

# How to manage: acute severe colitis

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## ABSTRACT

Acute severe ulcerative colitis (ASUC) is a medical emergency which is associated with significant morbidity and a mortality rate of 1%. ASUC requires prompt recognition and treatment. Optimal management includes admission to a specialist gastrointestinal unit and joint management with colorectal surgeons. Patients need to be screened for concomitant infections and thromboprophylaxis should be administered to mitigate against the elevated risk of thromboembolism. Corticosteroids are still the preferred initial medical therapy but approximately 30%–40% of patients fail steroid therapy and require rescue medical therapy with either infliximab or cyclosporine. Emergency colectomy is required in a timely manner for patients who fail rescue medical therapy to minimise the risk of adverse post-operative outcomes. We discuss current and emerging evidence in the management of ASUC and outline management approaches for clinicians involved in managing ASUC.

## INTRODUCTION

Acute severe ulcerative colitis (ASUC), as defined by the Truelove and Witts' criteria,<sup>1</sup> is a medical emergency. Up to 25% of patients with ulcerative colitis (UC), will require hospitalisation for ASUC during their disease course.<sup>2</sup> ASUC requires prompt recognition and admission to a specialist gastrointestinal unit and combined management between gastroenterologists and colorectal surgeons. Initial evaluation and assessment should focus on evaluation and correction of fluid and nutritional status, exclusion of concomitant infections (eg, *Clostridium difficile* and cytomegalovirus (CMV)) and administration of thromboprophylaxis. Intravenous steroids are the initial management of choice, but approximately 30%–40% of patients fail to respond adequately and require rescue medical therapy with either infliximab or cyclosporine (CyA). Patients who fail to respond to rescue therapy require emergency colectomy in a timely manner to minimise the risk of

adverse postoperative outcomes. Here, we review the diagnosis and management of ASUC and consider recent advances in its management.

## DIAGNOSIS, INITIAL ASSESSMENT AND GENERAL MANAGEMENT

The diagnosis of ASUC is established by fulfilment of the Truelove and Witts criteria<sup>1</sup> (table 1). Severe colitis is defined by the presence of six or more bloody stools with one or more features of systemic toxicity. Patients with ASUC require prompt hospitalisation to a specialist gastrointestinal facility for combined medical and surgical care.<sup>3</sup> Initial investigations should centre on a comprehensive biochemical blood panel, stool samples to exclude infection and additional investigations in anticipation of the need for rescue therapy with either CyA or infliximab as detailed in table 2. Stool testing for culture and *C. difficile* to exclude associated infectious causes and an abdominal radiograph to assess for toxic megacolon should be performed, along with early consideration of differential diagnoses (table 3). A colonic diameter of >5.5 cm in the presence of supporting clinical features of severe colitis warrants an urgent surgical assessment. General measures such as attention to fluid status, correction of electrolyte imbalances and assessment/optimisation of nutritional status are important measures. Routine use of bowel rest and total parenteral nutrition is ineffective; enteral nutrition is safer and was associated with a lower risk of complications in a small randomised trial of ASUC patients.<sup>4</sup> Anticholinergic, antidiarrhoeal and opiate medications should be avoided as they can precipitate colonic dilatation. A recent systematic review concluded that there is no evidence for use of antibiotics as adjunctive therapy in ASUC<sup>5</sup> despite the suggestion of some benefit in small cohort studies.

## TIMING AND ROLE OF ENDOSCOPY

A limited, unprepared sigmoidoscopy with minimal air insufflation should be



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**Table 1** Truelove and Witt's severity index

	Mild	Moderate	Severe
Bloody stools per day	<4	4–6	≥6 (plus at least one of the below features of systemic upset)
Blood in stools	No more than small amounts	Between mild and severe	Visible blood
Pulse >90	No	No	Yes
Temperature >37.8°C	No	No	Yes
Haemoglobin <100 g/L	No	No	Yes
ESR or CRP >30	No	No	Yes

CRP, C reactive protein; ESR, erythrocyte sedimentation rate.

performed by an experienced endoscopist to assess for severity of UC, and biopsies for CMV (see below) should be performed. Endoscopy is safe and helps in prognostication—for instance, extensive deep ulceration is associated with a high risk of colectomy.<sup>6</sup> Ideally, this should be performed as early as possible during the course of hospitalisation, as endoscopic assessment within the first 72 hours was associated with better outcomes in a large sample of ASUC patients by permitting timely and appropriate clinical decision making.<sup>7</sup>

### THROMBOPROPHYLAXIS IN ASUC

Inflammatory bowel disease (IBD) is associated with a heightened risk of both venous and arterial thromboembolism and this risk is particularly elevated during periods of hospitalisation with an eightfold risk in those with an active flare.<sup>8</sup> Multiple mechanisms including immobility related to hospitalisation, comorbidities and a higher circulating levels of coagulation factors as well as prothrombotic cytokines associated with

**Table 2** Initial investigation panel for acute severe ulcerative colitis

<b>Faeces – exclude infection</b>	Microscopy and culture Clostridium difficile
<b>Blood – routine biochemical panel</b>	Full blood count Urea and electrolytes Liver function tests C Reactive Protein
<b>Radiology</b>	Abdominal X-ray
<b>Pre-biologic/cyclosporine therapy screen</b>	HIV, Varicella zoster IgG Hepatitis B and C screen TB quantiferon Chest X-ray Lipid profile Magnesium

TB, Tuberculosis.

**Table 3** Differential diagnosis of acute severe ulcerative colitis

Acute severe ulcerative colitis	Ischaemic colitis
Infectious colitis	Radiation induced colitis
Diverticulitis	Vasculitis
Segmental colitis associated with diverticulosis (SCAD)	Drug induced colitis
Crohn's colitis	

systemic inflammation have been proposed as factors contributing to this risk.<sup>9</sup> Compression stockings and low-molecular-weight heparin should be routinely prescribed as recommended in the latest British Society of Gastroenterology (BSG) Consensus IBD guidelines (2019).<sup>10</sup> The safety of thromboprophylaxis is well established: a meta-analysis of eight randomised controlled trials (RCTs) comprising 454 patients with acute UC failed to identify any significant difference in adverse events including gastrointestinal bleeding.<sup>11</sup>

### MEDICAL MANAGEMENT

#### Screening and treatment for concomitant infections

Patients with ASUC may have coexisting infections such as *C. difficile* and CMV. It is important to screen and treat for these though it is unclear if either organism causes an acute flare of UC or is merely an epiphenomenon of severe disease.

#### Clostridium difficile

*C. difficile* infection (CDI) is more common in UC patients compared with Crohn's disease and is associated with adverse outcomes.<sup>12</sup> Contrary to the general medical population, *C. difficile* in patients with IBD is associated with younger age, less antibiotic/proton pump inhibitor (PPI) exposure, and is more likely to be recurrent.<sup>12</sup> While incidence of CDI in hospitalised patients with IBD was previously rising, it has fallen since 2007 from 8.7% to 0.4%, mirroring a similar rate of decline in the general population.<sup>13</sup> Patients with IBD and concurrent CDI tend to have worse outcomes with higher mortality (OR 4.7, 95% CI 2.9 to 7.9), longer hospitalisation (OR 3.0, 95% CI 2.3 to 3.7)<sup>14</sup> and higher colectomy rates (OR 10.0, 95% CI 2.7 to 36.3)<sup>15</sup> than those with IBD alone.

The optimal management of CDI in patients with IBD is not firmly established. Uncontrolled studies suggest superiority for vancomycin over metronidazole with a decreased colectomy rate<sup>16</sup> and significantly fewer readmissions. A longer duration of vancomycin (21–42 days) is superior to standard duration in reducing recurrence rates.<sup>17</sup> An open-label study evaluating the use of fidaxomicin in 81 patients with IBD showed that 90% of patients responded with symptom resolution.<sup>18</sup> There are no data to support use of faecal microbiota transplantation for CDI in severe UC patients.

There is debate about the optimal timing of rescue therapy in ASUC patients with concurrent CDI who

fail to respond to antibiotics and intravenous steroids. The BSG suggest that it is 'prudent not to escalate therapy or introduce rescue therapy with infliximab or calcineurin inhibitors' in those with ASUC owing to the lack of data to guide this.<sup>10</sup> The American College of Gastroenterology and European Crohn's and Colitis Organisation on the other hand suggest that escalation in therapy 'probably should be avoided for 72 hours after initiating therapy'/'should be guided by careful risk/benefit judgement'— respectively.<sup>19 20</sup> If rescue therapy is required, it appears to be safe based on a recent retrospective cohort study which compared outcomes among patients with concomitant CDI and IBD who had therapy escalation. In fact, the likelihood of adverse outcomes were lower (1.8%) among patients who had therapy escalation to immunomodulatory or biologic therapy compared with those that did not.<sup>21</sup>

#### Cytomegalovirus

The role of CMV in IBD exacerbations has been a matter of considerable debate. The prevalence varies depending on the diagnostic methods used to detect CMV but there is wide consensus of a higher prevalence among steroid refractory patients with prevalence rates ranging from 20% to 40%.<sup>22</sup> All patients should have CMV testing by endoscopic biopsy, with clinical suspicion being higher in those with refractory symptoms and systemic features such as fever and splenomegaly. Endoscopic features of superimposed CMV colitis are often non-specific but typical findings include punched-out, geographical, longitudinal and irregular ulcers.<sup>23</sup> It is recommended that biopsies are collected from the ulcer base or edge to maximise detection. One US retrospective study found an average of 11 biopsies from areas of active inflammation were needed to give an 80% probability of positivity for CMV<sup>24</sup> though such extensive sampling in ASUC is seldom indicated. Histological features of CMV inclusion bodies (owl's eye) are highly specific but have very low sensitivity and therefore needs to be combined with immunohistochemistry or PCR. Several blood-based assays measuring CMV antigenemia in polymorphonuclear leukocytes and PCR for CMV DNA in peripheral blood have poor sensitivity and optimal cut-off thresholds for detecting CMV colitis are not well established.

Treatment with infliximab or CyA in ASUC associated with CMV requiring ganciclovir has not been shown to worsen outcomes,<sup>25</sup> however, should there be evidence or suspicion of systemic CMV infection, immunosuppressive therapy should be discontinued while CMV is treated. CMV colitis is typically treated with intravenous (IV) ganciclovir (5 mg/kg twice daily) for 3–5 days, followed by oral valganciclovir (900 mg two times per day) for 2–3 weeks.<sup>26</sup> Initial intravenous antiviral therapy is recommended due to concerns of poor bioavailability of oral therapy in patients with

severe diarrhoea but liaison with local virologist for both diagnosis and therapy is recommended.

#### Strongyloidiasis

While rare, strongyloidiasis often follows an asymptomatic or indolent course, but can present with fulminant severe disease. Those who have lived in endemic areas in tropical and subtropical regions, even decades previously (owing to the life cycle completing within the human host), and especially those who are immunosuppressed should have serology and stool microscopy sent. Eosinophilia is often present, but absence does not reliably allow exclusion. Ivermectin 200 µg/kg for 2 days, repeated after 2 weeks, is generally sufficient.

#### CORTICOSTEROIDS

Intravenous corticosteroids are the mainstay of early treatment for ASUC since Truelove and Witts published their data in 1955. Hydrocortisone or methylprednisolone are commonly used, and although methylprednisolone has a lower mineralocorticoid effect, the choice usually depends on local policy. A systematic review of 32 trials of steroid therapy for ASUC involving 1991 patients reported an overall response to steroids of 67%, with 29% (95% CI 28% to 31%) requiring a colectomy.<sup>27</sup> Interestingly, there was a failure to demonstrate a relationship between dose and colectomy rate above the equivalent of 60 mg methylprednisolone (equivalent to 300 mg hydrocortisone) and higher doses are associated with an increased risk of complications.<sup>27</sup>

It is imperative that response to steroids is assessed early after institution of therapy. Response is defined as a score of <10 on consecutive days on the Modified Truelove and Witt's severity index (table 4), which should be checked on a daily basis. Non-response to steroids at 72 hours is associated with a high colectomy rate.<sup>28</sup> It would be considered unwise to continue steroids as sole therapy beyond 3 days; if there is no improvement, in these patients 'rescue therapy' is indicated (see section entitled: predicting failure of response to medical therapy).

It is important to be aware of the compounding negative effect on bone mineral density that steroids pose in the IBD population. A Cochrane review has confirmed that calcium and vitamin D supplementation for all patients treated with steroids prevented bone loss.<sup>29</sup> Coprescription of a PPI should not be routinely considered unless there is a high risk of gastrointestinal bleeding or active peptic ulcer disease. The risk of steroid-induced hyperglycaemia (or even steroid-induced diabetes) should be acknowledged and mitigated by regular measurement of capillary blood glucose and an assessment of overall glycaemic control by way of glycated haemoglobin (HbA1c).

#### CYA OR INFLIXIMAB?

In those patients identified as requiring salvage therapy, CyA and infliximab are both equally effective.

**Table 4** Modified Truelove and Witt's severity index

Score	0	1	2	3	4	5
Diarrhoea	0–2	3–4	4–5	6–7	8–9	>9
Nocturnal episodes	No	Yes				
Faecal incontinence	No	Yes				
Abdominal cramping	None	Mild	Moderate	Severe		
General well-being	Excellent	Very good	Good	Fair	Poor	Terrible
Blood in stool	None	<50%	>50%	100%		
Anti diarrhoeals	No	Yes				
Abdominal tenderness	None	Mild	Moderate	Severe		

Two RCTs investigated the efficacy of CyA and infliximab in patients with ASUC and demonstrated equivalence in avoiding colectomy.<sup>30 31</sup> In the French study, 115 patients were randomly assigned to receive either intravenous CyA (2 mg/kg per day for 1 week, followed by oral drug until day 98) or infliximab (5 mg/kg on days 0, 14 and 42). The primary outcome of treatment failure (defined by absence of a clinical response at day 7, a relapse between day 7 and day 98, absence of steroid-free remission at day 98, a severe adverse event leading to treatment interruption, colectomy or death) was not different between infliximab and CyA-treated patients.<sup>30</sup> In the larger UK-based CONSTRUCT study, 270 patients were randomly assigned to receive either infliximab (5 mg/kg at baseline, and again at 2 weeks and 6 weeks after the first infusion) or CyA (2 mg/kg per day by continuous infusion for up to 7 days, followed by two times per day tablets delivering 5.5 mg/kg per day for 12 weeks). The primary outcome of quality adjusted survival as well as the secondary outcomes of colectomy rates and time to colectomy was not significantly different between the two groups.<sup>31</sup> Interestingly, in the French RCT, infliximab-treated patients had significantly higher endoscopic remission rates at day 98 (73% vs 25%,  $p < 0.001$ ).<sup>32</sup> Choice of rescue therapy is based on factors other than efficacy and include (1) clinician familiarity and local protocol (2) prior therapies and (3) local availability of testing for CyA levels. Often, ease of use of infliximab relative to CyA makes this the rescue therapy of choice, in the absence of previous tumour necrosis factor (TNF) exposure. In patients who are naïve to prior thiopurine or biologic therapy, CyA can be used as a bridge to thiopurine or vedolizumab therapy.<sup>33</sup> If CyA is used as rescue therapy, pretreatment measurement of serum magnesium and cholesterol, appropriate monitoring of drug levels, renal function and blood pressure should be undertaken.

#### STANDARD OR INTENSIFIED INFlixIMAB?

Several lines of evidence suggest that infliximab pharmacokinetics (PK) may be altered in ASUC due to multiple factors, resulting in lower bioavailability of the drug, and probably an increased immunogenicity to the drug. First, patients with ASUC experience

faecal loss of infliximab through the gut lumen due to ulcerated epithelial surface and subsequent loss of integrity.<sup>34</sup> In keeping with this, faecal loss of infliximab on the first day following infliximab infusion independently predicted failure of endoscopic response to infliximab in a prospective Dutch study.<sup>34</sup> Furthermore, severe inflammation in ASUC results in higher serum and mucosal TNF concentrations<sup>35</sup> which acts as an 'antigen sink'. Finally, a low serum albumin, frequently noted in ASUC, has been consistently associated with low serum infliximab levels and non-response to infliximab.<sup>36</sup> In keeping with this, a retrospective study showed that patients with ASUC had lower levels of infliximab as well as antibodies to infliximab 2 weeks after induction dosing compared with moderately severe UC patients.<sup>37</sup>

All of this lends itself to the hypothesis that an intensified infliximab dosing regimen might overcome the increased drug clearance and potentially improve clinical outcomes. Indeed, an initial retrospective study from Dublin reported that the short-term colectomy rate was significantly better in patients treated with an accelerated regime, but colectomy rates were comparable at 1 year.<sup>38</sup> However, subsequent cohort studies have not replicated data to support the use of accelerated induction dosing regimen despite the compelling PK and pharmacodynamic data. In a recent systematic review from Choy *et al*,<sup>39</sup> while multiple dosing of infliximab was better than a single dose in reducing colectomy, there was no benefit in any the intensive dosing regimens (more frequent doses of 5 mg/kg or higher front loading dose of 10 mg/kg) in short-term or long-term colectomy rates. This is similar to findings from our own meta-analysis, which failed to show neither a benefit nor an increase in adverse events from intensified dosing.<sup>40</sup> Interestingly, a propensity matched analysis from a multicentre retrospective UK ASUC cohort concluded that accelerated dosing in selected patients was beneficial in reducing short-term colectomy rates.<sup>41</sup> This supports a role for accelerated or intensified dosing in selected patients. Accelerated dosing strategy is recommended in the recently published IBD guidelines from the BSG<sup>10</sup> despite evolving clinical data. More data, ideally from an adequately powered RCT, comparing different



accelerated induction dosing strategies to conventional induction dosing will inform clinical practice.

## EMERGING OPTIONS FOR ASUC

### Sequential CyA and infliximab

In ASUC patients who fail infliximab, CyA can potentially be used as second line rescue therapy. The BSG recommends that clinicians do not use sequential rescue therapy in ASUC based on the available evidence. An initial retrospective study in 2008 reported the use of CyA following infliximab failure or alternately infliximab following CyA failure in 19 patients. There was an unacceptably high incidence of serious adverse events in 16% of patients including one death.<sup>42</sup> A recent cohort study reported on a larger cohort of 40 patients who received CyA following infliximab failure in ASUC as second-line rescue therapy.<sup>43</sup> Colectomy-free survival was 65%, 59.4% and 41.8% at 1 month, 3 months and 1 year, respectively. Infliximab levels before CyA infusion were available for 26 patients (median level 17.5 mg/mL, IQR 8–34 mg/mL). Although 16 patients (40%) experienced adverse events after CyA treatment, including infections, hypertension and deranged liver function tests—none were serious enough to warrant drug discontinuation.

### Tofacitinib

There is scant data on use of tofacitinib, a pan-janus kinase inhibitor, in ASUC, however, its rapid onset of action theoretically lends itself to being a good agent of choice. The limited number of case series that are available also suggest there may be a role for its use.<sup>44,45</sup> In these, with between four and seven patients in each study and a high rate of prior anti-TNF therapy, the majority improved with tofacitinib and achieved colectomy free survival at discharge. Further RCTs are needed in this area before it can be considered for routine clinical practice, but tofacitinib is an option for selected patients. Given lack of trial data at present, its use should be restricted to those who have exhausted all established biologic therapies previously.

### CyA as a bridge to vedolizumab

In ASUC patients with prior anti-TNF failure or those with significant comorbidities, vedolizumab is often preferred due to its favourable adverse event profile. However, its slow onset of action renders it unsuitable for use in ASUC. An alternative strategy would be to use CyA as induction therapy (particularly in those with prior anti-TNF failure) as a bridge to maintenance vedolizumab therapy. This strategy was successful in a small cohort in 2018.<sup>33</sup> Subsequent data from the same group with a larger, more homogeneous dataset consolidated its efficacy in this setting, with similar 1-year colectomy rates (37.1%) compared with salvage with infliximab or CyA.<sup>46</sup> Further prospective studies are required to compare the long-term efficacy of this

approach to conventional treatment with infliximab induction and maintenance.

### Predicting outcomes in acute severe colitis

ASUC is a heterogeneous condition with severity ranging from exquisite response to steroids to failure of response to medical therapy and requirement for colectomy. Several prognostic markers have been investigated to predict the clinical course of ASUC; these markers range from simple clinical or biochemical markers to endoscopic markers of severity and composite indices derived from clinical, biochemical and endoscopic markers. These parameters have been evaluated at various time points including at admission or later time points during the hospitalisation.

### Admission parameters and outcomes

In addition to its use as an indicator for admission to hospital, the widely used Truelove and Witts' criteria (table 1) also aids prognostication. Increasing severity evidenced by the number of additional Truelove and Witt's criteria at admission predicts risk of colectomy. In a retrospective study from Oxford, the risk of colectomy was 8.5%, 31% and 48%, respectively, if they had one, two or three additional criteria at admission.<sup>47</sup> Faecal calprotectin at admission has also been shown to predict risk of colectomy with moderate sensitivity and high specificity. Using a cut-off point of 1922.5/g, 87% of patients underwent colectomy over a median follow-up of 1.1 years.<sup>48</sup> A recent study from Edinburgh investigated the utility of a simple UC severity score (ACE) derived from serum albumin, C reactive protein (CRP) and endoscopic parameters at admission. Patients with an admission CRP >50 mg/L, albumin <30 g/L and increased endoscopic severity predicted non-response to steroids with a positive predictive value of 78.1% and negative predictive value of 87.1%.<sup>49</sup>

### Predicting failure of response to medical therapy

The Travis criteria is probably the most widely acknowledged scoring system to predict failure to intravenous steroid therapy in ASUC. Patients with a stool frequency of >8/day or stool frequency between 3–8/day combined with a CRP of >45 mg/L after 3 days of intravenous steroid therapy had an 85% probability of undergoing emergency colectomy.<sup>28</sup> Ho *et al* proposed an alternative scoring system and reported that stool frequency, colonic dilatation on day 3 and a low serum albumin on day 1 predicted failure of corticosteroid therapy and colectomy.<sup>50</sup> More recently, Jain *et al* studied the role of calprotectin and UC endoscopic index of severity (UCEIS) and suggested that patients with UCEIS >6 on admission and day 3 calprotectin of >1000 µg/g failed intravenous corticosteroids.<sup>51</sup> Prognostic scores are summarised in table 5.

Predicting failure to rescue therapy with infliximab or CyA has also been assessed in a number of

**Table 5** Predicting outcomes in ASUC: a summary of prognostic tools

Assessment at day one corticosteroids	Assessment at day three corticosteroids	Chance of treatment failure,	Reference
NA	BO >8/day or BO 3–8/day and CRP >45 mg/L	85%	Travis <sup>55</sup>
NA	Mean stool frequency days 1-3: <4 (score 0) 4-6 (score 1) 7-9 (score 2) >9 (score 4) Transverse colonic dilatation on AXR >5.5 cm (score 4) Admission albumin <30 g/L (score 4)	11%(total score 0-1) 45% (total score 2-3) 85%(total score ≥4)	Ho <sup>50</sup>
NA	No of stools in 24 hours + (0.14×CRP (mg/L)) >8	72%	Lindgren <sup>60</sup>
NA	CRP/albumin ratio >0.85 combined plus stool frequency >3	74%	Gibson <sup>42</sup>
UCEIS >6	Calprotectin >1000 µg/g	100%	Jain <sup>57</sup>

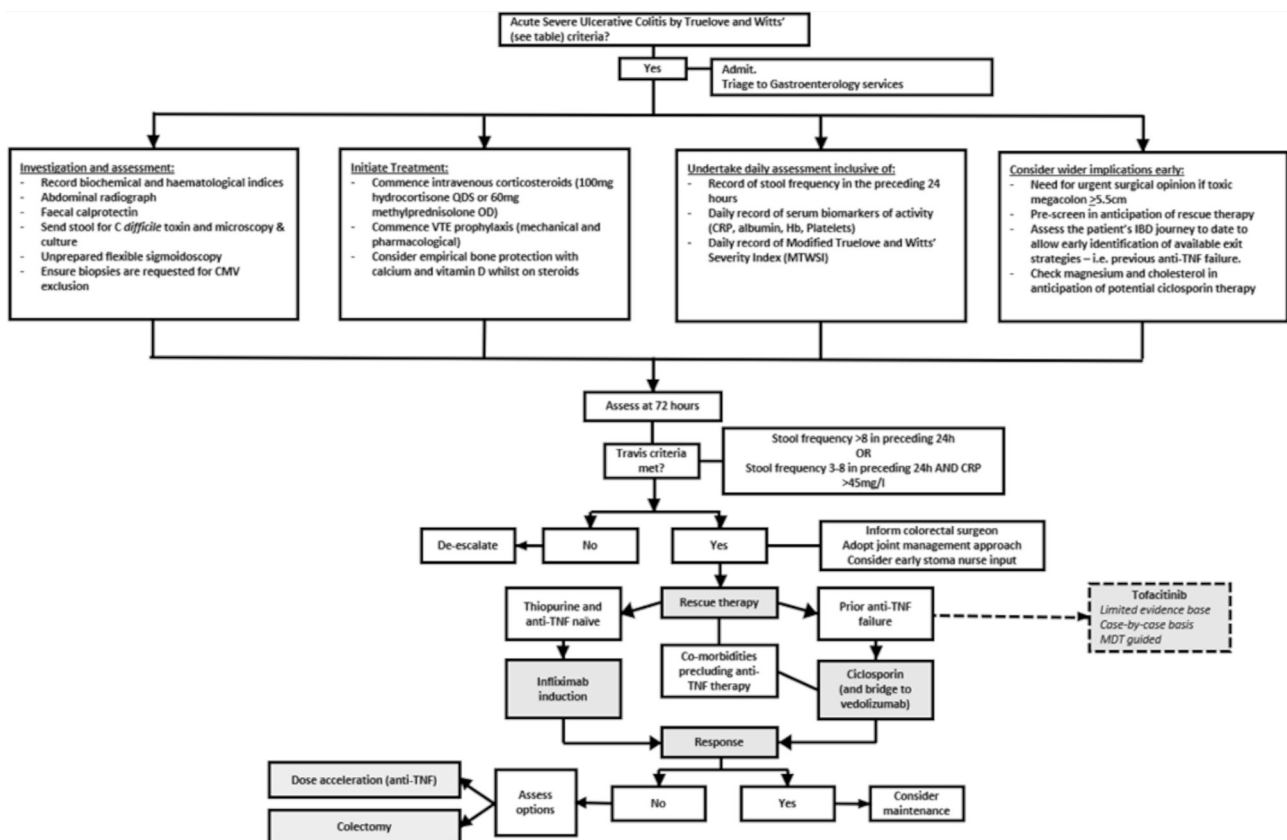
ASUC, acute severe ulcerative colitis; AXR, Abdominal X-ray; CRP, C reactive protein; NA, not applicable; UCEIS, ulcerative colitis endoscopic index of severity.

retrospective studies and in the French randomised trial of infliximab or CyA. A number of parameters such as high CRP on day 1 (>29 mg/L)<sup>52</sup> or age over 50 were associated with non-response to infliximab and severe endoscopic lesions,<sup>53</sup> and age (>49) was associated with non-response to CyA. In the French randomised trial of infliximab or CyA, age >40 and

low haemoglobin were associated with adverse outcomes to both infliximab and CyA.<sup>30</sup>

## ENDOSCOPIC SEVERITY AND OUTCOMES

Endoscopic severity has also been shown to aid prognostication in ASUC. For instance, the UCEIS was independently associated with adverse outcomes



**Figure 1** Flow chart demonstrating overview of investigation, assessment and management of ASUC. ASUC, acute severe ulcerative colitis; CMV, cytomegalovirus; CRP, C reactive protein; Hb, haemoglobin; IBD, inflammatory bowel disease; MDT, multidisciplinary team; QDS, four times daily; TNF, tumour necrosis factor; VTE, venous thromboembolism.

including the need for rescue therapy and colectomy in a retrospective study.<sup>54</sup> A further endoscopic assessment during hospitalisation may also be helpful to guide prognosis. A recent study investigated the role of a second endoscopy in ASUC and noted positive correlations with outcomes. Improved appearances at second endoscopy was associated with a lower risk of colectomy,<sup>55</sup> but there is no established consensus on the merits of repeating endoscopic assessment either as routine or in specific circumstances. Serial endoscopic assessment in the French randomised trial of infliximab or CyA in ASUC demonstrated endoscopic improvement as early as day 7 after rescue therapy.<sup>55</sup>

## COLECTOMY

Emergency surgery in ASUC is associated with significantly higher mortality, morbidity and postoperative infectious complication rates<sup>56</sup> when compared with an elective undertaking. In this setting, the operation of choice is a subtotal colectomy and end ileostomy with long rectal stump, with lower rates of postoperative infection reported in those undergoing a laparoscopic approach.<sup>57</sup> Despite advances in salvage therapy and dosing strategy, a significant number of patients with ASUC require colectomy and thus early surgical input facilitates appropriate planning and allows the patient time to come to terms with the reality of surgery. There is insufficient evidence to suggest that anti-TNF therapy increases the risk of postoperative complications in UC, however, their advent has been associated with worse surgical outcomes and is thought to be due to the unavoidable and understandable delay salvage therapy requires in order to allow patients the opportunity to potentially avoid emergency colectomy.<sup>58</sup> It is especially relevant as increasing number of days in hospital before colectomy is associated with worse outcomes with a higher likelihood of death.<sup>59</sup> This further emphasises the need for meticulous attention to timing throughout the admission in patients with ASUC.

## CONCLUSIONS

ASUC is a challenging condition to treat and requires close interaction between physicians, surgeons and patients. Patients who fail to respond to steroids require prompt consideration of rescue therapy and close monitoring to assess response to this (overview summarised in figure 1). There is evolving evidence to support the role for intensified infliximab in selected patients and other strategies such as CyA as a bridge to vedolizumab therapy and perhaps use of tofacitinib in highly selected patients. Despite optimal use of rescue therapy, some patients require timely surgical intervention to avoid adverse outcomes.

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Dear Prof Beattie

Many thanks for your recent review of our manuscript. We have made some amendments as detailed below in response to the comments made. In addition, we have attached a revised version with tracked changes and a clean copy. We hope this has further strengthened the manuscript.

Editor(s)' Comments to Author:

Please reduce to 60 references.

**Response:** Thank you for this comment. The reference list has now been reduced to 60.

Reviewer 3:

I have one small comment to make, which the authors can choose to add into the manuscript. On page 10, the authors discuss the importance of calcium and vitamin D supplementation with steroids. It may also be worth discussing risk of steroid-induced diabetes and the need to monitor blood glucose levels with these patients and recommendations of whether patients should be put on a PPI whilst on steroids.

**Response:** Thank you for this comment. In the corticosteroids section we have now included the sentence “The physicians should be aware of the potential adverse effects associated with corticosteroid use.” At the end of the same paragraph, we have also added “Co-prescription of a proton pump inhibitor (PPI) should not be routinely considered unless there is a high risk of gastrointestinal bleeding or active peptic ulcer disease. The risk of steroid-induced hyperglycaemia (or even steroid-induced diabetes) should be acknowledged and mitigated by regular measurement of capillary blood glucose and an assessment of overall glycaemic control by way of HbA1c.”

As well as the changes above, there have been some minor amendments primarily for typos and abbreviations as highlighted in the tracked changes document.

We hope the revised manuscript has addressed the comments satisfactorily.

Yours sincerely,

Sreedhar Subramanian  
On behalf of all co-authors