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Minor dissertation

TITLE: Predictors of emergency colectomy in patients admitted to Groote Schuur Hospital with Acute Severe Ulcerative Colitis between 1st January 2003 and 1st January 2013

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Abstract

INTRODUCTION: Acute Severe Ulcerative Colitis (ASUC) is a life threatening condition which requires urgent and aggressive medical therapy to reduce mortality, morbidity and avoid surgery; the mainstay of treatment is intravenous corticosteroids. To facilitate this process it is essential to identify patients at high risk of poor outcomes and emergency colectomy. Numerous risk factors predicting the need for surgery have described in the Western literature both at presentation and on day 3 of intravenous therapy, however there are no local data addressing this issue. As such it is unclear if these predictors are applicable in our setting. The aim of this study is thus to identify risk factors for emergency colectomy in patients admitted to Groote Schuur Hospital with ASUC.

METHODS: A retrospective cohort study of 98 patients admitted with ASUC between January 2003 and January 2013 was performed. Clinical, demographic, laboratory, radiological and endoscopic factors on admission and 3 days thereafter were analysed as predictors of colectomy by univariate and multivariate analysis. Patients were followed up retrospectively for 90 days

RESULTS: Twenty five percent of the cohort underwent emergency colectomy, 80% within 15 days of presentation. On univariate analysis factors on admission which predicted colectomy were exposure to oral corticosteroids ($p=0.01$), megacolon ($p=0.049$) or mucosal islands ($p=0.04$) on abdominal Xray, and a short duration from UC diagnosis until presentation with ASUC ($p=0.04$). There was no significant association between ethnicity, age at UC diagnosis, gender, family history of IBD, or smoking status. There was also no association with baseline haemoglobin or CRP. The only day 3 variable that significantly predicted colectomy was serum albumin ($p=0.01$). This was also the only variable to remain significant on multivariate analysis (OR 0.79, 95% CI 0.65-0.97, $p=0.01$).

CONCLUSION: ASUC is a medical emergency, predicting which patients will likely require colectomy is a very valuable tool in guiding therapeutic management. In our study the only variable significantly associated with colectomy was hypoalbuminaemia on day 3. However given the small study numbers a larger prospective study would be of value in identifying additional risk factors.

Study Protocol

BACKGROUND AND LITERATURE REVIEW

Idiopathic inflammatory bowel disease (IBD) comprises by and large two types of intestinal disorders, Crohns disease (CD) and ulcerative colitis (UC); both are characterized by chronic gastrointestinal inflammation. Their clinical course is marked by acute exacerbations and periods of remission. The exact etiology remains unknown, but accumulating evidence suggests that IBD is the result of complex interactions between the genetic makeup of the individual together with environmental factors, mucosal immunity and the gut microbiome (Gulliford et al. 2011).

Ulcerative colitis is characterized by continuous, superficial inflammation that is limited to the colon with no upper gastrointestinal or small bowel involvement. One exception is black wash ileitis seen in less than 10 percent of cases, almost always in patients with pan colitis (Satsangi at al. 2006) UC is classified using the Montreal classification (Appendix 1) according to the extent of involvement of the colon; 40 % have proctitis (limited to the rectum), 40 % limited disease (affecting the left side of the colon up to the splenic flexure), and 20 % pan colitis (involving the whole colon). Most flare ups of UC are mild to moderate in severity, however approximately 15% of patients will have an episode of acute severe UC (ASUC) in their lifetime, and for about 20 % this will be their first presentation.

ASUC is a medical emergency as it can be complicated by toxic megacolon and perforation. ASUC is usually diagnosed using True love and Witt's criteria which have been widely adopted by international bodies and is defined by the passage of six or more bloody stools per day together with any one of an additional 4 criteria: a tachycardia (>90 bpm), body temperature > 37.5°C, anaemia (hemoglobin <10.5 g/dl), or an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) >30 mm/h (Travis at el.2011).

Untreated ASUC has high mortality rates; ranging between 22 and 75 % and is therefore regarded as a medical emergency requiring aggressive medical and surgical therapy. The management of ASUC requires a multi-disciplinary approach which includes a Gastroenterologist, Colorectal surgeon, Clinical radiologist, Psychologist and stoma therapy expert. Initial evaluation includes a plain chest X-ray to exclude air under the diaphragm which is a sign of intestinal perforation as well as to rule out active tuberculosis. Erect and supine abdominal X-rays are also essential in the work up of a patient with ASUC to look for signs of severity which include colonic dilation, toxic megacolon (transverse colon diameter

of more than 5.5 cm), an haustral appearance, thumb printing, mucosal islands and dilated small bowel (suggesting an ileus). Abdominal X-ray may also be helpful in estimating the extent of colitis (Travis et al. 2010). The second European evidence based consensus on the diagnosis and management of UC recommends that laboratory investigations include electrolytes, full blood count, liver function testing and CRP (Dignass et al. 2012). It is important to exclude other causes of diarrhea and bleeding, therefore a stool examination for microscopy, culture and *Clostridium difficile* toxin analysis is imperative. Infective colitis should be excluded in all patients, but especially those with abrupt onset of diarrhea, vomiting or fever and those with a recent history of foreign travel (Gulliford et al. 2011). Endoscopic imaging of these patients involves use of rigid or flexible sigmoidoscopy (which is preferable) and biopsies to confirm the diagnosis of UC macroscopically and histologically. Biopsies are also taken to rule out concurrent cytomegalovirus (CMV) which often complicates ASUC. Normal rectal mucosa is uncommon in active UC and an alternative diagnosis such as CD colitis, infective colitis or ischemic colitis should be entertained.

The clock starts ticking the moment a patient with ASUC is hospitalized and urgent investigation and treatment is key. In ASUC there is often progression of inflammation beyond the mucosa, with associated systemic toxicity. These patients are at risk of developing toxic megacolon and perforation with high mortality and morbidity. To optimize the management of ASUC, meticulous attention should be given to confirming the diagnosis, establishing disease activity, excluding complications and initiating appropriate treatment. These very ill patients also require close monitoring by a multidisciplinary team. The mainstay of therapy is early and aggressive intravenous corticosteroids (Gulliford et al. 2011).

At presentation the severity of the UC flare and the risk of colectomy can be predicted. The number of positive True love and Witt's present criteria at presentation can be used as an index for predicting colectomy and correlate well with disease severity. In patients with 6 or more bloody stools per day plus 1 additional criterion 9% will undergo surgery, with 2 additional criteria 31% and 3 additional criteria 48% (Dinesen, 2010). Other predictors of colectomy at diagnosis include mucosal islands, colonic dilatation on abdominal X-ray (75%) and albumin < 30 g/l (42%) (Travis et al. 2011).

Approximately 60% of patients will respond rapidly to IVI corticosteroids; however the remainder fail to improve. It is important to identify these steroid failures early as there is a narrow window of opportunity to salvage the colon. Two treatment options can be used as rescue therapy in these people, cyclosporine and the anti-TNF α biologic infliximab (Croft et al, 2013). These 2 treatment options appear to be of equal efficacy. In order to avoid colectomy these agents need to be given early in the course of the disease. The Oxford Index severity scoring criteria on day three of intravenous corticosteroids is widely used to identify these steroid refractory patients. People fulfilling these criteria (8 or more stools per day or 3 to 7 stools per day plus a CRP >45) are regarded as having failed steroid therapy and 85 % will end up with a colectomy on that particular admission (Travis et al. 1996). These criteria are used in our institution to guide therapeutic decision making and help to decide whether early salvage therapy is indicated. Delayed colectomy following prolonged medical therapy (>8 days) leads to increased post-op complications (Leonard-Jones et al. 1975). A 2-fold increase in in-hospital mortality has been described if colectomy is performed after 6 days (Kaplan et al. 2008).

In conclusion the management of ASUC remains a challenge and clear identification of parameters that can identify patients at high risk of colectomy will facilitate the initiation of early and aggressive therapy within a multidisciplinary team. In addition timely colectomy in those who fail to respond will reduce surgical mortality and morbidity.

STUDY RATIONALE

Multiple indices have been used to predict colectomy in patients diagnosed with ASUC, mostly in Western cohorts. There is currently no local data on whether these variables are of value in our population. Our Institution manages most state patients with UC in the Western Cape and as such we are an ideal study site to address this research question. Limited resources, notably the availability of infliximab as colon salvage therapy, can be then optimized based on local evidence. Genetic, environmental and social factors in our population are different from other parts of the developed world and it is unclear if predictors evaluated in these populations are generalizable in our setting.

STUDY AIM

To analyze clinical, radiological, laboratory and endoscopic parameters at the time of admission, as well as on day 3 of admission, in patients with ASUC in order to establish

which are predictive of subsequent colectomy in our tertiary adult Hospital, Cape Town, South Africa.

STUDY OBJECTIVES

- 1) To identify factors predicting colectomy in patients with confirmed ASUC on day 0 and day 3 of admission.
- 2) To evaluate the Oxford criteria on day 3 of treatment and review its validity in our setting.

STUDY METHODS

Study design

A retrospective study of patients admitted to Groote Schuur Hospital with ASUC between the 1st January 2003 and 1st January 2013. Patients will be identified from inpatient admission records, surgical files, as well as our established IBD database

DATA COLLECTION

Case folders of all patients admitted with ASUC (GSH medical, surgical wards and ICU) during the study period will be evaluated and appropriate data extracted and entered into an Excel database. The following information will be collected:

- Demographic data: name, folder number, date of birth, age at diagnosis and on admission, gender, race, date of UC diagnosis, family history of IBD, date of ASUC diagnosis, smoking history, first time presentation or previously diagnosed, number of previous attacks of ASUC.
- Clinical factors on day 1 and day 3: number of stools per day, temperature, heart rate, hemoglobin, ESR, CRP, albumin, stool MC&S and *C difficile toxin*.
- Radiological findings on day 1: Chest X-ray, Abdominal X-ray findings.
- Medicine use on admission: 5-ASA, topical steroids, oral corticosteroids, azathioprine, TNF alpha blockers.
- Endoscopy features on admission: grade of colitis, deep ulcers, CMV.
- Medical management during admission: antibiotics, high dose IVI steroids, cyclosporine, infliximab.
- Surgical management: colectomy date, indication for colectomy (toxic megacolon, perforation, severe bleeding, failure of medical therapy, ongoing active UC)

- Surgical outcomes: perioperative morbidity and mortality, surgical complication up to 90 days post discharge
- Mortality rates. During admission and up to 90 Days post discharge

STATISTICAL ANALYSIS

The association between all baseline risk factors as well as those on day 3 of admission and the risk of colectomy will be assessed by univariate analysis. The distribution of all continuous variables will be evaluated and expressed as medians and interquartile ranges (IQR) or means \pm standard deviations (SD) as appropriate. Statistical analysis will employ Chi2, Fishers exact, Student t test, Wilcoxon rank sum test or Kruskal-Wallis testing as appropriate. Those variables with *P* values less than 0.10 will be further tested in a series of logistic multivariate regression models. The analysis will be performed using STATA version 11 (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP).

INCLUSION CRITERIA

- All patients with a confirmed diagnosis of ASUC using True love and Witt's criteria will be included in the study.

EXCLUSION CRITERIA

- Patients with incomplete data on admission for the inclusion criteria will excluded.
- Patients with a revised diagnosis at a later stage (within 90 days).

ETHICAL CONSIDERATIONs

Ethical considerations as per the local Ethics committee will be adhered to so as to limit harm and breach of patient confidentiality. Only the principal investigator and his immediate coworkers will have access to the identity of the study participants and their personal details. Names, hospital folder numbers or any other information which may allow identification of the subjects involved in the study will not be divulged to any other person or appear in the dissertation or any subsequent publication. Ethical approval from the local Ethics Committee will be obtained prior to study onset.

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Chapter 1

Literature Review

INTRODUCTION AND BACKGROUND

Idiopathic inflammatory bowel disease (IBD) is represented by and large by two types of intestinal disorders, Crohn's disease (CD) and ulcerative colitis (UC). Microscopic colitis, primary collagenous colitis, lymphocytic colitis and IBD- unclassified (IBD-U) are less common, but increasingly recognized. UC and CD are characterized by chronic relapsing-remitting immune activated gastrointestinal inflammation (Satsangi et al. 2006). CD is characterized by transmural segmental inflammatory involvement with either fistulising or stenotic phenotypes and can affect any part of the gastrointestinal tract, although the terminal ileum and caecum are predominantly affected. UC is characterised by continuous ascending mucosal inflammation exclusively involving the colon, with the rare exception of backwash ileitis (Haskell et al. 2005). IBD is currently classified using the Montreal classification system (Satsangi et al. 2006). CD is classified according to age at diagnosis, disease location and disease behaviour. UC is classified according to the extent of colonic involvement, and the severity of disease (Tables 1 - 3). UC is the most common form of IBD and was first described in the 1800s, whereas CD was first reported in 1932 as "regional ileitis" (Crohn et al. 1932). IBD has a variable clinical course with periods of quiescence and episodes of active disease where symptoms worsen. Most IBD flares are managed as outpatients. Severe flares are usually managed as inpatients as they require aggressive medical therapy and may also require surgery. This literature review describes the epidemiology, aetiology, pathogenesis and natural history of UC, with a focus on acute severe ulcerative colitis (ASUC). The diagnosis of ASUC, assessment of severity, medical therapy including rescue therapy and the decision regarding the need and timing of surgery will be discussed.

EPIDEMIOLOGY OF UC

The incidence of UC has plateaued or even decreased (Molinie et al. 2004; Lakatos et al. 2004) in developed countries of North America and Western Europe, while there is a rising trend in developing countries (Lakatos et al. 2004). The incidence of UC varies from 0.5 to 31.5 per 100 000 people per annum, depending on the studied population (Burisch et al 2013). The prevalence is lower in developing countries ranging from 5.3 to 63.6 per 100 000 people in Asian populations (Asakura et al. 2009). The disease typically follows a relapsing-

remitting course and usually presents with a bimodal pattern of incidence with a predominant peak between the ages of 15 and 30 years, and a second smaller peak between ages 50 and 70 years (Loftus et al. 2002). In recent studies, the majority of patients with UC were between 30-40 years at diagnosis (Burisch et al. 2013). UC was previously considered rare in children, but recent studies from different countries have demonstrated an increase in paediatric and adolescent populations (Pant et al. 2013). Henderson et al showed an increased incidence in children less than 16 years of age when comparing periods 1990 – 1995 to 2003 – 2008, with incidence rates of 1.59 to 2.06/100 000 per year respectively (Henderson et al. 2012). The incidence of ulcerative colitis is higher in developed countries (Northern Europe and USA) than in developing countries, and in urban versus rural areas. Lowest rates of incidence and prevalence have been described in Eastern and Southern countries, with increasing numbers recorded in those countries that have adopted a western lifestyle (da Silva et al. 2014). North America and northern Europe have the highest incidence and prevalence rates of ulcerative colitis, with incidence rates varying from 9 - 20 cases per 100 000 person-years, and prevalence rates from 156 - 291 cases per 100 000 (Ordás et al. 2012). Bernstein showed that there is a slight predominance of males affected by UC as compared to females (Bernstein et al. 2006). Loftus however showed no gender difference in UC incidence (Loftus et al. 2002). Cigarette smoking (in particular current smokers) has a protective effect for UC (Mahid et al. 2006). Former or non-smokers have an increased risk of acquiring UC with higher rates of hospital admission and colectomy (Beaugerie et al. 2001; Birrenbach et al. 2004).

First-degree relatives have a 5.7 – 15.5 % risk of developing UC. Henriksen et al in their prospective study described a 10.1% incidence of a family history of IBD among 454 individuals with UC (Henriksen et al. 2006).

There is some published data on the demographics of IBD in South Africa. In a 1986 Cape Town IBD cohort Wright et al showed that only 30% of 197 UC patients were either coloured or black. There was an increase in the incidence of UC between 1970 and 1977 and again between 1980 and 1984. The age distribution of patients presenting for the first time ranged between 20 to 40 years (Wright JP et al 1986). These racial demographic appear to have changed dramatically over the past 30 years. Data from the newly instituted South African IBD Registry (personal communication – Dr David Epstein) has shown that there remains a Caucasian predominance (39.6%), but this is now closely followed by coloured (39%), then Asian (7.3%) and black (5.6%) populations. This increase in incidence in non-Caucasians may reflect changes in environmental risk factors. Chu et al in their study of 370 patients (63

were UC, 88 were CD patients and 219 were controls) in the Western cape of South Africa, described a protective relationship of childhood Helminth exposure against development of IBD. They showed in multivariate analysis that, helminth infection as well as mixed race, smoking and shared housing were protective against developing UC(Chu et al. 2013). Environmental and host genetic factors play a role in UC pathogenesis.

AETIOLOGY AND PATHOGENESIS OF UC

UC is a complex and multifactorial disease, of which the exact aetiology remains uncertain. Current evidence suggests that UC results from an inappropriate inflammatory response to intestinal microbes in a genetically susceptible host. The triggering event remains unclear although a genetic predisposition as well as environmental factors appears to be of importance. Multiple potential pathways have been studied, mostly in animal models, and UC is thought to stem from dysregulated microbial handling by the gut, epithelial barrier damage and aberrant immunological responses. (Dixon et al. 2015).

Defective goblet and paneth cell function has been described, resulting in abnormalities in the mucous layer, intercellular tight junctions and cellular adhesion molecules. Ultimately the epithelial barrier is impaired which increases permeability and antigenic uptake (Ordás I et al.2012), Antigen presenting cells (APCs) are activated through pattern recognition receptors as well as by these antigens directly as they penetrate the epithelial barrier and lamina propria. Stimulation of NF- κ B pathways in the APCs leads to the transcription of pro-inflammatory cytokines, notably Tumor Necrosis Factor alpha (TNF α), Interleukin-12 (IL-12), IL-6, IL-23, IL-1 β . The release of these cytokines further stimulates APCs to activate naïve CD4 T-cells (Th0 cells) and promote their differentiation into effector Th₂ cells, which produce additional inflammatory cytokines such as IL 4. Regulator and effector T cell homeostasis is disturbed in UC and this leads to atypical Th₂ responses mediated by non-classical natural killer T cells (NKT) which produce interleukin IL 13 and IL 5 (Zenewicz et al. 2010). IL 13 exerts cytotoxic effects against epithelial cells, promotes apoptosis and alters the structure of proteins forming tight junctions in the epithelial layer. The resultant inflammatory response (through expression of mucosal addressin-cell adhesion molecule 1 on endothelial cells) attracts circulating T cells bearing integrin- α 4 β 7 to the gastrointestinal microvasculature. These then adhere to colonic endothelial cells allowing them to diapedese into areas of colonic inflammation. This upregulated response leads to the release of specific chemokines such as CXC L1, CXC L3 and CXC L8 by humoral cells, and thereby potentiates the recruitment of polymorphonuclear cells resulting in perpetuation of inflammation and a

systemic inflammatory response. This vicious cycle driven by pathogen activated APCs, defective tight junctions, increased permeability, and activation of a dysregulated immune response ultimately leads to epithelial breakdown, ulcer formation, bloody diarrhoea, abdominal pain and systemic signs of inflammation.

THE DIAGNOSIS AND NATURAL HISTORY OF UC

The diagnosis of ulcerative colitis is based on clinical symptoms as well as typical endoscopic and histological features. The differential diagnosis includes infective causes (especially *Clostridium difficile*, shigellosis, amoebiasis, haemorrhagic *E coli*, typhoid species and cytomegalovirus infection in immunosuppressed patients). These need to be ruled out before a diagnosis can be made. With a few exceptions, UC always involves the rectum with varying degrees of proximal extension. It is confined to the colon, although infrequently UC may involve the terminal ileum and is called backwash ileitis. UC is classified by the Montreal classification (Appendix 1) according to the extent of colonic involvement as proctitis (30-50%), left-sided colitis (20-30%) or extensive colitis (20%) (Satsangi et al. 2006). Disease extent can progress with time in 25-50% of patients to involve more proximal colon. The severity of UC is also classified by the Montreal classification (Appendix 1)

The majority of UC patients present with mild-moderate disease (S1-S2), however 25% will have severe disease (S3) at diagnosis. Additionally, over the course of their lifetime, 15% of affected patients will develop an acute severe flare requiring hospitalisation (Van Assche et al. 2011). Dinesen et al described a cohort of 186 patients admitted with ASUC for intensive treatment. The first attack occurred at presentation in 34%, within 1 year of diagnosis in 24% (cumulative total 54%), and 18% within 1 to 5 years of diagnosis. Twenty eight percent presented with ASUC for the first time more than 5 years after diagnosis. Patients who are diagnosed at a young age (15–30 years), and those with concurrent primary sclerosing cholangitis, are more likely to have extensive disease at presentation than those without these risk factors (Dinesen et al. 2010). Disease flares that are associated with progression of anatomic extent (from proctitis to left-sided colitis or extensive colitis) usually follow a more severe course and require more intensive medical treatment (Etchevers et al. 2009) than those who's UC does not progress. The anatomical extent of mucosal inflammation is clearly one of the most important factors determining disease course. Patients with more severe disease tend to have more extensive forms of UC (pancolitis) than do those with less severe disease.

Despite the often severe disease manifestations, patients with ulcerative colitis do not have an increased mortality risk compared with the general population (Selinger et al. 2013).

The long term natural history and clinical behaviour pattern of UC is best described in the IBSEN study, which followed a large population based IBD cohort (including 519 UC patients) over a 10 year period. Four distinct patterns of UC symptom behaviour were described. The majority of patients (55%) had significant intestinal symptoms in the first year after diagnosis, followed by symptoms suggesting remission or mild disease. Thirty seven percent of UC patients described chronic intermittent symptoms, while 22% had chronic continuous symptoms. Only 1% described an increase in symptom severity following an initial mild presentation (Solberg et al. 2009).

ASSESSING THE SEVERITY OF UC AT PRESENTATION

Acute severe ulcerative colitis is characterised by bloody diarrhoea of six or more stools per day with one or more additional systemic signs (Heart rate >90 /min, Temperature > 37.8 °C, Haemoglobin <10.5 g/dL and C-reactive protein (CRP) or Erythrocyte sediment rate > 30) as initially described by True Love and Witts (Truelove & Witts 1955; Dignass et al. 2012).

These criteria are aligned with the more recent Montreal classification of UC severity (Appendix 1). Less than 10% of UC patients with ASUC will present at diagnosis (Langholz et al. 1991), although in Deneson's fore mentioned cohort this figure was as high as 34%. Most patients present as a UC relapse or as a complication of corticosteroid dependence (Macken & Blako. 2015). Multiple indices used to assess disease severity have been published. However Truelove and Witt's criteria remain the corner stone of identifying ASUC, especially in daily clinical practice. Laboratory markers have been studied extensively with varying degrees of success. The widely used acute phase reactant CRP is inferior in assessing disease activity in UC when compared to Crohn's disease, except for ASUC, where it has established value in both adults and children (Dignass et al. 2012).

Among objective clinical features, bloody stool frequency, increased body temperature and tachycardia are good predictors of severity and outcome. Radiological findings which include Megacolon (colon dilatation of ≥ 5.5 cm), an ahaustral lining, thumb printing (suggestive of mucosal oedema) and features of a small bowel ileus are predictors of severity in UC (Chew et al. 1991). Megacolon and mucosal islands on plain radiographic films have been described as predictors of colectomy in ASUC with 75% risk of colectomy (Lennard-Jones et al. 1975). The Modified Mayo Score is used more frequently in clinical trials and it includes stool frequency, rectal bleeding, endoscopy findings and Physicians global assessment. The

maximum Mayo score assessment index is 12. Clinical response is defined as a decrease of at least 3 points and at least a 30% decrease from the baseline Mayo score, accompanied by a rectal bleeding sub-score decrease of at least 1 point and an absolute rectal bleeding sub-score of 0 or 1. Clinical remission as a Mayo score of 2 or less and no sub-score more than 1; and mucosal healing as an absolute Mayo endoscopy sub-score of 0 or 1 (Côté-Daigneault et al.2015). The Second European evidence based consensus (ECCO) acknowledges the importance of microscopic findings at endoscopy (chronic inflammatory cell infiltrate, crypt abscesses, mucin depletion and branches in the surface epithelium) as predictors of severity in patients recurrent of UC relapses (Dignass et al. 2012).

MEDICAL MANAGEMENT OF ASUC

Acute severe ulcerative colitis should be approached as a medical emergency. Prompt evaluation of ASUC patients is mandatory, laboratory studies including a full blood count, liver function testing, inflammatory markers (CRP,ESR), renal function testing, electrolytes (calcium, magnesium and phosphate), albumin levels and stool studies to rule out infectious causes especially *Clostridium difficile* are required. In addition it is prudent to perform a limited evaluation of the colon with flexible sigmoidoscopy to confirm the presence, severity and extent of the inflammation and also to take biopsies for confirmation of UC and exclusion of cytomegalovirus infection (which frequently complicates ASUC). Full colonoscopy should be avoided as it can precipitate toxic megacolon and increases the risk of perforation. Plain abdominal and chest radiography at presentation is mandatory as it helps to determine the extent of disease, will detect the presence of megacolon, thumb printing and mucosal islands and pick up other pathologies like pulmonary infections and bowel perforation. Bowel rest is not recommended in patients with ASUC. Although it might help reduce stool volume, there is no established benefit in terms of disease activity (Mcintyre et al. 1986). Nutritional support is recommended in patients who are malnourished. Enteral nutrition is preferred as it has shown benefit in the metabolism and repair of the colon epithelial cells form short chain fatty acids when compared to parenteral nutrition which deprives the colon of short chain fatty acids (González-Huix et al. 1993). ASUC patients should always receive thrombotic prophylaxis with standard doses of heparin as there is evidence of a prothrombotic state during this period (Grainge et al. 2010). Although ASUC is difficult to distinguish from infective colitis; treatment should not be delayed until stool microbiology results or histology is available. It may be appropriate to commence both corticosteroids and antibiotics (Mowat et al. 2011). Geographic area

determines the standard practice in terms of using empiric antimicrobials. The routine use of intravenous antibiotics in patients with uncomplicated ASUC is not recommended, although it may be appropriate when incipient colonic perforation, toxic dilatation or infection is suspected (Mantzaris et al. 2001). Any medications that can precipitate colonic dilatation, including opiates, NSAIDs, anti-cholinergics and anti-diarrhoeas, should be avoided (Macken & Blaker. 2015).

Corticosteroids remain the mainstay medical treatment of ASUC and will induce remission in the majority (70%) of cases. Corticosteroids are given intravenously, usually at high doses (Turner et al. 2007). Most patients will respond to intravenous steroid therapy and may be switched to oral prednisolone 1mg/kg (40-60 mg daily with tapering down over the next 2-3 months). Response to steroids is indicated by improvement in patients' symptoms decreased stool frequency, urgency and rectal bleeding, improved stool consistency, reduction in abdominal pain, and improvement in general well-being and improved laboratory parameters (reduced CRP and improvement in haemoglobin and albumin). Intensive inpatient treatment with intravenous corticosteroids and early surgical intervention has reduced the UK mortality from ASUC to 2.9% (Arnott I et al. 2009).

CORTICOSTEROID FAILURE IN ASUC

Although most patients with severe UC respond to intravenous steroid therapy, approximately 30% of patients fail to respond after 5-7 days and are termed steroid refractory (Turner et al. 2007). Corticosteroid failure is an indication for either medical rescue therapy or emergency colectomy. Severe steroid side effects like Psychosis, Osteoporosis, and bleeding peptic ulcer are also an indication for medical rescue therapy. Response to intravenous corticosteroids should be assessed early. It is important to identify failures timeously as there is a small window of opportunity to save the colon. Objective markers of steroid failure should be used to diagnose steroid refractory ASUC. Clinical markers that suggest corticosteroid refractoriness include the passage of >4 stools per day with blood after 3 days of intravenous glucocorticoid therapy (Lindgren et al. 1998); in patients not responding after 3 days the immediate risk of colectomy rises to 85% (Travis et al. 1996). In addition to assessing UC severity there are other criteria that are used to identify corticosteroid failure in patients receiving this therapy for ASUC. Travis et al suggested in their prospective study that a stool frequency of > 8/d or 3-8/d and C-reactive protein (CRP) > 45 mg/dL on the third day of corticosteroid therapy is sufficient evidence of corticosteroid failure and should prompt rescue therapy. These criteria known as the Oxford Index are still

clinically relevant and widely used (Travis et al. 1996). Lindgren subsequently described the fulminant colitis index to identify early those patients that are steroid refractory and would need rescue therapy (Lindgren et al. 1998). The fulminant colitis index was calculated on day 3 after the initiation of IV steroids according to the following formula: number of bowel movements/day + (0.14 x CRP > 8mg/L), Seventy-two percent of patients with a value ≥ 8.0 required a colectomy. The Seo index includes variables calculated from the preceding day (day 2 of corticosteroid therapy) and is derived from the following formula: $60 \times \text{blood in faeces} + 13 \times \text{bowel movements/day} + 0.5 \times \text{ESR} - 0.4 \times \text{Hb (g/l)} - 1.5 \times \text{albumin (g/l)} + 200$. Constants are as follows: for blood in faeces 0 indicates none and 1 indicates present; for bowel movements 0 indicates 0–3 stools per day; 1 indicated 4 stools per day ; 2 indicated 5–7; and 3 indicated ≥ 8 . A value < 150 – 220 corresponds with remission or mild UC, 150–220 corresponds with moderately severe UC, and > 220 corresponds with severe UC (Seo et al. 1992). Ho proposed the Scottish Index based on stool frequency, presence of colonic dilatation, and hypoalbuminemia (Ho et al. 2004). In children the Paediatric UC Activity Index (PUCAI) score on days three and five of steroid therapy has been validated as a predictor of initiating rescue therapy (Randal et al.2010; Turner et al.2010).

MEDICAL RESCUE THERAPY

Two main agents are used as rescue therapy in ASUC; infliximab and cyclosporine. Infliximab is a chimeric IgG-1 monoclonal antibody that specifically targets free and membrane-bound tumour necrosis factor-alpha. Infliximab is the only biologic that has proven efficacy in management of ASUC as an induction and maintenance therapy (Côté-Daigneault et al. 2015). Cyclosporine is the second option in steroid refractory ASUC. It is an inhibitor of the transcription factor NF- κ B of activated T cells and attenuates the production of interleukin-2 from these cells. There is no definite preference on which of these 2 salvage therapies to use as they have advantages and disadvantages depending on the patients clinical status and physician`s preference.

The GETAID study found that infliximab was not inferior to cyclosporine as a rescue treatment to avoid colectomy (Laharie et al. 2012). They documented clinical response rates for cyclosporine of 84% (2mg/kg IV daily dose for 1 week) and Infliximab clinical response rates of 84% (5mg/kg as a single dose). Treatment failure rates were also competitive at day 90 (60% for cyclosporine and 54% for Infliximab). Azathioprine was initiated on day 7 in those patients that showed a clinical response. Early results from another randomised controlled trial (CONSTRUCT) comparing cyclosporine with infliximab also suggests that

there is no significant difference in quality adjusted survival, colectomy rates, mortality and serious adverse reactions between the two treatments (Seagrove et al. 2014).

Jarnerot et al showed that infliximab was significantly better than placebo in his small study of patients with ASUC: more patients in the placebo group (14/21) than in the infliximab group (7/24) had a colectomy; this difference was statistically significant ($P < 0.017$) with an odds ratio (OR) of 4.9 (95% confidence interval [CI], 1.4–17) in favour of infliximab (Jarnerot et al. 2005).

Cyclosporine as a rescue therapy is also supported by the ECCO consensus (Dignass, et al. 2012). Cyclosporine has shown proven efficacy in ASUC since 1994 with response rate of 64 to 84 %. It has a rapid onset of action and allows timely intervention to prevent colectomy in non-responders. Its clinical efficacy whilst proven, comes with risks of toxicity including nephrotoxicity, hypertension, seizures/ neurotoxicity. Its short term value as rescue therapy should be balanced by the longer term colectomy rates seen despite its use (88% colectomy rate at seven years), and high rates of colectomy in patients previously exposed to thiopurines (Eun & Hand.2015). Sequential use of calcineurin inhibitors followed by infliximab or vice versa may be successful in approximately 25%-40% of adult patients, but is associated with significant morbidity and even mortality (Dayan & Turner. 2012). Other biologicals like adalimumab, certolizumab and golimumab have no clinical trials published as treatment options for ASUC. The ultimate management of ASUC is colectomy when medical rescue therapy fails.

COLECTOMY IN ASUC

Clinical parameters which have been studied as predictors of colectomy in ASUC include a stool frequency of more than 12 per day on day 2, which conferred a 55% rate of colectomy in a retrospective study of 166 patients (Lennard-Jones et al. 1975), while stool frequency greater than 8 per day on day 3 was associated with a 85% colectomy rate in another prospective study of 55 admissions (Travis et al. 1996). Disease extent is also an important predictor of colectomy; patients with extensive colitis have a four-fold increased risk when compared to those who have proctitis alone.(Solberg et al. 2009). Extensive deep ulceration on endoscopy is a very strong predictor with a 93% risk of colectomy (Daperno et al. 2004). Serum albumin may also be a useful predictor in that in a retrospective study of 189 admissions colectomy was required in 42% of patients with a serum albumin < 30 g/L (Lennard-Jones et al. 1975; Ho et al.2004). However albumin as an independent predictor of colectomy showed less convincing results in other prospective studies (Travis et al.

1996;Turner et al.2010). Toxic megacolon (which is defined as colonic dilatation of ≥ 6 cm or caecal diameter > 9 cm, with systemic symptoms) and mucosal islands on plain abdominal X-ray have been described as predictors of colectomy in ASUC with a 75% risk of colectomy. Indications for colectomy in ASUC include non-response to medical rescue therapy (especially patients with prior exposure to thiopurines or biologicals),toxic megacolon and severe bleeding (Sandborn et al. 2009; Nicholls et al.2002). The exact timing of surgery is still debatable; application of the standard IBD multidisciplinary team (MDT) recommendations (based on a study that was conducted in 2 UK regions) attempts to ensure quality of care and consensus with regard to decision making (Morar et al. 2014). Early surgical intervention removes the source of inflammation that drives the illness, leading to decreased morbidity associated with prolonged steroid use and rescue therapy. However surgery comes with its own complications which include wound sepsis and dehiscence, stoma failure, dehydration and hygiene challenges related to the stoma effluent. Colectomy is indicated from 4-7 days after rescue therapy in non-responders. Prolonged medical therapy in refractory systemic ill patients results in poor outcomes if surgery is instituted. The recommended operation in ASUC is subtotal colectomy and end-ileostomy, with the rectum left in situ as a non-functioning Hartmann's pouch or occasionally as a mucus fistula, reconstruction is not an option in the acute setting (Arnott I et al. 2010). Laparoscopic colectomy when performed in large volume centres has less morbidity than an open operation. Patients are allowed to fully recover from the surgery and learn to manage and cope with their ileostomy. Several options are available for restoration of bowel continuity. They are dependent on how severely the rectum is involved, the strength of the anal sphincter and the patient's circumstances and preference. A completion proctectomy with ileal pouch anal anastomosis in those who have completed their family is what the majority will opt for. An ileorectal anastomosis spares the risk of sexual dysfunction due to a proctectomy and is the preferred option for those who wish to procreate. In those with poor sphincter control they will be best served by a proctectomy and remain with their ileostomy. This staged approach with a minimally invasive completion proctectomy and ileal pouch-anal anastomosis resulted in no mortality and only one anastomotic leak in a series of 50 patients (Holubar et al. 2009). Delayed surgery in patients with prolonged in-hospital medical treatment (8 versus 5 days; $P = 0.036$) was the only factor associated with increased post-operative complications (OR 1:12; $P = 0.044$).

CONCLUSION

Ulcerative colitis is a complex chronic autoimmune inflammatory disease of variable severity. ASUC is a potentially fatal condition with an associated mortality ranging from 2.9% in peripheral centres to less than 1% in specialist inflammatory bowel disease centres. It has well defined diagnostic criteria, severity assessment parameters and treatment algorithms based on clinical response. The medical treatment, directed by a consultant gastroenterologist in close liaison with a colorectal surgeon, aims to allow the patients to recover from the acute systemic response and avoid an emergency colectomy with its high morbidity. These management pathways and outcomes are derived from data obtained in developed countries. There are no recent reports on ASUC behaviour, therapy and outcomes in patients from our region and in particular if multiple indices used to predict colectomy elsewhere are applicable to our patients.

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Chapter 2

Manuscript

Journal “ready” manuscript for submission to the South African Medical Journal

(Instructions for authors are recorded in Appendix 2. As per these instructions references are in the Vancouver style, thus differing from Part A and B)

PREDICTORS OF EMERGENCY COLECTOMY IN PATIENTS ADMITTED WITH ACUTE SEVERE ULCERATIVE COLITIS

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ABSTRACT

INTRODUCTION: Acute Severe Ulcerative Colitis (ASUC) is a life threatening condition which requires urgent and aggressive medical therapy to reduce mortality, morbidity and avoid surgery. To facilitate this process it is essential to identify patients at high risk of poor outcomes and emergency colectomy. Numerous such risk factors have been described in the Western literature however there are no local data addressing this issue. As such it is unclear if these predictors are applicable in our setting. The aim of this study is thus to identify risk factors for emergency colectomy in patients admitted to Groote Schuur Hospital with ASUC.

METHODS: A retrospective cohort study of 98 patients admitted with ASUC between January 2003 and January 2013 was performed. Clinical, demographic, laboratory and endoscopic factors on admission and 3 days thereafter were analysed as predictors of colectomy by univariate and multivariate analysis.

RESULTS: Twenty five percent of the cohort underwent emergency colectomy. On univariate analysis factors predicting colectomy on admission were exposure to oral corticosteroids ($p=0.01$), megacolon ($p=0.049$) or mucosal islands ($p=0.04$) on abdominal X-ray, and a short duration from UC diagnosis until presentation with ASUC ($p=0.04$). The only variable that was significantly associated with colectomy on day 3 was serum albumin ($p=0.01$). This was also the only variable to remain significant on multivariate analysis (OR 0.79, 95% CI 0.65-0.97, $p=0.01$).

CONCLUSION: ASUC is a medical emergency and predicting colectomy risk aids in therapeutic management. The only variable significantly associated with the need for surgery in our study was hypoalbuminaemia on day 3. Given the small study numbers a larger prospective study would be of value.

INTRODUCTION

Ulcerative colitis (UC) is the most common form of Inflammatory Bowel Disease (IBD). It is characterised by a relapsing and remitting course. Most episodes of active UC are mild to moderate in severity and can be managed as outpatients, however about 15% will have an acute severe flare of their disease in their life time, requiring admission.^[1] Acute severe UC (ASUC) is best defined using Truelove and Witts criteria by the presence of ≥ 6 bloody stools per day with any of the following 4 criteria: a tachycardia (>90 bpm), fever ($\geq 37.8^\circ$), anaemia (haemoglobin <10.5 g/dl), or an elevated erythrocyte sedimentation rate (ESR) or CRP (>30 mm/h) (Appendix 1).^[2] ASUC is a medical emergency which carries a high risk of colectomy. Fortunately the majority of cases respond rapidly to intravenous corticosteroids, which were first used as therapy in 1955. This simple intervention together with correction of fluid and electrolyte abnormalities, treatment of concurrent infections, close monitoring by a multidisciplinary team and timely colectomy has significantly reduced mortality rates to less than 1% in specialist units.^[3]

In order to optimise management of this life threatening condition it is important to identify patients at presentation who will be at high risk of complications and may require colectomy; these individuals would then receive urgent and aggressive therapy with intravenous corticosteroids. Multiple predictors of severity in ASUC have been described. These include stool frequency, fever, tachycardia, disease extent, young age, serum albumin, haemoglobin, C-reactive protein (CRP), and extensive deep ulceration on endoscopy.^[3-6] In addition megacolon and mucosal islands on plain abdominal X-ray have been described as predictors of colectomy in ASUC, conferring a 75% risk of surgery.^[4] Unfortunately 30% of patients will not respond to corticosteroids and it is essential to identify these patients early so as not to prolong ineffective therapy but rather initiate salvage therapies in the form of cyclosporine or infliximab, or alternatively perform colectomy.^[5] Several scoring systems have been proposed to identify corticosteroid failures; the one most commonly used is the Oxford Index, whereby a stool frequency exceeding 8/day or 3-8/day plus a CRP > 45 mg/dL on the third day of corticosteroid therapy is sufficient evidence of corticosteroid failure and should prompt rescue therapy.^[2]

The fore mentioned predictors of colectomy (on admission and on day 3 of corticosteroid therapy) have been identified from cohorts in other regions of the world, mostly USA and Europe. There is no data from South Africa and it is thus unclear whether they are of value in our population.

The aim of this study is thus to evaluate the role of these predictors of emergency colectomy in our IBD cohort and reflect on outcomes of ASUC in our setting. Limitation of access to rescue therapy (biologics) in our setting has prompted us to identify these predictors so as to minimize prolonged ineffective inpatient medical therapy and reduce the economic constraint associated with delayed colectomy complications.

METHODS

A retrospective review of folders of all patients admitted to Groote Schuur Hospital, (Cape Town, South Africa) with a diagnosis of ASUC. The study period was from the 01 January 2003 to 31 December 2013. This study received approval from the UCT Human Research Ethics Committee (Appendix 2).

Definitions:

ASUC was defined using the Truelove and Witts criteria: that is frequency of six or more bloody stools per day together with any one of the following criteria:

- Tachycardia (>90 bpm)
- Temperature greater than 37.8°C
- Anaemia (haemoglobin <10.5 g/dL)
- An elevated ESR (>30 mm/h) or CRP (>30)

Corticosteroid failure was defined on day 3 of intravenous steroids by the presence of either of the following Oxford Index criteria:

- Stool frequency exceeding 8 stools per day
- 3 - 8 stools per day together with a CRP > 45

Inclusion criteria for the study:

- Patients admitted with a clinical diagnosis of ASUC satisfying Truelove and Witts criteria (Appendix 1).

- Patients who had undergone a colectomy with a confirmed clinical and histological diagnosis of ASUC. Patients with a revised secondary diagnosis within ninety days were excluded.

Patients were identified from inpatient admission records, surgical files, as well as an established IBD database. All patients admitted to a medical ward were treated with intravenous corticosteroids at standard doses.

Data collected included baseline demographics (age, gender, family history, ethnicity, smoking status, duration of UC prior to ASUC diagnosis, time from diagnosis to presentation, and medication exposure on admission). Clinical, biochemical, laboratory variables, radiological and sigmoidoscopy findings on admission and on day 3 of intravenous corticosteroids were also extracted, as were indications for colectomy and 90 day outcomes. Outcome measures assessed were death within 90 days of presentation, colectomy free survival at 90 days and surgical complications

STATISTICAL ANALYSIS

The distribution of all continuous variables was evaluated and expressed as medians and interquartile ranges (IQRs) or means \pm standard deviations (SD) as appropriate. Statistical analysis employed Chi², Fishers exact, Student t test, Wilcoxon rank sum test or Kruskal-Wallis testing as appropriate. Those variables with *P* values below 0.10 were further tested in a series of logistic multivariate regression models. The analysis was performed using STATA version 11 (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP). This study was approved by the Ethics Committee of the University of Cape Town (Appendix 3)

RESULTS

Ninety eight patients with ASUC were eligible for study inclusion. Sixty four percent were female. The mean age at first diagnosis of UC was 39 years and the mean age at the time of the ASUC flare was 43 years; only 47% were older than 40 years of age at the time of the attack. The mean duration between diagnosis and admission for ASUC was 61 months. For 17% this was the first presentation of their disease. All the patients had extensive colitis (Appendix 1) with deep ulceration (figure 1). Forty one percent of the cohort were Caucasian, 37% Coloured, 11% Asian and 11% Black. With regards to medication use at the time of admission: 76% were using 5-aminosalicylates (5-ASAs) and 26% thiopurines, none were receiving maintenance biologics. Only 5% of patients had a positive family history of IBD.

Overall 47% were non-smokers. These baseline demographics are presented in table 1. On initial work up only 1 patient (who did not require colectomy) had concurrent *Clostridium difficile* infection and was treated with metronidazole with good effect. No cases of cytomegalovirus were detected.

Twenty five of the 98 patients (25%) underwent a colectomy during the study period, 64% were female which was similar to patients who did not require surgery (Table 2). Eighty percent of patients had their emergency colectomy within 15 days of admission; only half of these were operated on within 7 days. 38% of patients had complications within 90 days post admission which included sepsis (pneumonia, wound sepsis). There were no deaths within the 90 day follow up.

Of patients undergoing colectomy 52% were of Caucasian ethnicity, 40% were Coloured, and 8% Asian. None of the black patients required surgery. There was no significant association between colectomy and ethnicity. The mean age of patients at colectomy was 39 years which was not significantly different from those who did not require colectomy. The group of patients undergoing surgery for ASUC had a significantly shorter duration of disease than those in whom colectomy was avoided; 16 months and 41 months respectively ($p=0.04$). On univariate analysis non-smoking status was not associated with an increased risk of colectomy, nor was a positive family history of IBD or exposure to 5-ASAs or thiopurines (Table 2). In contrast patients requiring colectomy were significantly more likely to have received treatment with oral corticosteroids than those who avoided surgery ($p=0.01$). None of the patients were on maintenance Infliximab at the time of ASUC admission, however 4 patients received Infliximab as rescue therapy and all of them avoided colectomy. On univariate analysis there was no significant difference with regards to any of the baseline laboratory or clinical variables (median number of stools per day, body temperature, haemoglobin, serum albumin, or CRP) when comparing patients requiring colectomy with those who did not (Table 3). In contrast radiologic evidence of megacolon or mucosal islands on abdominal X-ray were significantly more likely to be present in subjects requiring surgery than in those who did not (32% and 40% respectively)

Analysis of day 3 data showed that serum albumin was significantly associated with the need for colectomy ($p=0.01$). In contrast all the other variables analysed at this time point (haemoglobin, temperature, and CRP) did not correlate significantly with the risk of colectomy (Table 4). Furthermore patients meeting the Oxford Index criteria for

corticosteroid failure on day 3 were no more likely to require colectomy than those who did not.

On multivariate logistic regression only serum albumin on day 3 was significantly associated with colectomy (OR 0.79, 95% CI 0.65-0.97, p=0.003)

DISCUSSION

Acute severe ulcerative colitis is a medical emergency because of the risk of colonic perforation; prompt recognition and timely medical or surgical intervention within the setting of a multidisciplinary team is crucial to reduce morbidity and mortality. ^[1] In order to optimise care and facilitate aggressive management strategies there is an urgent need to identify patients at very high risk for colectomy. As a consequence the role of prognostic factors in patients with ASUC has been the subject of much interest.

Multiple predictors of severity have been described. Among objective clinical features, bloody stool frequency, increased body temperature and tachycardia are good predictors of severity and outcome. ^[1] In a retrospective study of 166 patients a stool frequency of more than 12 per day conferred a 55% risk of colectomy. ^[2] Laboratory markers have also been studied extensively with varying degrees of success. The widely used acute phase reactant CRP has established value in ASUC in both adults and children. ^[1] Serum albumin may also be predictive; in a retrospective study of 189 admissions hypoalbuminemia (serum albumin less than 30 g/L) on the first day of admission was associated with a 42% risk of colectomy. ^[4] However results from multiple prospective studies have shown less convincing results.

Radiological findings which include megacolon (colon dilatation of > 5.5 cm), thumb printing (suggestive of mucosal oedema), the presence of mucosal islands and features of a small bowel ileus are also predictors of severity in UC. ^[2] Megacolon and mucosal islands on plain abdominal X-ray have been shown to confer a 75% risk of colectomy. ^[4] Disease extent is also an important predictor of the need for surgical intervention; patients with extensive colitis have a risk 4 times higher than those with limited UC. Deep ulceration on endoscopy is also an ominous sign in ASUC; 93% will require surgery. ^[6,7] Patients who present with a disease flare and any of these risk factors require immediate admission and urgent intervention.

Intravenous corticosteroids are the mainstay of therapy. Unfortunately 30% of patients will fail to respond to corticosteroids and it is essential to identify these patients early so as not to prolong ineffective therapy but rather initiate salvage therapies in the form of cyclosporine or

infliximab, or alternatively perform colectomy. ^[2] Colectomy is a lifesaving intervention and the ability to predict the need for surgery and its timing is key in decreasing morbidity and surgical complications.

Response to steroids should be assessed at day 3 of admission and partial or non-responders considered for rescue medical therapy or surgery. Several scoring systems have been proposed to identify corticosteroid failures; the one most commonly used is the Oxford Index, whereby a stool frequency exceeding 8/day or 3-8/day plus a CRP > 45 mg/dL on the third day of corticosteroid therapy is considered sufficient evidence of corticosteroid failure and should prompt rescue therapy. ^[2] Colectomy is indicated from 4-7 days after rescue therapy in non-responders. Prolonged medical therapy in refractory systemic ill patients results in poor outcomes if surgery is delayed. ^[8]

Our study evaluated all of these fore mentioned risk factors and has identified several which significantly predict colectomy during admission for ASUC. Firstly a shorter duration of disease conferred a higher risk of subsequent surgery than patients with a longer duration of disease. This is in keeping with other publications which show that most severe attacks of UC occur within 3 months of diagnosis. ^[6] In our study the use of thiopurines and 5-ASAs did not impact on colectomy rates. In contrast (and not surprisingly) patients who were already on oral steroids on admission were more likely to undergo colectomy. This has been described previously and oral corticosteroids are a well described risk factor for colectomy in ASUC. ^[9] It is common practise in our institution to admit patients who have failed to respond to oral steroids and give them a trial of intravenous therapy. These individuals likely have more severe UC and have already shown themselves to be (at least partially) steroid refractory. As such they would inherently be at greater risk of needing emergency surgery. ^[9,10] All other baseline demographics were not significantly associated with the risk of colectomy.

Interestingly most of the ASUC patients were female. This is not in keeping with international literature which reports a male predominance; with a male to female ratio of 36:16. ^[10-11] Of interest is the 0% colectomy rate in the black population; this likely reflects the small numbers included but merits further evaluation. With regards to baseline laboratory investigations, none were shown to increase the risk of colectomy. This is at odds with what is reported in the literature where the risk of colectomy increases as more Truelove and Witts criteria are fulfilled. ^[13] As such it appears logical that baseline haemoglobin and CRP levels would be of value. Similarly a low serum albumin on presentation is a well described predictor of the need for surgery. ^[14] Serum albumin levels on admission did not predict colectomy in our study however hypoalbuminaemia on day 3 was significantly associated

with an increased need for surgery. This was the only variable that remained statistically significant on multivariate analysis and likely reflects ongoing, severe inflammation which has failed to respond to corticosteroids and which should prompt escalation of therapy.

There are some other interesting observations which have emerged from this study. The 1st is the 100% success rate of infliximab in patients failing corticosteroids. Although numbers were small this suggests that appropriate patients are being selected. Another observation which is somewhat disturbing is that 40% of patients had their colectomy between 8 and 15 days of admission. It is unclear why surgery was delayed in these individual but this could explain the high incidence of post-operative complications. It is well described in the literature that delaying surgery is associated with higher morbidity and mortality in ASUC.^[8]

This study has several weaknesses, mostly as a consequence of its retrospective design. Due to inconsistent documentation of admission data in both medical and surgical wards, it is likely that some cases of ASUC would have been overlooked. However this data is likely missing at random and should not impact study results to any great extent. This is supported by our colectomy rate of 25 % which is in keeping with that reported in the world literature.^[15] A second study weakness is the relatively small numbers of study subjects. This could have led to a Type 11 error which could explain the lack of significance of many of the variables analysed on presentation and on day 3 (notably the Oxford index of severity). A prospective cohort is highly recommended.

CONCLUSION

ASUC is a medical emergency, predicting which patients will likely require colectomy is a very valuable tool in guiding therapeutic management. In our study the only variable significantly associated with colectomy was hypoalbuminaemia on day 3. However given the small study numbers a larger prospective study would be of value in identifying additional risk factors.

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Table 1: Baseline demographic and clinical parameters of patients with ASUC

Variable	Value
Gender	
Female	61 (62%)
Median age at UC diagnosis in years	38 (27 – 52)
Mean age at ASUC flare diagnosis in years	43.2 ± 15.48
Median duration of disease from UC to ASUC diagnosis in months	30 (6 -106)
Race	
Caucasian	40 (41%)
Coloured	36 (37%)
Black	11 (11%)
Asian	11 (11%)
Medication exposure prior ASUC	
5 ASA	65 (66%)
Thiopurines	24 (24%)
Oral steroids	40 (41%)
Non-smoking status	46 (47%)
Positive family history of IBD	5 (5%)
Clinical	
Median albumin day 1®	34 (22 - 41)
Median haemoglobin day 1®	12 (10.8 – 13.2)
Median C reactive protein day 1®	53 (17 – 130.1)
Median number o of stools day 1®	8 (6 - 10)
Median ESR®	47 (32 – 68)
Median temperature ®	36.8 (36 – 37.2)
ASA = Aminosalicylate. Continuous variables are recorded as medians (IQR, 25% - 75%) or mean.± SD. CRP = C reactive protein; ESR = Erythrocyte sedimentation ratio.	

Table 2. Differences in baseline demographic Information by colectomy

<u>Variable</u>	<u>Colectomy</u> n = 25	<u>Non colectomy</u> n=73	<u>P value</u>
First presentation of UC	7 (28%)	10 (14%)	0.50
Mean age at UC diagnosis (years)	39.16± 16.26	38.78 ± 15.66	0.92
Mean age at ASUC presentation (years)	42 ± 17.1	43.52 ± 15.01	0.73
>40 years of age at ASUC presentation	14 (56%)	32 (44%)	0.18
Median duration in months from UC diagnosis to ASUC diagnosis	16 (1 – 56)	41 (7.5 – 111)	0.04
Gender :female	16 (64%)	45 (62%)	0.83
Ethnicity			0.15
Caucasians	13 (52%)	27 (37%)	
Coloureds	10 (40%)	26 (36%)	
Blacks	0 (0%)	11 (15%)	
Asians	2 (8%)	9 (12%)	
Family history of UC	1 (4%)	4 (5%)	0.77
Non smoker	10 (40%)	36 (49%)	0.19
Medication prior ASUC			
5 ASA	16 (54%)	49 (67%)	0.78
Thiopurines	7 (28%)	17 (23%)	0.56
Corticosteroids	15 (60 %)	25 (34 %)	0.01
UC = Ulcerative Colitis; ASUC = Acute Severe Ulcerative Colitis; * All continuous variables are recorded as medians (IQR, 25% - 75%); ASA = Aminosaliclylate			

Table 3: Factors predicting colectomy in ASUC patients on admission

Variable	Day 1		
	Colectomy (n=25)	No colectomy (n =73)	P value
Median number of stools per day	8 (6 -10)	8 (6 – 10)	0.24
Median Temperature	36.8 (36 – 73.5)	36.8 (36.1 – 37.2)	0.76
Median Haemoglobin	12.2 (11.2 – 13.3)	11.6 (10.1 – 12.8)	0.24
Median CRP	48.3 (15.5 – 156)	53.2 (16.3 – 118.2)	0.10
Median serum Albumin	36.4 (33 – 40.6)	37 (33 – 42)	0.51
Radiology findings			
Megacolon	8 (32%)	12 (16%)	0.05
Mucosal islands	10 (40%)	9 (12%)	0.04
All continuous variables are recorded as medians (IQR, 25% - 75%). CRP = C reactive protein.			

Table 4: Factors predicting colectomy on day 3 of intravenous steroids

Variable			
	Colectomy (n -25)	No colectomy (n - 73)	P value
Median number of stools per day	4 (2-6)	3 (2-4)	0.21
Median temperature	36.15 (36-36.8)	36 (36.5)	0.15
Median Haemoglobin	10.8 (9.5-11.6)	10.6 (9.9-11.8)	0.81
Median CRP	55 (19-103)	27 (10.5-50.5)	0.10
Median albumin	26 (25-32)	34 (30-36)	0.01
Patients meeting the oxford Index Criteria	4/19 (21%)	9/70 12.9%)	0.46

Appendix 1

Montreal classification of Ulcerative colitis

Montreal classification of extent of Ulcerative colitis (UC)	
Extent	Anatomy
E1 Ulcerative proctitis	Involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction)
E2 Left sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3 Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure

Montreal classification of severity of Ulcerative Colitis (UC)	
Severity	Definition
S0 Clinical remission	Asymptomatic
S1 Mild UC	Passage of four or fewer stools/day (with or without blood), absence of any systemic illness, and normal inflammatory markers (ESR)
S2 Moderate UC	Passage of more than four stools per day but with minimal signs of systemic toxicity
S3 Severe UC	Passage of at least six bloody stools daily, pulse rate of at least 90 beats per minute, temperature of at least 37.5°C, haemoglobin of less than 10.5 g/100 ml and ESR of at least 30 mm/hr.
ESR = Erythrocyte sedimentation rate	

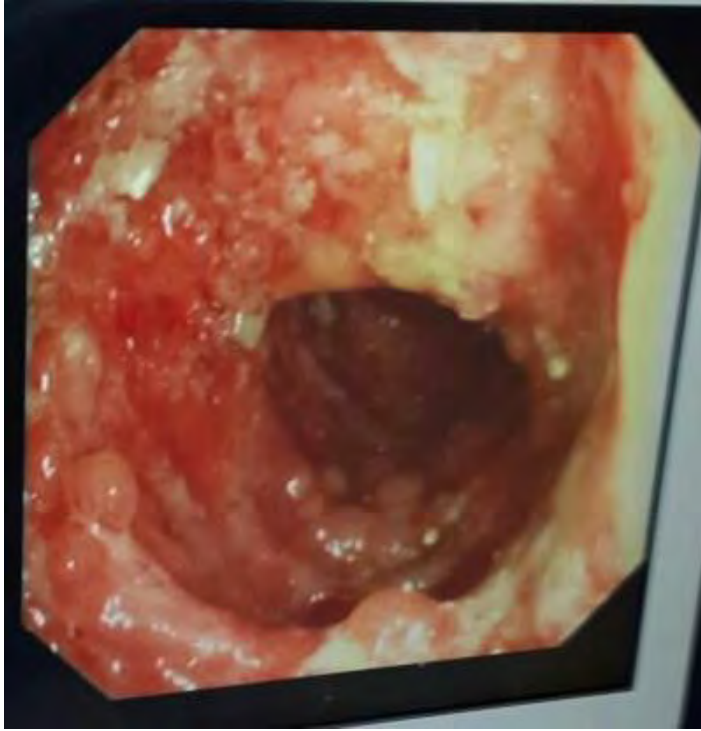


Figure 1. Deep ulceration in ASUC

Appendix 2

Ethics approval



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E52-24 Old Main Building
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22 April 2014

HREC REF: 232/2014

Dr G Watermeyer
Gastroenterology
GIT Unit
NGSH

Dear Dr Watermeyer

PROJECT TITLE: PREDICTORS OF EMERGENCY COLECTOMY IN PATIENTS ADMITTED WITH SEVERE ULCERATIVE COLITIS (Masters - Dr N Mokhele)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

- Please re-submit the FHS013 application form to reflect the supervisor as the PI of this study. The student will be included in all communication.

Approval is granted for one year until the 30th April 2015

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

We acknowledge that the Master student, Dr Nnete Nimrod Mokhele is also involved in this study.

Please quote the HREC reference no in all your correspondence.

Yours sincerely ,

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

HREC 232/2014

Appendix 3

Author guideline for the South African Medical Journal

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

AUTHORSHIP

Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; or (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

RESEARCH ETHICS COMMITTEE APPROVAL

Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to www.icmje.org.

ETHNIC CLASSIFICATION

References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Research articles (previously 'Original articles') not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to clinical medicine and related fields. *References should be limited to no more than 15.* Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results, and Conclusion.*

Scientific letters will be considered for publication as shorter **Research articles**.

Editorials, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the *SAMJ* peer review process.

Review articles are rarely accepted unless invited.

Letters to the editor, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address.

Forum articles must be accompanied by a short description (50 words) of the affiliation details/interests of the author(s). Refer to recent forum articles for guidance. Please provide an accompanying abstract not exceeding 150 words.

Book reviews should be about 400 words and must be accompanied by the publication details of the book.

Obituaries should be about 400 words and may be accompanied by a photograph.

Guidelines must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed. A structured abstract not exceeding 250 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2. etc.) and summarised in a Table of Contents. References, appendices, figures and tables must be kept to a minimum.

Guidelines exceeding 8 000 words will only be considered for publication as a supplement to the SAMJ; the costs of which must be covered by sponsorship or advertising. The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - www.icmje.org. Manuscripts must be provided in **UK English**.

Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age'. The same applies to \pm and $^{\circ}$, i.e. '35 \pm 6' and '19 $^{\circ}$ C'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...' Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file or provided as '**supplementary files**'. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes or tabs), and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Figure legends: Fig. 1. 'Title...' All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable, but images must not be resized to increase resolution.

Unformatted and uncompressed images must be attached individually as '**supplementary files**' upon submission (not solely embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft Powerpoint or Excel must be accompanied by the original workbook.

REFERENCES

References must be kept to a maximum of 15. Authors must verify references from original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists must be generated manually and **not** with the use of reference manager software. Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,^[2] and others.^[3,4-6] All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al. First and last page, volume and issue numbers should be given.

Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID). Authors are encouraged to use the DOI lookup service offered by **CrossRef**.

Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. *Stat Med* 1998;289(1):350-355. [<http://dx.doi.org/10.1000/hgjr.182>] [PMID: 2764753]

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Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. <http://www.who.int/whr/2002> (accessed 16 January 2010).

Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet

published can be included as references followed by '(in press)'. Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.