and entry

Data has been collected prospectively on consecutive patients with ASUC admitted to the Royal Brisbane and Women's hospital a tertiary referral centre from January 1996 – May 2014. Patients are identified by the inflammatory bowel disease team at the weekly inpatient meeting and a pre-defined list of variables entered by the inpatient medical team during their admission. This data is entered into a secure inflammatory bowel disease database "IBD Prime" under a research programme created by Associate Professor Graham Radford-Smith. A wide range of parameters has been collected over this time period including clinical, biochemical, genotypic, radiologic and endoscopic data a subset of which was used to examine the research questions in this thesis. Written informed consent was obtained from all patients included in this study and the study protocol approved by the Royal Brisbane and Women's hospital medical ethics committee.

20 parameters were collected which can be grouped into the following categories:

1. Medication use: Oral steroid, oral 5-ASA, Immunomodulator use for 4 months prior to admission.

2. Clinical phenotype : Age, gender, smoking status, disease duration, first presentation of ulcerative colitis status and extent of disease

3. Admission related data: Clinical parameters were collected and Laboratory parameters were accessed from the AUSLAB pathology system, radiology results were accessed from the PACS system. Parameters were collected on day 1- 3 of admission: ESR, CRP, Albumin, Haemoglobin, Temperature, Heart rate, Abdominal radiograph result, Details of rescue therapy if given and duration of intravenous steroid use. The inflammatory bowel disease database "IBD PRIME" was also cross referenced for any missing parameters not located in the systems listed above.

4. Outcome related data: Colectomy rate at 30 days post admission to RBWH

In patients transferred for care from regional hospitals all relevant clinical and laboratory data was requested and entered prospectively into our database for later analysis. Patients were followed up clinically until 30 days post discharge and their outcomes recorded. All prospectively collected data will then analysed retrospectively. Data was not collected in regards to mortality, length of stay or operative complications.

Cohort selection

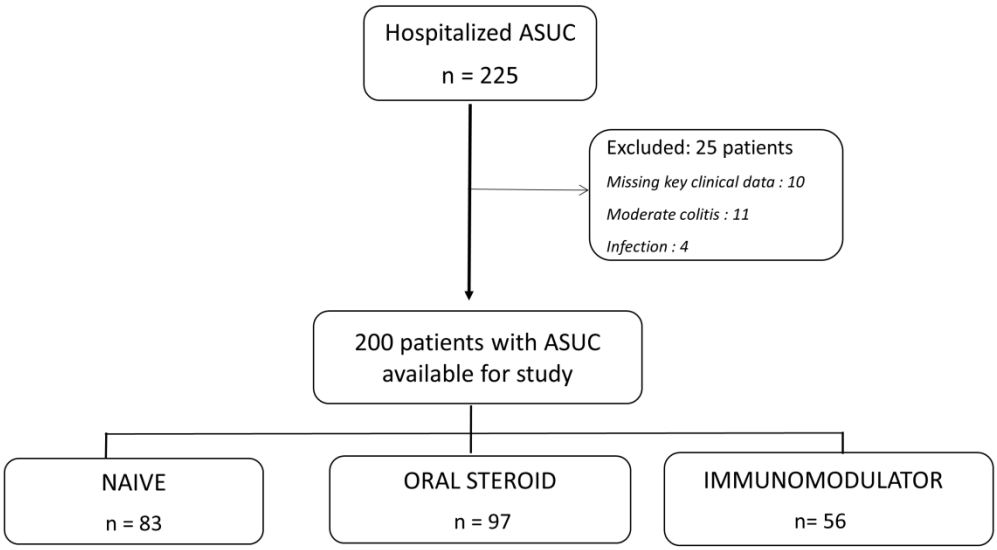
The severe ulcerative colitis patients in the study are a subset selected from a large cohort of inflammatory bowel disease patients which have been managed and had their data prospectively entered since 1996 after creation of the inflammatory bowel disease program at the Royal Brisbane and Women's hospital by Associate Professor Graham Radford-Smith. In this study cases were the index ASUC episode for each patient and therefore patient's subsequent admissions were not included.

Cohort size

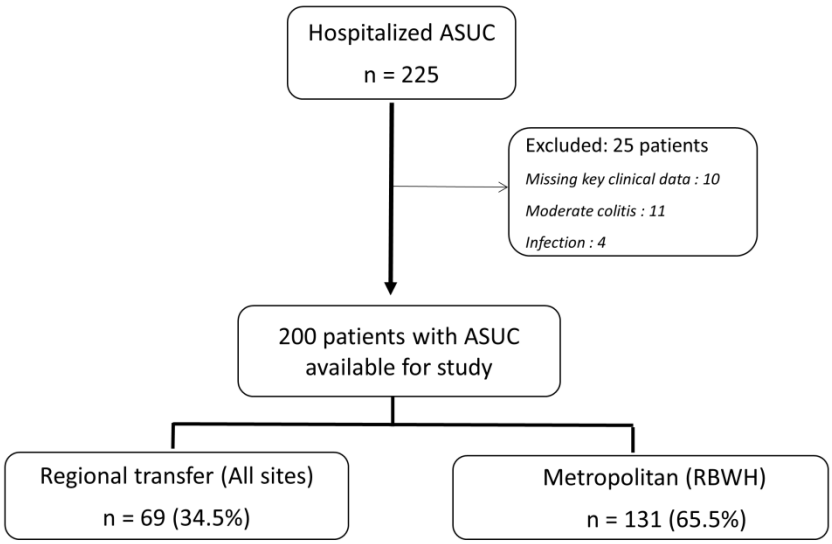
Our cohort size of 200 patients is determined by the number of patients who met our inclusion criteria. It is comparable to other cohorts of acute severe colitis published in the literature in terms of size and will be able to give an indication of the effect of treatment and mode of presentation on the outcomes of these patients. A calculation of statistical power was not performed as it would not have changed our approach as there is no capacity to increase the cohort size of a prospectively collected real life cohort of patients.

Cohort derivation

Aim 1



Aim 2



Statistical approach

Aim 1

Demographic and clinical parameters of the cohort were compared between those who either had or did not have a colectomy at the 30-day endpoint. Age at the time of admission was compared using the independent samples t-test, disease duration was compared using the Mann Whitney U test, while all other parameters were compared using the Chi-Square test. Odds ratio's (95% confidence intervals (95%CI)) are presented to define effect sizes and estimated error for each parameter to predict outcome. Multivariate analyses were conducted using the stepAIC function with the Generalised Linear Model (binomial GLM) to ascertain the optimum combination of biomarker associated with colectomy. Bonferroni correction was applied to the comparative alpha value, such that p-values were compared to an adjusted alpha (α=0.05/ K (K=number of characteristics tested), 0.05/18 = 0.00278). All statistical analyses were conducted using the R statistical environment Version 3.2.3[33]

Aim 2

Sample demographic and clinical parameters were assessed between metropolitan and regional groups. Laboratory parameters including bowel actions, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin and haemoglobin were assessed between colectomy/no colectomy at 30 days, stratified by whether patients initially presented to a metropolitan or regional hospital. Quantitative parameters were assessed either via the independent samples t-test or the Mann Whitney U test, while categorical factors were assessed with the Chi square test. Laboratory parameters were transformed into binary factors based upon previously defined thresholds. Adjustment for multiple comparisons was performed separately for metropolitan vs regional, and colectomy vs no colectomy comparisons, whereby the comparative alpha was divided by the number of parameters tested (origin: α=0.05/20 (0.0025), colectomy: α=0.05/7 (0.007)). All statistical analyses were performed using the R statistical environment (version 3.2.3).[33]

Rationale for pre-determined cut-off selection for laboratory and clinical values

Clinical and laboratory parameters were assessed in a binary manner, using previously published thresholds in comparable cohorts of ASUC patients, with a 0 referring to low risk, and 1 referring to high risk. This was approach was chosen was as the aim of this study was not to develop new predictive markers of colectomy but to examine the effect of immunosuppressive therapy and regional versus metropolitan hospital origin on colectomy rate. We chose the most effective and reproducible clinical and biochemical markers that have been demonstrated in the literature from similar ASUC cohorts as closely correlating with colectomy to demonstrate the effect of the variables of interest in this case immunosuppression and regional versus metropolitan hospital origin.

Manuscript (Aim 1): Pre-admission immunosuppression does not affect the outcome of acute severe ulcerative colitis

Significance of this study

What is already known on this subject?

- 19-40 % of patients still fail medical therapy and undergo early colectomy
- Risk stratification and prediction of medical therapy failure remain vital in the optimal management of acute severe ulcerative colitis (ASUC) to allow early rescue therapy administration and timely and frank discussions with colorectal surgeons
- Immunosuppressive treatment status on admission may help to guide risk stratification and selection of patients for early and more aggressive therapy but its effect on colectomy rate is currently unknown

What are the new findings?

- Immunosuppressive treatment with an immunomodulator or oral steroids prior to admission does not significantly increase the colectomy rate
- First presentation of UC is associated with a higher risk of colectomy than severe flares of known UC

How might it impact on clinical practice in the foreseeable future?

- Risk stratification based on baseline immunosuppression at the time of presentation with ASUC is not useful in predicting colectomy

- Patients should be selected for early and aggressive rescue therapy based on the high risk features confirmed in this study

Abstract

*Background and aims***:** Patients on immunosuppression at the time of ASUC 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 an observational cohort study examining the 30 day colectomy rate using prospective data on 200 consecutive patients with an index episode of acute severe ulcerative colitis defined by Truelove and Witts' criteria.

*Results***:** Immunosuppression on admission was shown not to be an important predictor of colectomy at 30 days post-admission (immunomodulator: P = 0.422, oral steroids: P= 0.555). Predictors of colectomy from multivariate analysis included: Colonic dilation ≥ 5.5 cm on abdominal radiograph: OR 4.0 (95 % CI: 1.46 – 10.96; P = 0.007), transfer from a regional hospital: OR 2.39 (95% CI 1.18 – 4.83; P = 0.016), CRP ≥ 45 mg/L on day 3: OR 2.41 (95% CI: 1.15 – 5.08; P = 0.02), first presentation of ulcerative colitis: OR 2.21 (95 % CI: 1.05 – 4.68; P = 0.037) and bowel frequency on day 3 ≥ 8: OR 2.1 (95 %CI: 1.03–4.29; P = 0.041).

Conclusion: Immunosuppression status on admission does not predict colectomy and cannot be used in risk stratification. Patients with the high risk features identified in this study should be selected for early and aggressive rescue therapy given their higher risk of early colectomy.

Ke*ywords*: Corticosteroids; Immunomodulator therapy ; Ulcerative colitis; Colectomy

Introduction

Acute severe ulcerative colitis (ASUC) is common, occurring in 1 in 5 patients with ulcerative colitis (UC) during their disease course and accounting for 75 % of hospitalizations.[34] Of these patients 19-40 % will come to colectomy after failing medical therapy.[10, 35, 36]

Over half the patients admitted with ASUC are taking immunosuppressive treatment at the time of admission.[34, 35] 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 immunosupression naïve patients.[3, 37] This study explores the question: Is the outcome of a patient treated oral steroids or immunomodulator therapy prior to admission comparable to a patient not on 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 this is limited to a few studies and key confounders were not accounted for. [14, 38] Immunomodulator treatment at the time of admission has not been demonstrated to significantly increase the colectomy rate in the majority of studies.[22-24, 39] There is a single large retrospective study demonstrating a 24 % higher one-year colectomy rate in patients presenting with ASUC established on an immunomodulator compared with immunomodulator-naïve patients receiving ciclosporin rescue therapy.[25] This issue requires clarification for clinicians assessing, risk-stratifying and treating patients with ASUC.

We hypothesized that patients already on immunosuppression at the time of hospitalization with ASUC would be more likely to fail medical therapy and require colectomy. Knowledge of the effect of immunosuppressive treatment on the outcome of ASUC would help clinicians to better risk stratify patients and personalize medical therapy to avoid colectomy. To address this clinical question we conducted a restrospective observational cohort study using prospective data to determine the colectomy rate at 30 days post-admission in immunosupressed versus non-immunosupresessed patients with ASUC.

Methods

A retrospective observational cohort study was conducted. Conduct of this study was approved by the Royal Brisbane and Women's Hospital (RBWH) Ethics Committee. All patients provided written informed consent. 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 from January 2000 – May 2014. All subjects were followed by clinical outpatient review until 30 days post admission. By this time, subjects had either undergone a colectomy or were censored.

Definitions

Immunosuppressive treatment prior to hospitalization

Immunomodulator therapy was defined as being on a stable dose of azathioprine, mercaptopurine, thioguanine, methotrexate or mycophenelate for at least 4 months prior to admission. Oral steroid treatment was defined as oral prednisolone use of 40mg for at least 5 days prior to admission.

Treatment response

Complete intravenous steroid response was defined as < 4 bowel actions per day without blood assessed on day 4 of intravenous steroid treatment. Incomplete intravenous steroid response was defined as ≥ 4 bowel actions per day with or without blood assessed on day 4 of treatment. Patients with < 4 bowel actions per day but with blood were considered incomplete intravenous steroid responders.

Case selection

Hospitalized patients aged ≥ 18 years old with an index episode of ASUC meeting Truelove and Witts' criteria on admission with at 30 days of follow-up were included. Disease extent was defined as maximal endoscopic or radiographic extent of disease at the time of admission.[40] In addition all patients had to demonstrate a Mayo endoscopic score of ≥ 2 on their admission flexible sigmoidoscopy. Abdominal radiographic colonic dilation was defined as maximal transverse colon diameter ≥ 5.5cm demonstrated on plain abdominal radiograph during the first 3 days of admission. [41, 42]. Patients who had received prior therapy with either infliximab or ciclosporin were excluded from the study. Patients with concomitant enteric infection as proven on stool microscopy and culture including clostridium difficile toxin were excluded from the study. (Figure 1)

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 during the admission (Figure 2).[43] This management protocol was consistent over the 14 years included in this study. Incomplete intravenous steroid responders on day 4 of treatment were treated with rescue therapy with ciclosporin infusion at 4 mg/kg (2000 -2003) or 2 mg/kg (2003-2014) or a single infusion of infliximab at 5mg/kg (2001-2014). Choice of rescue therapy was determined by the patient after being presented with an evidence based overview of the risks and benefits of the available options of infliximab and ciclosporin. The treating physician did not suggest a particular rescue therapy based on the severity of the case. Patients who failed medical 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. (Figure 2)

Data Collection

All data were prospectively collected and entered into our secure inflammatory bowel disease database. In the case of patients transferred for care from a regional hospital all relevant clinical and laboratory data were requested at the time of admission to our metropolitan hospital and entered at that time point.

Clinical and laboratory parameters were assessed in a binary manner, using previously published thresholds in comparable cohorts of ASUC patients, with a 0 referring to low risk, and 1 referring to high risk. Abdominal radiographic colonic diameter was defined as abnormal in this study as ≥ 5.5cm as this has been demonstrated in prior studies to correlate with medical therapy failure and colectomy.[35, 44] CRP on day 3 of ≥ 45 mg/L was chosen as a cut-off as it is the key component of both the Oxford and Swedish adult indexes for predicting colectomy.[11, 38, 45] The same cut-off was used in evaluating CRP on day 1 in this study for consistency.

Number of bowel actions ≥ 8 on day 3 has been strongly correlated with medical therapy failure and colectomy in multiple adult and a paediatric study.[11, 38, 45] Cut-offs for haemoglobin on admission (< 105 g/L) and ESR on admission (≥ 31 mm/hr) 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[10]. The cut-off for albumin on admission was chosen as < 30 g/L as it has been associated with intravenous steroid failure in previous studies.[35, 44]

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 endpoint. Age at the time of admission was compared using the independent samples t-test, disease duration was compared using the Mann Whitney U test, while all other parameters were compared using the Chi-Square test. Odds ratios (95% confidence intervals (95% CI) are presented to define effect sizes and estimated error for each parameter to predict outcome. Multivariate analyses were conducted using the stepAIC function with the Generalised 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 to an adjusted alpha (α = 0.05/ K (K = number of characteristics tested), 0.05/18 = 0.00278).

Assessing all possible parameters, (demographic, clinical and laboratory) in the multivariate setting using the stepAIC function (the stepAIC function reduces the model parameter space sequentially via optimal Akaike information criterion (AIC) assessment), seven parameters were chosen linearly associated with colectomy (Table 2). While not all parameters have p-values less than the nominal levels of significance, each contribute to the likelihood of having a colectomy by the 30-day endpoint. All statistical analyses were conducted using the R statistical environment version 3.2.3 [33]

Results

Patient cohort

A total of 225 index admissions of ASUC were identified from January 2000 to May 2014. Comprehensive review of the cases resulted in 200 patients who met the inclusion criteria (89 % of the cohort). Of these 131 (65.5 %) presented directly to the RBWH and 69 (34.5 %) were transferred for care after initial management in a regional hospital.

Overall 62 patients failed medical therapy and went on to colectomy within 30 days of admission (31 %). Twenty-two patients proceeded directly to colectomy after failing intravenous steroids (22%). Rescue therapy was administered to 113 patients (51 %) who failed intravenous steroids during the initial severe episode. Forty-six patients received ciclosporin (41%) and 67 received infliximab (59 %).

Univariate and multivariate analysis of clinical, radiographic and laboratory parameters

Results for the univariate analyses of demographic, clinical, radiographic and laboratory parameters are shown in Table 1. 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) and those that were ex-smokers were marginally less likely to have colectomy (P = 0.047).

For the clinical characteristics there were higher rates of colectomy for those patients with ≥ 8 bowel actions on day 3 (P = 0.0006), first presentation of UC (P = 0.001) and transfer from a regional hospital (P = 0.0006) which remained significant post adjustment for multiple comparisons. Extensive disease distribution was not significant post adjustment for multiple comparisons (P = 0.009). Those who were on an immunomodulator or oral steroid at the time of admission with ASUC were at no increased risk for colectomy (immunomodulator P = 0.422), oral steroids P = 0.555). Abdominal radiograph colonic diameter of ≥ 5.5cm remained predictive of colectomy post-adjustment for multiple comparisons (P = 0.0004)

Of the laboratory parameters, only bowel actions ≥ 8 per day and CRP ≥ 45 mg/L on day 3 (P = 0.001) remained significant post adjustment for multiple comparisons. Erythrocyte sedimentation rate (ESR) (P = 0.034) and albumin (P = 0.04) levels at day 1 although not significant post adjustment for multiple comparisons, were still moderately associated with colectomy at the nominal significance level.

Discussion

In our study we assessed the effect of immunosuppression prior to hospitalization on the outcome of ASUC in the largest cohort of patients to date examined in this regard. In reviewing 200 consecutive ASUC patients admitted over a 14-year period we have demonstrated that immunosuppressive use prior to admission does not significantly increase the risk of colectomy.

Selected patient-related parameters however were most important in determining their likelihood of medical therapy failure and colectomy. Our study demonstrates no significant association between immunosuppression with oral steroid or immunomodulator therapy prior to admission and risk of colectomy. A single retrospective study reported that in intravenous steroid-refractory *moderate-severe* ulcerative colitis patients, prior oral steroid use existed in 70 % of patients undergoing colectomy compared with 42 % who avoided colectomy.[38] 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* CRP level on day 3 were predictive of colectomy at 30 days.[38]

There is a paucity of published data examining the effect of immunomodulator therapy on the ASUC population overall with little to guide clinical management of patients established on these medications at time of presentation. 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.[35] 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. [16-20] The immunomodulator azathioprine used in combination with infliximab therapy in *moderate-severe* ulcerative colitis outpatients has also been demonstrated to increase clinical remission, clinical response and mucosal healing when compared with infliximab or thiopurine monotherapy.[21]

Although no studies have looked at an entire cohort of ASUC patients to determine the effect of immunosupressive treatment, studies have investigated the effect of prior immunomodulator use on the outcome of intravenous steroid-refractory patients receiving rescue therapy. In these studies, sub-analysis with small numbers all showed no significant increase in colectomy rate when infliximab was used as rescue therapy. [22-24] When looking at ciclosporin treated patients two sub-analyses 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.[39] [24]

There is a single study demonstrating a higher colectomy rate in patients established on immunomodulator therapy prior to an ASUC episode requiring rescue therapy. A large retrospective study by Moskovitz *et al.* found patients receiving ciclosporin rescue therapy demonstrated a higher 1-year colectomy rate if already on an immunomodulator (azathioprine) (59 %) compared to those starting azathioprine de novo at the time of rescue therapy (35 %). [25] Our results differ from the Moskovitz *et al*. study and agree with the majority of published literature.[22-24, 39] The Moskovitz *et al* study gives valuable insights into the use of ciclosporin for this indication, however we notice that several potential confounders were not addressed in their comparison of immunomodulator experienced and de novo patients.[25] These include the presence or absence of abdominal radiographic colonic dilation, bowel frequency on day 3 and CRP level on day 3, all of which are strong predictors of colectomy and would likely have influenced the outcome more so than treatment with an immunomodulator.

In our study results from multiple logistic regression analysis confirmed several key parameters which can stratify a patient as high risk for colectomy at 30 days post-admission. Abdominal radiographic colonic dilation ≥ 5.5 cm, transfer from a regional hospital, CRP > 45 mg/L on day 3, first presentation of UC and bowel frequency of ≥ 8 on day 3 of treatment predicted the need for colectomy post-index ASUC episode. Abdominal radiographic colonic dilation, bowel frequency ≥ 8 on day 3 and CRP ≥ 45 mg/L on day 3 of treatment successfully replicate the findings of previous studies of colectomy predictors in ASUC.[35, 38, 44, 45] A trend towards lower colectomy rates were seen in patients on an oral 5-ASA at the time of admission compared to those who were not (23.7 % vs. 36.1 $p = 0.06$).

Patients admitted to hospital with ASUC as their first presentation of ulcerative colitis were at higher risk for colectomy than those admitted with a severe flare of established disease in our cohort. First presentation with ASUC was seen in 25 % of our cohort which is marginally lower than the 34-48 % described in similarly defined cohorts [10, 11, 35] Our results differ from previous studies of similar cohorts in the modern era that show no significant increase risk of colectomy during the first presentation of UC.[7, 10, 35] We postulate this may be due to diagnostic and treatment delays in patients presenting to our regional referring hospitals (all with no gastroenterologist during the study period) leading to a prolonged bout of colitis, which may adversely affect rescue with medical therapy.

There are several limitations to this study. Firstly this is a real life study and therefore the patients could not be randomized into the various immunosuppressive treatment groups prior to admission. This introduces the possibility of selection bias as the more unwell patients potentially end up on immunosuppression. Also 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. There is also the possibility that the sample size was inadequate to detect a difference in colectomy rate between the different treatment regimes. As a real life cohort we had no capacity to increase the number of patients studied.

The results of this study demonstrate that immunosuppressive use prior to admission with ASUC does not increase the risk of colectomy and cannot reliably identify patients at higher risk for medical therapy failure. Patients with the following key parameters: abdominal radiographic colonic dilation $\geq$ 5.5cm, transfer from a regional hospital, CRP $\geq$ 45 mg/L on day 3, first presentation of ulcerative colitis or a bowel frequency $\geq$ 8 per day on day 3, should be considered high risk for colectomy and have rescue therapy discussed and given early along with stomal therapist and colorectal surgery consultation.

Funding interests

None

Conflicts of interest

None

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Table 1: Baseline demographics and univariate analysis

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
Gender				
Male	74	23	ref (1.0)	
Female	64	39	1.95 (1.06 - 3.65)	0.0306
Smoking status				
Never	88	28	ref (1.0)	
Ex	42	28	0.48 (0.25 - 0.91)	
Current	8	6	0.42 (0.14 - 1.33)	0.047
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				
< 5.5cm	129	47	ref (1.0)	
≥ 5.5cm	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
Origin of initial presentation				
Metropolitan hospital (RBWH)	101	30	ref (1.0)	
Regional hospital (All sites)	37	32	2.89 (1.55 - 5.45)	0.0006
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
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/hr	30	6	ref (1.0)	
≥ 31 mm/hr	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

Table 2: Multivariate analysis of variables associated with colectomy

Characteristic	OR (95%CI)	p-
Abdominal radiograph colonic diameter		
< 5.5cm	ref (1.0)	
≥ 5.5cm	4.0 (1.46 -	0.007
Origin		
Metropolitan hospital (RBWH)	ref (1.0)	
Regional hospital (All sites)	2.39 (1.18 -	0.016
CRP on Day 3		
< 45 mg/L	ref (1.0)	
≥ 45 mg/L	2.41 (1.15 -	0.02
First presentation of UC		
No	ref (1.0)	
Yes	2.21 (1.05 -	0.037
Bowel actions on Day 3		
< 8	ref (1.0)	
≥ 8	2.1 (1.03 - 4.29)	0.041
Age at presentation	1.02 (1 - 1.04)	0.084
Disease Extent		
E1/E2	ref (1.0)	
E3	2.26 (1 - 5.11)	0.051

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Manuscript (Aim 2): Regional transfer patients are three times as likely to undergo colectomy compared with metropolitan patients with acute severe ulcerative colitis

Significance of this study

What is already known on this subject?

- Patients are commonly transferred from regional hospitals with acute severe ulcerative colitis (ASUC) not responding to medical therapy for further management. A higher mortality and rate of peri-operative complications has been demonstrated in regionally managed ASUC in the literature but no data on colectomy rates.

What are the new findings?

- Patients transferred from a regional hospital have three times the risk of colectomy at 30 days post admission compared with metropolitan presenting patients with ASUC

- Intravenous steroid failure is high in the regional transfer cohort of patients compared with metropolitan presenting patients. Regional transfer patients with ASUC are more likely to have significant hypoalbuminemia, be first presentations of ulcerative colitis, have a shorter disease duration and more extensive disease distribution

- Bowel frequency $\geq$ 8 on day 3 and CRP $\geq$ 45 mg/L on day 3 are confirmed to predict colectomy in this high risk group of regional transfer patients with ASUC

How might it impact on clinical practice in the foreseeable future?

- Patients with either a UC flare or a new presentation admitted to regional hospitals without a gastroenterologist should be discussed with the nearest specialist IBD unit within the first 24 hours of admission. This allows for risk stratification and management according to an evidence-based algorithm with high risk patients receiving earlier specialized and more intensive treatment to improve their outcomes.

- Following case discussion with an IBD centre, regional hospital patients satisfying the criteria for an acute, severe attack should be promptly transferred to the nearest tertiary hospital with an IBD and colorectal surgical team, for intensive medical therapy, which may include rescue therapy and/or surgery.

Abstract

Background and aims: Patients are commonly transferred from regional to metropolitan hospitals with acute severe ulcerative colitis (ASUC) not responding to initial medical management for further care. We aimed to compare the colectomy rates and baseline characteristics of ASUC patients presenting directly to the front door of our metropolitan hospital versus patients transferred in from regional hospitals.

Method: An observational cohort study was conducted in a tertiary referral metropolitan hospital to examine the 30 day colectomy rate in metropolitan versus regional transfer patients using prospectively collected data on 200 consecutive index ASUC patients meeting Truelove and Witts criteria.

Results: The 30 day colectomy rate was 46.4 % (32/69) in regional transfer patients compared with 22.9 % (30/131) in metropolitan presenting patients (p = 0.0006). Complete intravenous steroid response was seen in 21.7 % (15/69) of regional transfer patients versus 42 % (55/131) (p = 0.004) in metropolitan presenting patients. There was trend towards poorer rescue therapy success at 30 days in regional transfer patients 55 % (25/45) compared with metropolitan patients 71 % (47/66) (p = 0.069). Predictors of high risk of colectomy in regional transfer patients were bowel actions ≥ 8 per day on day 3 (p = 0.003) and CRP ≥ 45 mg/L on day 3 (p = 0.003).

Conclusion: Regional transfer patients have a three-fold increased risk of colectomy at 30 days compared with metropolitan patients, driven by more severe disease and hence a lower intravenous steroid and rescue therapy response. An agreed model of care for regional ASUC patients between regional and metropolitan centers, including day 1 communication, appropriate patient transfer, and early intensive, multidisciplinary care in a metropolitan center, may improve the outcomes for these patients.

Keywords: Regional; Rescue therapy; Ulcerative colitis; Colectomy

Introduction

Acute severe ulcerative colitis (ASUC) is a major, potentially life-threatening complication of inflammatory bowel disease (IBD). The overall response to intravenous corticosteroid therapy has plateaued at between 60 and 70%[1], while the colectomy rate in this severe subgroup is between 30 and 40%[2,3]. Mortality is 1-3% across all types of hospitals, significantly driven by older age at presentation[4]. The availability of rescue therapy with either ciclosporin or infliximab has reduced the short-term colectomy rate, but long term results are less impressive [5,6].

Many incident and prevalent IBD patients live in regional or rural areas and those who develop severe symptoms may present to their local hospitals for initial assessment and investigation. A proportion of these are transferred to a metropolitan tertiary hospital for specialized, intensive care but their outcomes are not described in the literature. Many regional and rural hospitals lack a gastroenterologist and hence are not familiar with the highly specialized care required for patients with ASUC.[46] The impact of this lack of direct access to specialized IBD care is currently not known specifically with respect to the outcomes of ASUC patients presenting to regional and rural hospitals.

Higher mortality has been demonstrated in the past with case series from regional hospitals managing ASUC in the United Kingdom as high as 24 %. [5, 30, 34] There are also data from the United States demonstrating higher post-operative mortality and morbidity for patients having colectomy for ulcerative colitis performed in low volume surgical centers.[5, 31] Significantly different colectomy rates for hospitalized ulcerative colitis patients in the United States have been demonstrated in regional and rural patients depending on their geographic location, insurance status, ethnicity and hospital type.[32]

This raises the question: Does where a patient lives affect their access to appropriate care and their eventual outcome if they present with ASUC? Our inflammatory bowel disease unit, like many around the world, strongly encourages the referral of all IBD patients living in regional and rural areas where there is no direct access to specialized IBD and surgical care.

Regional and rural disparity in patient outcomes has been well demonstrated in a number of non-gastrointestinal chronic diseases including asthma, chronic obstructive pulmonary disease, myocardial infarction and cancer related deaths of all types.[27-29] Given the vast geographic distances in regional and rural Australia as in many countries across the world, residential location may be a major factor in ASUC patients gaining access to appropriate and timely medical therapy leading to potentially avoidable colectomies. Many regional and rural UC patients have no local access to a gastroenterologist which may result in delayed recognition of the condition, delayed identification of a severe episode and delayed initiation of optimal therapy, all of which impact on outcome.[1] In Australia this issue is of particular relevance as under our pharmaceutical benefits scheme a gastroenterologist or consultant physician specializing in gastroenterology is required to prescribe rescue therapy with a biologic agent.

No studies to date have compared the colectomy rate in patients presenting with ASUC and living in a regional or rural area as compared to those living in a metropolitan area. To address this and identify any modifiable factors to improve outcome, we performed a retrospective observational cohort study using prospectively collected data to: 1. evaluate the colectomy rates of our regional transfer versus metropolitan patients with ASUC and 2. Identify any modifiable factors to improve outcome.

Methods

Sample selection and observations

A retrospective observational cohort study was conducted using prospectively collected data on ASUC patients admitted directly to the Royal Brisbane and Women's hospital (RBWH) (Metropolitan) or transferred from a regional hospital (Regional transfer – all sites) from January 2000 – May 2014. Conduct of this study was approved by the RBWH ethics Committee. All patients provided written informed consent. All subjects were followed by clinical outpatient review from admission until 30 days post admission by which time they either had a colectomy or were censored.

Definitions

Metropolitan patient (RBWH)

Metropolitan patients were defined as those presenting directly to the front door of the RBWH, an academic teaching secondary and tertiary hospital located in the metropolitan area of a capital city (Brisbane, Australia) with an inflammatory bowel disease team managing the inpatient admissions.

Regional transfer patient (Regional transfer – All sites)

Regional transfer patients formed a cohort of patients consisting of patients transferred from one of ten regional hospitals without a gastroenterologist outside the metropolitan area of our capital city (Brisbane, Australia). Our estimated referral area covers 550,000 square kilometers with a combined population of 1.4 million people.[47] The median distance from the regional referring hospitals(Regional transfer – All sites) to the RBWH (Metropolitan) was 255.1 km (IQR 47.0 – 435.9 km).[48] Regional patients were admitted and managed under the general medical or surgical inpatient teams during their initial admission prior to transfer to our tertiary hospital.

Acute severe ulcerative colitis

Ulcerative colitis cases were confirmed on the basis of consistent clinical, biochemical and histologic features as per the Lennard Jones criteria.[49] ASUC was defined as having satisfied Truelove and Witts criteria of ≥ 6 bloody bowel actions per day and at least one of the following features of systemic toxicity: Temperature > 37.8 °C, Tachycardia > 90 beats/minute, Haemoglobin < 105 g/L or Erythrocyte sedimentation rate (ESR) > 30 mm/hr.[40] All cases had confirmed significant colonic inflammation based on endoscopic mayo score ≥ 2 on admission flexible sigmoidoscopy.

Response to treatment

Complete intravenous steroid response was defined as < 4 bowel actions on day 3 of intravenous steroid treatment without blood. Patients with > 4 bowel actions on day 3 or less than 4 bowel actions but persistent blood in the stool were considered incomplete intravenous steroid responders. Rescue therapy success was defined as avoidance of colectomy.

Management

Patients once admitted to our metropolitan hospital were managed according to our department protocol for managing ASUC.[43] Metropolitan patients and regional patients once transferred received close electrolyte monitoring and replacement to maintain values in the normal range. Thromboembolic prophylaxis with subcutaneous heparin was used in all cases. Second daily abdominal radiographs were obtained and maximal colonic diameter recorded. Patients who had an incomplete intravenous steroid response after three days of hydrocortisone therapy at RBWH were offered rescue therapy with ciclosporin or infliximab. Patients selected rescue therapy after being presented with an evidence based overview of the two therapies providing explanation of the potential risks and benefits of the therapies. Patients who failed rescue therapy or developed complications of severe colitis such as toxic megacolon, perforation, colonic haemorrhage or multi-organ dysfunction were referred for emergent colectomy.

Outcomes

Colectomy rates at 30 days post admission were evaluated in the two cohorts of patients (Regional transfer and metropolitan). Intravenous steroid response on day 3 of the index hospital admission was evaluated. Rescue therapy success at 30 days post admission in cases of intravenous steroid failure was also evaluated.

Statistical methodology

Demographic, radiographic and clinical parameters were assessed between metropolitan and regional transfer cohorts. Laboratory and clinical parameters including bowel actions, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin and haemoglobin were assessed between colectomy / no colectomy at 30 days, stratified by whether patients initially presented to a metropolitan or regional hospital. Quantitative parameters were assessed either via the independent samples t-test or the Mann Whitney U test, while categorical factors were assessed with the Chi square test. Laboratory parameters were transformed into binary factors based upon previously defined thresholds. All statistical analyses were performed using the R statistical environment (version 3.2.3).[33]

Results

A total of 225 patients with an index admission with ASUC were identified between January 2000 and May 2014. Of these 200 patients met the inclusion criteria and were included in the study. (Figure 1) One hundred and thirty-one patients had presented directly to our metropolitan hospital (65.5%) and 69 were transferred after initial assessment in a regional hospital (34.5%).

The regional cohort included a greater number of incident cases of UC and thus a shorter disease duration as compared to the metropolitan cohort. Regional patients also demonstrated more extensive disease as compared to metropolitan patients. (Table 2) Regional patients were three times as likely to have significant hypoalbuminemia (≤ 30 mg/L) at baseline as compared with metropolitan patients (p = 0.0001). There was no significant difference in immunosuppressive treatment prior to admission between the two cohorts (oral steroids: p = 0.29, immunomodulator: p = 0.27). There was no significant difference in the median number of Truelove and Witt criteria on admission between the two cohorts at 2.0 (p = 0.844).

Clinical outcomes

Colectomy rate

The 30 day colectomy rate was significantly higher in regional patients as compared with metropolitan patients (46.4 % vs. 22.9% $p = 0.0006$). Bowel frequency ≥ 8 per day on day 3 ($p = 0.003$) and CRP ≥ 45 mg/L on day 3 ($p = 0.003$) were associated with risk of colectomy at 30 days. (Table 3) There was no statistically significant difference in the proportion of patients from each cohort who went directly to early colectomy after failing intravenous steroids and without receiving rescue therapy as a consequence of fulminant colitis or development of complications (metropolitan : n =11, regional transfer : n = 11, $p = 0.105$).

Intravenous steroid response

Regional patients were less likely to make a complete response to intravenous steroids (21.7%) as compared to metropolitan patients (42.0%) ($p = 0.004$). Across the two cohorts, regional patients received a longer total course of intravenous steroids as compared to metropolitan patients: 8.0 days versus 6.0 days respectively ($p = 0.001$). Regional patients spent a median of 5.0 days in their regional hospital prior to transfer to our metropolitan hospital.

Rescue therapy

Of the 200 patients included in this study 111 (55.5%) received rescue therapy with infliximab or ciclosporin after failing to respond to intravenous steroids. Regional patients required rescue therapy more frequently as compared with metropolitan patients: 65.2 % versus 50.4 % (OR: 1.85 (1.01-3.37) p = 0.045). No regional patients received rescue therapy prior to transfer to our metropolitan hospital due to the lack of a gastroenterology service required to prescribe and monitor the therapy. There was no significant difference in median number of days on intravenous steroids prior to commencing rescue therapy in the regional transfer versus metropolitan cohorts at 5.0 vs. 5.0 days (p = 0.22)

To further investigate the characteristics of patients requiring rescue therapy, we ran additional analyses comparing the demographic, clinical and biochemical parameters of this severe subgroup within both cohorts. Regional patients had shorter disease duration and a more extensive disease distribution as compared to metropolitan patients, consistent with the pattern seen in the overall cohort. There was no significant difference in age, gender, smoking status, inflammatory markers, colonic dilatation, or number of Truelove and Witts criteria met on admission between the two cohorts requiring rescue therapy. (Supplementary table 1) Regional patients demonstrated a lower response rate to rescue therapy at 30 days as compared to metropolitan patients (55 % versus 71 %) (p = 0.069).

Discussion

In this study, we assessed the 30-day colectomy rate in regional transfer and metropolitan patients who present with an attack of ASUC. We have demonstrated for the first time that those patients who initially present to a regional hospital requiring transfer have a three times increased risk of colectomy at 30 days compared with those presenting directly to a metropolitan hospital. Regional patients were more than twice as likely to fail intravenous steroids as compared to metropolitan patients. Parameters predictive of colectomy in regional patients were bowel frequency ≥ 8 and CRP ≥ 45 mg/L on day 3 of therapy. Regional patients with these features were almost five times more likely to undergo colectomy at 30 days as compared to those with a bowel frequency < 8 per day and CRP < 45 mg/L.

The primary factor identified for the higher colectomy rate in regional patients was poor response to intravenous steroids. This is likely because these patients are a selected group of non-responders to initial therapy which in essence marks them as high risk for colectomy. The complete intravenous steroid response rate in regional patients was very low at 21.7 % as compared with the metropolitan cohort response rate of 42 %. Response to intravenous steroids has been identified as the primary factor in avoiding colectomy in patients presenting with ASUC across multiple studies. [36, 50-52] From the literature the response to intravenous steroids is 60-70 % but the figures in individual cohorts vary widely due to heterogeneity in definitions of steroid failure, severity of colitis and treatment regimes.[2, 53, 54]

There are a number of factors that may have contributed to this poor steroid response rate in regional patients. These include hypoalbuminemia, disease extent, disease duration and fraction of incident cases of ASUC.

Regional patients were three times as likely to have significant hypoalbuminemia on admission (< 30 g/L) compared to metropolitan presenting patients (OR 3.16 : p = 0.0001). Hypoalbuminemia has been demonstrated to predict failure or slow response to intravenous steroids in cohorts of ASUC.[35, 45, 50] Previous studies have demonstrated that a serum albumin of < 30 g/L on day 1 predicts intravenous steroid therapy failure on day 3 of treatment.[35, 44] Hypoalbuminemia has also been demonstrated to predict infliximab rescue therapy failure due to a significant loss of the drug due to protein losing enteropathy and colopathy in an extensively ulcerated colon.[55]

This may in part explain the trend towards poorer success of rescue therapy seen in our regional transfer cohort of patients compared to our metropolitan presenting patients. Hypoalbuminemia in acute illness is a poor prognostic marker of outcome and unlikely causative in itself. In a meta-analysis of 90 cohort studies in a wide variety of non-gastrointestinal diseases hypoalbuminemia was associated with increased morbidity, mortality, length of stay and resource utilization.[56]

Regional patients had a higher frequency of extensive disease distribution as compared to metropolitan patients. Extensive disease is correlated with a higher risk of colectomy.[10] Patients with an attack of ASUC and extensive disease are three times more likely to come to colectomy as compared to those with left sided disease or proctitis. [10, 57]

We saw a significantly higher proportion of incident ASUC in our regional cohort as compared with the metropolitan cohort (37.7 % versus 19.0 %: OR 2.55, p = 0.0041). The rate of incident ASUC across all cases in published cohorts is between 34 and 48 %.[10, 11, 35] The rate of incident ASUC was significantly lower in our metropolitan cohort which is likely due to our metropolitan hospital having a larger proportion of existing IBD patients in regular specialist follow-up as opposed to regional hospitals without access to a gastroenterology service where a higher proportion of hospitalized patients will be first presentations of UC. These differences in disease characteristics were consistent with findings in our subgroup analysis of patients receiving rescue therapy. (Supplementary table 1)

The majority of intravenous steroid non-responders in both cohorts received rescue therapy with either ciclosporin or infliximab. Regional patients were more likely to require rescue therapy as compared to metropolitan patients (p = 0.045). Response to rescue therapy at 30 days was lower in regional patients compared with metropolitan patients (55 % vs 71 %) (p = 0.069). The response rate in metropolitan patients is consistent with published short term response rates for ciclosporin (64-91%) and for infliximab (61-85 %).[58] Regional patients had a lower than expected rescue therapy response rate. Factors contributing to a poor steroid response, described above, are likely to have contributed to this poor response to rescue therapy.

The timing of rescue therapy administration is an important factor in the management of ASUC. Regional patients in our study received rescue therapy at a median of day 6 of intravenous steroids, similar to metropolitan patients (p=0.22). However, patients with high risk features including hypoalbuminemia, extensive disease, and incident status, are likely to benefit from earlier rescue therapy, specifically day 3.

Factors predicting colectomy in our regional patients were limited to bowel frequency of ≥ 8 per day and CRP 45 ≥ mg/L on day three of intravenous steroid treatment. Regional patients with these features were almost five times more likely to undergo colectomy at 30 days than those with a bowel frequency < 8 per day and CRP < 45 mg/L. Although these parameters are established predictors of outcome in patients with ASUC, this is the first study to replicate these observations in a regional transfer cohort of patients. [38, 44, 45]

This study was conducted in a major metropolitan referral hospital that provides specialist IBD care to a group of smaller regional hospitals without dedicated gastroenterology services. The results demonstrate significant differences in disease characteristics and treatment outcomes for ASUC in regional patients as compared to metropolitan patients. Potential weaknesses of the study include its retrospective analysis of a prospectively-collected cohort and the inclusion of only one referral center. Strengths of the study include the prospective collection of data on all cases of acute colitis managed at the RBWH and the role of this hospital as the only referral center for regional and rural hospitals in the region.

Patients requiring transfer from a regional hospital have already identified themselves as high risk for colectomy as they have failed initial treatment but until now the magnitude of that risk was unknown. Whilst their initial non-response to intravenous steroids confers them significant risk for colectomy it is not clear from the available data what other factors including management protocols at regional hospitals, delay to optimal treatment and delay to diagnosis have on the colectomy rate. This is an important avenue for further study but unfortunately reliable data on the pre-admission management of patients with ASUC is scant as investigations are performed by their general practioner and through emergency department visits.

The results of this study have implications for clinical practice. Patients with an acute severe colitis presenting to a regional hospital without a dedicated gastroenterology service are a very high risk group of patients. Thus, a combination of early recognition of the diagnosis, communication with the nearest IBD centre, and transfer for intensive medical (and colorectal surgical treatment if necessary) therapy is essential.

This will provide patients with access to optimized, evidenced-based care within a "high-volume" hospital environment and minimize any variance in care. At a broader level, however, our study illustrates some of the challenges faced by individuals living in regional and rural areas as compared to those who choose to live in metropolitan areas. The lack of rapid access to specialist services within regional and rural areas is likely to have contributed to some of the differences in baseline disease characteristics identified in this study, including the frequency of extensive disease, hypoalbuminemia and incident ASUC. All these point to potential delays in diagnosis in the regional and rural settings. Lack of specialist services in these areas has long been recognized both within Australia and the United States.

In summary, patients with UC living in regional and rural areas of Queensland, Australia, who present to their local hospital with ASUC have a significantly higher risk of colectomy at 30 days as compared to those who present to a metropolitan hospital with a dedicated IBD team. Regional ASUC patients have a number of high risk features contributing to these poorer outcomes including higher rates of extensive disease, hypoalbuminemia, and incident ASUC.

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Table 1: Treatment outcomes

Characteristic	Metropolitan	Regional	OR (95%CI)	p-
Complete IV steroid response (day				
No	76	54	ref (1.0)	
Yes	55	15	2.61 (1.33 –	0.0043
Direct to colectomy after IV				
No	120	58	ref (1.0)	
Yes	11	11	0.48 (0.20 –	0.105
Received rescue therapy				
No	65	24	ref (1.0)	
Yes	66	45	1.85 (1.01 –	0.0448
Rescue therapy success at 30 days				
No	18	20	ref (1.0)	
Yes	47	25	2.09 (0.94 –	0.0693
Colectomy at 30 days				
No	101	37	ref (1.0)	
Yes	30	32	2.91 (1.56 –	0.0006

Table 2: Univariate analysis of demographic and clinical parameters

Characteristic	Metro	Region	OR (95%CI)	p-value
N	131	69		
Age				
Mean +/- SD	37.75	37.16		0.808
Gender				
Male	68	29	ref (1.0)	
Female	63	40	1.48 (0.82 - 2.7)	0.1839
Smoking status				
Never	79	37	ref (1.0)	
Ex	40	30	0.62 (0.34 - 1.15)	0.131
Current	12	2	2.81 (0.6 - 13.2)	0.174
Disease duration (Years)				
Median (IQR)	2 (8.77)	1 (2.81)		0.006
Disease extent				
E1/E2	49	15	ref (1.0)	
E3	81	54	2.16 (1.12 - 4.36)	0.0218
Abdominal radiograph colonic diameter				
< 5.5cm	116	60	ref (1.0)	
≥ 5.5cm	15	9	1.17 (0.46 - 2.8)	0.7417
First presentation of UC				
No	106	43	ref (1.0)	
Yes	25	26	2.55 (1.32 - 4.94)	0.0041
5-ASA on admission				
No	72	47	ref (1.0)	
Yes	58	22	0.58 (0.31 - 1.07)	0.0813
Oral steroid on admission				
No	71	32	ref (1.0)	
Yes	60	37	1.37 (0.76 - 2.47)	0.2927
Immunomodulator on admission				
No	91	53	ref (1.0)	
Yes	40	16	0.69 (0.34 - 1.34)	0.2714
CRP day 1				
< 45 mg/L	58	26	ref (1.0)	
> 45 mg/L	72	41	1.27 (0.7 - 2.33)	0.4348
ESR day 1				
< 31 mm/hr	26	10	ref (1.0)	
> 31 mm/hr	75	38	1.31 (0.58 - 3.12)	0.513
Bowel actions day 1				
< 8	27	12	ref (1.0)	
≥ 8	104	57	1.22 (0.58 - 2.7)	0.5849
Albumin day 1				
> 30 g/L	88	27	ref (1.0)	
≤ 30 g/L	43	42	3.16 (1.73 - 5.86)	0.0001
Haemoglobin day 1				
> 105 g/L	95	51	ref (1.0)	
≤ 105 g/L	36	18	0.93 (0.47 -1.80)	0.8328

Table 3: Comparison of clinical and laboratory parameters predictive of colectomy at 30 days

Characteristic	**Metropolitan (N=131)**			
	No	Colecto	OR (95%CI)	p-
N	101	30		
Bowel actions Day 1				
6-7	23	4	ref (1.0)	
≥ 8	78	26	1.86 (0.63 -	0.261
Bowel actions Day 3				
<8	74	18	ref (1.0)	
8+	25	12	1.97 (0.81 -	0.117
CRP Day 1				
< 45 mg/L	45	13	ref (1.0)	
≥ 45 mg/L	55	17	1.07 (0.47 -	0.872
CRP Day 3				
< 45 mg/L	78	19	ref (1.0)	
≥ 45 mg/L	22	10	1.86 (0.73 -	0.170
ESR Day 1				
< 31 mm/hr	23	3	ref (1.0)	
≥ 31 mm/hr	53	22	3.04 (0.92 -	0.07
Albumin Day 1				
>30 g/L	71	17	ref (1.0)	
≤ 30 g/L	30	13	1.8 (0.76 - 4.2)	0.162
Haemoglobin Day 1				
> 105 g/L	76	19	ref (1.0)	
≤ 105 g/L	25	11	1.76 (0.72 -	0.193
Characteristic	**Regional (N=69)**			
	No	Colecto	OR (95%CI)	p-
N	37	32		
Bowel actions Day 1				
6-7	8	4	ref (1.0)	
≥ 8	29	28	1.88 (0.52 -	0.318
Bowel actions Day 3				
<8	28	13	ref (1.0)	
8+	8	18	4.68 (1.65 -	0.002
CRP Day 1				
< 45 mg/L	18	8	ref (1.0)	
≥ 45 mg/L	18	23	2.81 (1.01 -	0.042
CRP Day 3				
< 45 mg/L	31	16	ref (1.0)	
≥ 45 mg/L	6	16	4.97 (1.68 -	0.002
ESR Day 1				
< 31 mm/hr	7	3	ref (1.0)	
≥ 31 mm/hr	20	18	2.02 (0.47 -	0.324
Albumin Day 1				
>30 g/L	15	12	ref (1.0)	
≤ 30 g/L	22	20	1.13 (0.42 -	0.796
Haemoglobin Day 1				
> 105 g/L	25	26	ref (1.0)	
≤ 105 g/L	12	6	0.49 (0.15 -	0.196

Supplementary Table 1: Comparison of clinical characteristics of patients who received rescue therapy in regional transfer and metropolitan cohorts

Characteristic	Metro	Regional	OR (95%CI)	p-value
N	66	45		
Rescue therapy type				
Ciclosporin	31	15		
Infliximab	35	30		
Age				
Mean +/- SD	37.7 (16.3)	35.8 (14.5)		0.54
Gender				
Male	32	18		
Female	34	27	0.71 (0.33 - 1.53)	0.3777
Smoking status				
Never	44	23		
Ex	17	20	0.55 (0.20 - 1.01)	0.051+
Current	5	2		0.134*
Disease duration (Years)				
Median (IQR)	2 (9)	1 (3)		0.014
Disease extent				
E1/E2	21	7		
E3	44	38	0.39 (0.14 - 1)	0.0474
Abdominal radiograph colonic diameter				
< 5.5cm	56	42		
≥ 5.5cm	10	3	2.4 (0.67 - 11.82)	0.1723
First presentation of UC				
No	51	31		
Yes	15	14	0.65 (0.27 - 1.56)	0.3236
Median duration of IV steroids (days)	8 (5)	9 (5)		0.007
Median duration of IV steroids (transfer, days)				
Before transfer		4 (4)		
After transfer		5 (6)		
CRP day 1				
< 45 mg/L	29	15		
≥ 45 mg/L	37	30	0.64 (0.29 - 1.41)	0.262
ESR day 1				
< 31 mm/hr	13	9 (5)		
≥ 31 mm/hr	53	36	1.02 (0.38 - 2.65)	0.9686
Bowel actions day 1				
< 8	13	8		
≥ 8	53	37	0.89 (0.32 - 2.35)	0.7999
Albumin day 1				
> 30 g/L	29	12		
≤ 30 g/L	37	33	0.47 (0.2 - 1.06)	0.0641
Haemoglobin day 1				
> 10.5 g/dL	46	32		
≤ 10.5 g/dL	20	13	1.07 (0.46 - 2.51)	0.8728
Truelove and Witts on admission				
Median number of criteria met (IQR)	2(1)	2(1)		0.271

* p-value from a 2*3 comparison using the Fishers Exact approximation for significance due to expected cell counts less than 5.

+ p-value and odds ratio from a 2 by 2 comparison for never vs ex-smokers. Results from never vs current results not shown due to small sample size

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