# Optimal management of acute severe ulcerative colitis

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## ABSTRACT

Acute severe ulcerative colitis is a life-threatening medical emergency, which can be associated with significant morbidity and is preventable through prompt and effective management. Corticosteroids remain the cornerstone of initial therapy, although a third of patients will not respond. Further management hinges on timely decisions with use of rescue therapy with ciclosporin or infliximab, without compromising the health or safety of the patient, or timely surgery. Although such patients need specialist care, it is imperative that emergency care physicians are aware of the important principles of management of this condition to achieve successful outcomes. Risk stratification and the use of predictive models using clinical parameters have reduced the morbidity associated with this condition. We discuss current evidence and present a clinical approach to clinicians involved in the emergency care of patients with acute severe ulcerative colitis in this review.

## INTRODUCTION

Ulcerative colitis (UC) is an inflammatory condition that affects the mucosal surface of the colon and rectum, characterised by a chronic and relapsing course. It is believed to result from a dysregulated immune response to intraluminal microbiota and other environmental factors in a genetically susceptible host.[1] UC typically affects the rectum and the left colon in most patients but can involve the colon proximal to the splenic flexure (extensive/pancolitis) with rectal bleeding, diarrhoea, tenesmus and lower abdominal crampy discomfort.[2 3]

The majority of patients tend to have a mild-moderate disease course, but 20%–25% of patients may experience a severe exacerbation (flare) requiring hospitalisation[4] for prompt medical treatment and due consideration for colectomy if medical therapy fails. The morbidity associated with acute severe UC (ASUC) is considerable with a 30%–40% risk of colectomy after one or more severe exacerbations and 10%–20% likely to need colectomy in their first admission.[4–7] The UK National IBD audit reported that despite improvements in quality standards, and improving outcomes for patients with ASUC, there remains considerable morbidity and 1% mortality associated with it.[6] Although it is imperative that a gastroenterologist with expertise in inflammatory bowel disease (IBD) manages these patients, clinicians involved in emergency care should also be aware of the important principles and considerations in the management of these patients to achieve successful outcomes. This review discusses the diagnosis and management of ASUC, current and evolving evidence with the use of medical salvage therapies and presents a practical approach for management to clinicians.

## Principles of supportive management

### Initial assessment

ASUC typically presents as an acute on chronic disease and also in a relapsing–remitting pattern but may be the presenting feature of new onset UC in approximately a third of patients.[4] ASUC is defined by the Truelove and Witts criteria[8] (table 1) and European Crohn's and Colitis Organisation criteria, which includes C reactive protein (CRP) >30 mg/L.[2] Patients with ASUC require immediate hospitalisation for intensive management in a specialist gastroenterology facility for joint medical, surgical and nursing care. Criteria for admission are defined in table 1.

Haemoglobin levels (an additional criterion of the definition) in the general population in developing countries are lower than in the population of developed countries. Jain *et al* showed that Truelove and Witts criteria can be used to define acute severe colitis, despite lower mean haemoglobin in the native population.[9]

The immediate objective is to achieve clinical remission as defined by ≤3 stools per day without rectal bleeding.[2]

### Investigations on admission

On admission, a full blood count, urea, electrolytes (including serum magnesium), creatinine, CRP, erythrocyte sedimentation rate, liver chemistry, a lipid profile, abdominal radiograph and stool tests for culture, microscopy and sensitivity along with *Clostridium difficile* testing should be arranged (figure 1). The differential diagnosis of diarrhoea with bleeding should be considered and is listed in table 2.

In anticipation for the need for medical rescue therapy with either infliximab (IFX) or ciclosporin, additional tests should be arranged and include TB screening (interferon gamma release assay and chest radiograph), hepatitis B serology (HbsAg, HbcAb), thiopurine methyltransferase activity (if not known previously), cytomegalovirus (CMV) IgG and IgM, HIV and varicella zoster serology.[2 10]

### Hydration, electrolytes and nutritional status

Most patients will need intravenous fluids with correction of electrolyte imbalance; in particular, serum potassium as hypokalaemia can predispose to colonic dilatation.

**Table 1** Disease activity in ulcerative colitis, adapted from Truelove and Witts

| | Mild | Moderate 'in between mild and severe' | Severe |
|---|---|---|---|
| Bloody stools/day | <4 | 4 or more if | ≥6 and |
| Pulse | <90 bpm | ≤90 bpm | >90 bpm *or* |
| Temperature | <37.5°C | ≤37.8°C | >37.8°C *or* |
| Haemoglobin | >115 g/L | ≥105 g/L | <105 g/L *or* |
| ESR | <20 mm/h | ≤30 mm/h | >30 mm/h *or* |
| CRP | Normal | ≤30 mg/L | >30 mg/L |

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

Nutritional assessment and optimisation of nutritional status under the supervision of an expert dietician is important for successful outcomes. There is no proven advantage to the routine use of bowel rest or parenteral nutrition and enteral nutrition is associated with lower complications as compared with parenteral nutrition.[11][12] Nutritional deficiencies should be corrected. Oral iron therapy is probably best avoided, with anecdotal reports suggesting that it can aggravate mucosal inflammation through oxidative stress from oxygen free radicals, the 'Fenton' reaction.[13] Blood transfusion may be considered on a case-to-case basis if absolutely necessary.

### Endoscopic assessment
Endoscopic assessment with a limited, unprepared sigmoidoscopy and biopsies with minimal air insufflation should be performed by an experienced operator with biopsies taken to exclude CMV.[14][15] A full colonoscopy is unnecessary and may be associated with an increased risk of perforation.[2] The use of a validated endoscopic scoring system such as the Mayo endoscopic score or the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) adds uniformity and objectivity to initial and subsequent assessment and should be used (figure 2).[2][16][17]

**Table 2** Differential diagnoses of diarrhoea with rectal bleeding

| | |
|---|---|
| Inflammatory bowel disease | Crohn's disease<br>Ulcerative colitis |
| Infection drug induced | *Clostridium difficile*<br>*Campylobacter*<br>*Salmonella*<br>*Shigella*<br>*Escherichia coli* (0157:H7/VTEC)<br>*Yersinia*<br>*Aeromonas*<br>*Listeria*<br>Amoebiasis<br>Tuberculosis<br>Schistosomiasis<br>Herpes and cytomegalovirus infection in immunocompromised |
| Drug induced | Non-steroidal anti-inflammatory medication<br>Antibiotics<br>Gold |
| Miscellaneous | Ischaemic colitis<br>Radiation colitis<br>Vasculitis (polyarteritis nodosa, Behcet's disease)<br>Diverticulitis<br>Colorectal cancer |

### Imaging
Abdominal radiographs may provide vital information. Mucosal islands (or 'thumb printing'), when seen, is a predictor of failure of medical treatment. The presence of faecal residue is consistent with uninflamed or normal colonic mucosa. Proximal constipation may be noted in left-sided or distal colitis. It may exacerbate distal disease and paradoxically require laxatives to clear, in addition to treatment of colitis. Measurement of the transverse colonic and caecal diameter (diameter >5.5 cm) supports the presence of colonic dilatation and impending toxic dilatation (figure 3). An erect chest radiograph or a lateral decubitus abdominal film may reveal colonic perforation.
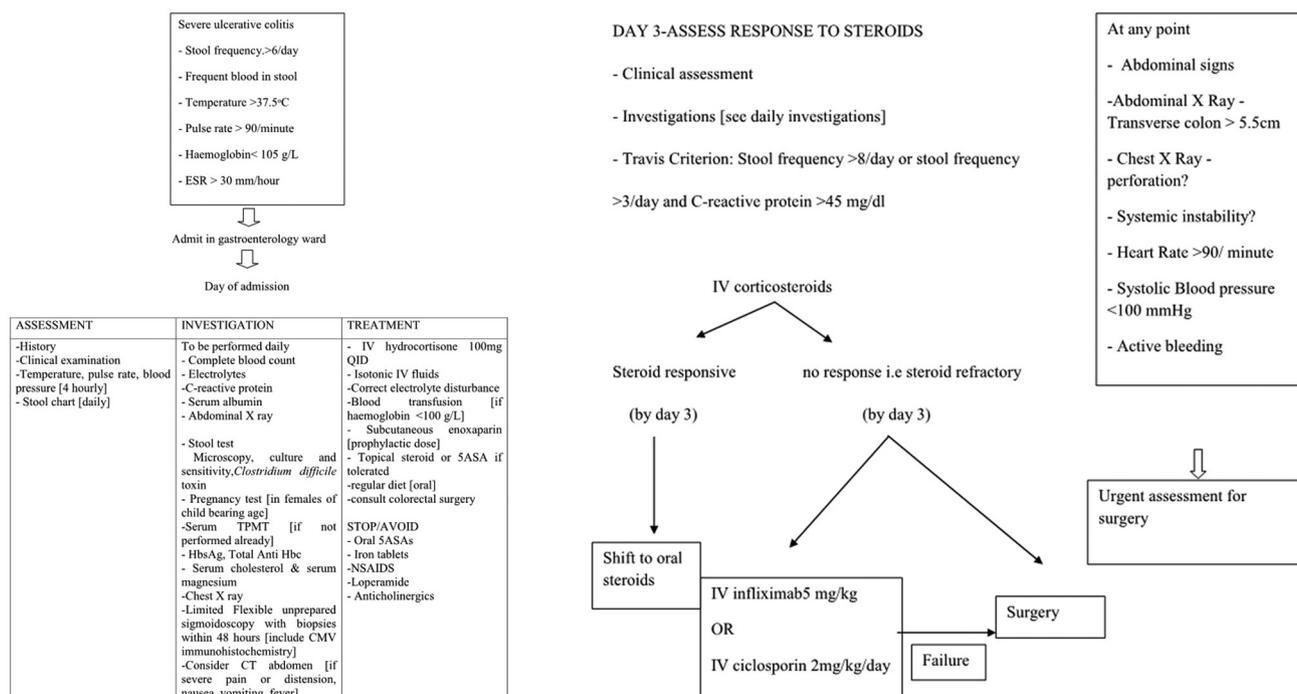


**Figure 1** Algorithm for management of acute severe ulcerative colitis. CMV; cytomegalovirus, ESR; erythrocyte sedimentation rate, 5ASA; 5-aminosalicylic acid, TPMT; thiopurine methyl transferase.

**Figure 2** Flexible sigmoidoscopy image of patient showing Ulcerative Colitis Endoscopic Index of Severity=7 (V2/B3/U2=7/8).

## Consider the differential diagnosis

The differential diagnosis of diarrhoea with bleeding is broad (table 1). It is vital that infective colitis be excluded, especially in those with an abrupt onset of diarrhoea, vomiting or fever, those with a history of contact and those with recent foreign travel. Non-steroidal anti-inflammatory drugs may cause de novo colitis (which typically settles after withdrawal of the drug) but
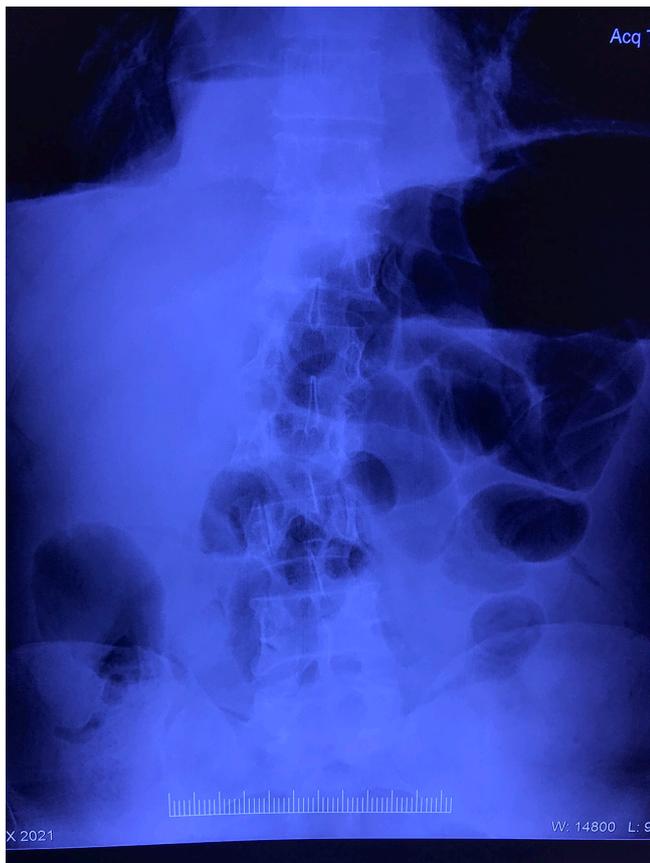


**Figure 3** Abdominal radiograph showing toxic dilatation in a patient with acute severe ulcerative colitis.

may trigger a relapse (flare) of UC. Radiation colitis should be considered in the differential diagnosis in patients with a history of abdominal or pelvic radiation, and ischaemic colitis should be considered in patients with risk factors for (or established) vascular disease. It is characterised by an abrupt onset of abdominal pain with bloody diarrhoea. Raised venous lactate, although not specific, may point towards ischaemic colitis.

CMV colitis is associated with poorer outcomes and higher rates of colectomy.[18] It needs to be carefully distinguished from a subclinical, self-limiting and uncomplicated CMV infection that does not impact on colitic activity. The diagnosis of CMV colitis hinges on tissue analysis with immunohistochemistry (IHC) and PCR from colonic biopsy specimens. Steroid and concomitant thiopurine therapy may be associated with CMV infection, but anti-tumour necrosis factor (TNF) therapy does not appear to increase risk.[18 19] Accordingly, current guidelines recommend screening for CMV infection in the context of steroid-resistant colitis.[15] Patients with ASUC should have a sigmoidoscopy with biopsy within 2 days of admission for CMV analysis from histopathology, IHC and PCR.[18] Patients with confirmed CMV infection need treatment with 2–3 weeks of ganciclovir. Although due consideration may need to be given to delaying immunosuppressant therapy, this may not be feasible in steroid non-responder patients, when sequential or concurrent antiviral and salvage therapy may need to be employed on a careful case-to-case basis.

## Clinical assessments

Patients should have a daily (or more frequent) clinical assessment which should include physical examination, assessment of haemodynamic status, stool charts, blood tests as outlined above and abdominal radiographs. Commencement of intravenous corticosteroids notwithstanding, assessment of these parameters provides valuable metrics of clinical response and the need for 'rescue therapy' as outlined later. Acknowledging that successful outcomes for ASUC hinge on multidisciplinary decisions, colorectal surgeons should be consulted early in the course of admission, should medical treatment fail or indeed surgery be more appropriate.

## MEDICAL MANAGEMENT
### Thromboprophylaxis

Patients with ASUC are at high risk of venous thromboembolism and patients with IBD have twofold to threefold higher risk of deep venous thrombosis than patients without IBD. Compression stockings and subcutaneous prophylactic low molecular weight heparin should be prescribed.[20–22] Thromboprophylaxis does not precipitate or exacerbate colonic bleeding.[23]

### Antibiotics

Three RCTs have investigated the role of adjunctive antibiotics (ciprofloxacin, metronidazole and tobramycin) in patients with ASUC and did not show any benefit over steroids.[24–26] Thus, routine use of intravenous antibiotics offers no therapeutic advantage in uncomplicated colitis, although they may be appropriate in patients in whom infection is suspected.

### Aminosalicylates, antidiarrhoeals and anticholinergics

A retrospective multicentre study of 209 episodes of ASUC showed combination of 5-ASA with intravenous corticosteroids to have lower risk of treatment failure 11% versus 31% as compared with intravenous corticosteroids alone. A significant confounder was the impact of preadmission corticosteroid treatment, the most significant factor associated with the need

## Box 1  Principles of management (supportive therapy) in acute severe ulcerative colitis

► Admit to a specialist gastroenterological ward for multidisciplinary care (joint medical and surgical).
► Daily clinical assessment and examination.
► Daily electrolytes and C reactive protein and abdominal X-ray.
► Nutritional assessment and optimisation of nutritional status.
► Bowel rest is of no proven benefit.
► Unprepared flexible sigmoidoscopy at the earliest opportunity.
► Fluid resuscitation as required.
► Correction of electrolyte abnormalities.
► Prophylaxis against venous thromboembolism with low molecular weight heparin.
► Empirical antibiotics are of no benefit, except where infection is suspected, or there is incipient perforation or toxic megacolon.
► Avoid anticholinergics, opiates and antidiarrhoeal agents, as they increase the risk of colonic dilatation and perforation.

for salvage therapy in multivariable analysis.[27] There is no definite evidence for continuation of 5-ASA therapy during acute exacerbation of UC and most clinicians (including the authors) would stop 5-ASA therapy avoiding the risk of idiosyncratic diarrhoea from 5-ASA therapy confounding response to intravenous corticosteroids.[28]

Antidiarrhoeal and anticholinergic agents and opiates should be avoided, as they may prove harmful by decreasing colonic motility and increasing the risk of colonic dilatation and toxic megacolon.[15]

The principles of supportive therapy in ASUC are summarised in box 1.

### Corticosteroid therapy

Intravenous corticosteroid therapy in the form of hydrocortisone (100 mg three to four times a day or methylprednisolone 60 mg/day) is the recommended standard.[2] There is no real advantage from giving higher doses, but lower doses are less effective.[29 30] The optimal dose of methylprednisolone and hydrocortisone for the induction of clinical remission is unknown. Indeed, in the absence of comparative effectiveness studies, the choice of either agent rests with the physician. Most patients will respond to intravenous steroid therapy and may be switched to oral prednisolone (40–60 mg daily with taper over the next 2–3 months). A systematic review of 32 trials of steroid therapy for ASUC involving 1991 patients reported an overall response to steroids of 67%.[29]

### Predicting response to intravenous corticosteroids

Up to a third of patients will fail to respond to intravenous corticosteroids and are termed 'steroid refractory'.[29] It is therefore imperative that early clinical risk stratification tools be employed to identify such patients to enable salvage therapy with medical treatment using either ciclosporin or IFX and indeed surgery. Patients who do not respond to steroid therapy between days 3 and 5 are at high risk of intravenous corticosteroid therapy failure and should be considered for second-line 'rescue' therapy or surgery (table 3 and figure 1).

Several mathematical risk stratification tools incorporating clinical criteria have been developed and predict the need for timely rescue therapy or colectomy (table 3).

### Table 3  Prediction of corticosteroid failure in acute severe ulcerative colitis and need for 'rescue therapy'

| Index | |
|---|---|
| Oxford[31] | Stool frequency >8/day OR stool frequency >3/day with CRP >45 mg/L on day 3 of intravenous corticosteroid |
| Lindgren[90] | Serum CRP (mg/L)×0.14 stool frequency on day 3 of intravenous corticosteroid |
| Ho[91] | Stool frequency, colonic dilatation, serum albumin levels (cut-off >4 on day 3 of intravenous corticosteroid) |
| Seo[92] | Stool frequency, blood, nocturnal stools, abdominal pain, activity level |
| Jain[17] | UCEIS >6 at admission and faecal calprotectin >1000 µg/g on day 3 of intravenous corticosteroid |

CRP, C reactive protein; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

One of the most widely used risk stratification metrics used is the Travis criterion. At day 3 of corticosteroid therapy, patients who have a stool frequency of more than 8 per day or a stool frequency of 3 per day plus CRP >45 mg/dL have an 85% likelihood of requiring colectomy during the admission.[31]

A pitfall with the use of the Travis criterion is its use of stool frequency as a predictive factor for steroid failure, which is a patient-reported outcome and a subjective clinical variable dependent on rectal inflammation, which may in turn be influenced by tenesmus and/or local therapy. Among studies without the use of stool frequency for prediction for steroid failure, studies have used UCEIS, a validated composite score ranging from 0 to 8 and incorporating vascular pattern, bleeding and the presence of erosions and ulcers in unprepared sigmoidoscopy.[16] A retrospective study of 89 patients found all patients of UCEIS >6 (within 2 weeks of admission) failed intravenous steroids.[32] A prospective study of 90 patients with ASUC noted that faecal calprotectin (FC) was significantly higher in patients undergoing colectomy during the hospital stay, with a level >1992.5 µg/g associated with the need for colectomy over the next year.[33] A recent prospective study of 49 patients from India found that all patients with UCEIS >6 on admission and FC >1000 µg/g on day 3 failed steroid therapy.[17] These new indices without stool frequency, if validated, would provide an objective measure of risk of steroid failure.

### Ciclosporin in ASUC

Lichtiger et al in his study demonstrated the efficacy of ciclosporin in acute steroid-refractory UC. Nine out of 11 patients with steroid-refractory UC who received ciclosporin (4 mg/kg) as a continuous intravenous infusion improved, whereas all nine patients who received placebo showed no improvement.[34] Three of 11 and 4 of 9 patients underwent colectomy in the ciclosporin and placebo groups, respectively.

Van Assche and colleagues in a randomised controlled trial (RCT) compared 4 mg/kg with 2 mg/kg intravenous ciclosporin and showed equal efficacy for the two treatment groups in treating severe steroid-refractory UC. Response rates at day 8 were similar in the two groups at 82% and 83%, respectively, and there was no difference in short-term colectomy rates.[35]

Long-term efficacy of ciclosporin hinges on concomitant immunosuppression with a thiopurine. In a study of 71 patients with ASUC treated with intravenous ciclosporin and with a median follow-up of 1.5 years, concomitant thiopurine therapy was the only factor associated with a reduced risk of colectomy (OR 0.01, 95% CI 0.00 to 0.09, p<0.0001).[36]

Oral ciclosporin is then used as bridging therapy with the simultaneous introduction of thiopurine, either azathioprine (AZA) or mercaptopurine and the aim of tapering ciclosporin in a few months.[37–39] Thus, patients who have had an inadequate response to thiopurine maintenance therapy previously are not suitable candidates for ciclosporin treatment.[2 10]

Ciclosporin therapy may be associated with significant toxicity. Serious infections have been reported in 5% of patients and mortality in 1%–3%.[37 40 41] Major adverse events related to ciclosporin therapy include nephrotoxicity (6.3%), seizures (3.6%), anaphylaxis (0.9%) and death (1.8%).[41] Other adverse events include paraesthesia, hypertension, hypertrichosis, headache, minor infections, hyperkalaemia, hypomagnesaemia and gingival swelling.

There are some practical considerations when using ciclosporin that deserve mention here. The initial dose is 2 mg/kg/day intravenously with a target ciclosporin concentration of between 150 and 250 ng/mL by monoclonal assay. Patients who respond should be switched to an oral dose, twice the intravenous dose which is administered orally in divided doses twice daily aiming for a trough concentration of 100–200 ng/mL. An exit strategy in the form of AZA or 6-mercaptopurine should be initiated during hospitalisation and continued at discharge. Prophylaxis for *Pneumocystis carinii* (sulfamethoxazole and trimethoprim) must also be initiated for the duration of triple therapy for 3 months, after which patients may be able to stop ciclosporin therapy and continue AZA.[42 43]

### Tacrolimus
Tacrolimus (FK506) is also a calcineurin inhibitor. It has a similar side-effect profile to ciclosporin. It is administered orally and has good bioavailability. A single RCT of 62 patients demonstrated improvement in 68% of patients randomised to receive tacrolimus as opposed to a 10% response in the placebo group.[44] A recent meta-analysis demonstrated that clinical response at 2 weeks was significantly higher with tacrolimus than with placebo (RR (relative risk) =4.61, 95% CI 2.09 to 10.17; p=$0.15\times10^{-3}$). Colectomy-free rates at 1, 3, 6 and 12 months were 86%, 84%, 78% and 69%, respectively.[45] Tacrolimus rescue therapy is recognised by European Crohn's and Colitis Organisation guidelines and may be considered by units with experience in using it.[15]

### IFX in ASUC
IFX is a chimeric IgG1 monoclonal antibody that specifically targets free and membrane-bound TNF-α. Järnerot et al demonstrated early evidence of efficacy in UC, randomising 45 patients with acute severe steroid-refractory UC (4 days after initiating steroids) to a single infusion of IFX (5 mg/kg) or placebo. In the IFX group, 7 of 24 patients (29%) had a colectomy within 3 months of randomisation as opposed to 14 of 21 patients in the placebo group.[46] Long-term follow-up data of this cohort revealed significantly lower colectomy rate in IFX versus control (50% vs 76%) (p=0.01) at 3 years' follow-up. No maintenance IFX was given during follow-up.[47] IFX was licensed for treatment of moderate to severely active UC after two large placebo-controlled trials, Active UC trial (ACT I and II), demonstrated efficacy.[48]

A pilot study explored predictive markers of response following first dose IFX in ASUC and found that early assessment of serum/faecal IFX, calprotectin and partial Mayo scores can predict future remission and colectomy.[49]

That said, IFX induces immunosuppression-related risks such as reactivation of latent TB, opportunistic infections and sepsis, mandating screening for tuberculosis, and hepatitis and avoidance in the presence of such infection or sepsis.[42] IFX is contraindicated in congestive cardiac failure (New York Heart Association Class III/IV), demyelinating disease, sepsis, active TB and active infection. Mortality risk from IFX therapy is comparable with ciclosporin.[50–52]

The evidence for the impact of IFX therapy on surgical outcomes and perioperative complications is conflicting, with a meta-analysis reporting a higher rate of postoperative complications in patients treated with IFX and trend towards a higher rate of infections[53] and other investigators reporting a risk of early readmission, intra-abdominal abscess and postoperative complications.[54] However, recent studies have not found preoperative IFX to be associated with postoperative complications.[55–58]

### IFX versus ciclosporin for ASUC
Head-to-head comparisons between ciclosporin and IFX have demonstrated equal efficacy.[50 52] The open-label CySIF trial included 115 patients previously naïve to IFX and ciclosporin with a Lichtiger score >10 points (range 0–21), who had colitis refractory to at least 5 days of intravenous steroids. Patients were randomised in a 1:1 ratio to receive intravenous ciclosporin (2 mg/kg per day for 1 week, followed by oral ciclosporin until day 98) or IFX (5 mg/kg on days 0, 14 and 42). In both groups, AZA was started at day 7 in patients with a clinical response. The primary end point was 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. There was no statistically significant difference between treatment failure in patients given ciclosporin (60%) and given IFX (54%) (p=0.52). Nine (16%) patients in the ciclosporin group and 14 (25%) in the IFX group had severe adverse events which was also not statistically different.[50] Similar rates of mucosal healing were achieved in both groups (47% in the ciclosporin group and 45% in IFX-treated patients) and colectomy rates (17% in the ciclosporin group and 21% in IFX-treated patients) were also comparable (69). Furthermore, long-term follow-up of patients treated in CySIF trial revealed that there was no difference in colectomy-free survival at 1 year and 5 years in patients treated with either ciclosporin or IFX.[59]

The CONSTRUCT trial 2010–2013 was a mixed-methods, open-label, pragmatic randomised trial including 270 patients. Patients were randomly allocated (1:1) to receive either IFX (5 mg/kg intravenous infusion given over 2 hours at baseline, and again at 2 weeks and 6 weeks after the first infusion) or ciclosporin (2 mg/kg per day by continuous infusion for up to 7 days, followed by twice-daily tablets delivering 5.5 mg/kg per day for 12 weeks). The primary outcome was quality-adjusted survival. There was no statistically significant difference between the two for the primary end point as well as the secondary end point of colectomy rates, time to colectomy, serious adverse events or death. IFX, however, was associated with a greater cost of treatment as compared with ciclosporin.[52] That said, biosimilars to IFX are now available and cost of therapy is reducing.

A meta-analysis of IFX and ciclosporin for ASUC also did not show any difference in short-term response, 3 months and 12 months in RCT.[60]

A recent study involving 740 patients with steroid-refractory ASUC with median follow-up of 71 months did not reveal any difference in colectomy rates between patients treated with IFX versus ciclosporin (26.2% vs 25.4%) at 5 years and also reported

a significantly lower rate of serious adverse events in ciclosporin versus IFX (15.4% vs 26.5%) (p=0.001).[61]

### Practical considerations in choosing between IFX and ciclosporin

With current evidence demonstrating equivalence in outcomes between both agents, the clinician must have a critical understanding of the subtle nuances of these studies and the potential implications therein. The CysIF study had low statistical power (80% power to detect a 30% difference between groups) with the potential for a type II error, that is, not detecting a difference between drugs if one does exist. Ciclosporin levels were tightly monitored for this trial whereas IFX was dosed according to the standard induction regimen. Indeed, much of the current controversy about IFX dosing stems from our evolving understanding of IFX pharmacokinetics as discussed later in this review. A high TNF burden, proteolytic degradation of drug[62] and increased intestinal loss of IFX[63] are all factors that will influence the success of IFX therapy. As surrogates, a high CRP (indicating inflammatory burden) and low albumin (severely ill patients with marked increase in intestinal permeability and drug loss through stool) and severe endoscopic lesions are predictors of poor outcomes.[63]

IFX therapy has been associated with a reduced length of stay in one study—median 4 days (IQR 4.0–5.75) with IFX compared with 11 days (IQR 7.75–13.25) with ciclosporin.[64] Although the CONSTRUCT trial did not find any difference in the length of stay with either therapy, patients and physicians noted greater treatment satisfaction with IFX.[52] It seems very likely that the current evolution in our understanding and application of pharmacokinetics of IFX in ASUC will shape and favour the use of IFX as preferred salvage therapy in most units.

### Sequential rescue therapy

Few studies have studied efficacy of ciclosporin and IFX as rescue therapy for each other and show modest efficacy but a high risk of adverse effects. Maser and colleagues reported an increased risk of serious side effects (16% patients) including one death.[65] Another study involving 86 patients receiving sequential therapy (ciclosporin followed by IFX) revealed colectomy-free rates of 61% and 41% at 3 and 12 months, respectively, but the rate of infectious complications was 10%.[66] Chaparro et al reported a 30% colectomy-free survival for sequential therapy (ciclosporin followed by IFX), 23% rate of adverse effects and a death from nosocomial pneumonia.[67] A systematic literature review including 10 studies and 314 participants receiving sequential therapy reported short-term response rate of 62.4% and remission rate of 38.9%, with colectomy rates 28.3% at 3 months and 42.3% at 12 months.[68] Taken together, although the evidence for sequential therapy is insufficient to make a favourable recommendation, the risks of profound immunosuppression should warrant concern and as such is not supported by current guidelines.[15]

### Evidence for optimising anti-TNF dosing: evolving paradigms

Recent studies have demonstrated an association between higher serum levels of anti-TNF and better outcomes.[69 70] The complex interplay of various variables including a high TNF burden in ASUC, proteolytic degradation of anti-TNF associated with increased drug clearance and faecal losses from increased gut permeability associated with severe inflammation have provided further impetus and credible evidence to support dose optimisation of IFX in the acute phase.[71]

The implication that patients with ASUC may need higher and/or more frequent dosing to exert effect has been borne out through

further studies. Brandse et al demonstrated that a high baseline CRP (>50 mg/L) and a low serum albumin (<35 g/L) as surrogates for severe inflammation and extensive colitis independently correlated with lower IFX concentrations from weeks 0 to 6.[72] In another retrospective study, patients with ASUC had lower week 2 IFX concentrations than those with less severe disease.[73]

Protein losses through an inflamed colon can lead to the drug sink effect, when therapeutic monoclonal antibodies can pass through colonic mucosa and are lost in stool (58). Brandse and colleagues reported detectable IFX in the faeces of patients after the first IFX infusion (58). Patients not showing endoscopic response at weeks 6–8 had higher faecal losses at day 1 and lower IFX levels at week 6, often associated with the development of antibodies (61).

### IFX dose intensification

One of the reasons for failure of IFX as a rescue therapy could be subtherapeutic dosing of IFX in ASUC. Adedokun et al, in a post hoc analysis of ACT 1 and 2 studies, noted that patients in the lowest quartile of IFX trough distribution were less likely to achieve clinical response, remission and mucosal healing, independent of randomised dose (5 mg/kg or 10 mg/kg).[69] Gibson et al administered three doses of IFX 5 mg/kg over a median 24 days to patients with steroid-refractory ASUC and noted a colectomy rate of 6.7% compared with 40% in the historical cohort (standard 5 mg/kg induction at 0, 2 and 6 weeks) (62). At a median 2.4 years' follow-up, the colectomy rate was 27% in the dose-intensified group versus 51.4% in the historical cohort (62). In another study, the 90-day colectomy rate in 17 patients with ASUC treated with intensified IFX dosing (an additional infusion at day 3 for patients with CRP >70 mg/L) was compared with 40 patients receiving standard dosing. The 90-day colectomy rate was 47% in the dose-intensified group versus 12.5% in the standard induction group (p=0.01). A recent review of all cohort and case–control studies suggests a benefit for IFX dose optimisation in at least 50% of patients with ASUC with an 80% reduction in colectomy rates.[74] However, a recent retrospective multicentre study and meta-analysis involving seven studies (181 patients receiving accelerated IFX and 436 receiving standard IFX) found no significant differences in short- or long-term outcomes between the two.[75]

Taken together, the evidence for improved outcomes from dose intensification, underpinned by the altered pharmacokinetics in ASUC and the lack of any pronounced risk of side effects, is gathering momentum, and it is likely that if supported by RCTs, will translate into clinical practice which is an urgent and unmet need.

### SURGICAL MANAGEMENT
### Colectomy for ASUC

Surgical excision of the colon, proximal rectum and distal rectal mucosa provides a definitive 'cure' for acute colitis, removing inflamed mucosa and eliminating the future risk of recurrence and malignancy. Semi-elective surgery decreases mortality and may improve quality of life, but emergent surgery carries a significant risk of perioperative complications and functional outcomes that may not always be acceptable to all patients.[76–78] Emergency indications for surgery include toxic dilatation, refractory haemorrhage, intestinal perforation or inadequate response to medical therapy. Delaying surgery in patients with worsening symptoms or development of clinical instability can lead to risk of adverse outcomes including death.[77 79] This underpins the importance of contingency planning with an 'exit strategy' in steroid-refractory

patients by day 5 of admission, a decision which should be taken with patients involving gastrointestinal surgeon and a stoma therapist. The policy of early colectomy, within 7 days, in patients with ASUC who fail to respond to intensive steroid-based therapy improves perioperative outcomes with significantly low in-hospital mortality and morbidity.[80 81]

A three-stage approach is typically undertaken, with the first stage being subtotal colectomy and ileostomy and the aim of performing a low-risk operation without pelvic dissection. A more definitive procedure (a 'second stage' with ileal pouch anal anastomosis (IPAA) with definitive total proctocolectomy followed by a 'third' stage involving closure of covering) is performed when the patient's nutritional status has improved and ideally when the patient is off immunosuppressive medication. A laparoscopic approach is feasible, associated with fewer adhesions, incisional hernias and a shorter interval to completion proctectomy.[82]

Colectomy is not without risk, although arguably less than the futile continuation of medical therapy in severely ill patients. Reported complications include wound infection (18.4%), abscess (9.2%), haemorrhage (4.5%) and bacteraemia/sepsis (18%).[83] A lower incidence of intra-abdominal abscess, wound infection and shorter duration of hospital stay were seen with laparoscopic surgery as compared with open surgery.[84] Common problems reported include nocturnal faecal soiling (52% male, 32% female patients, intermittent urgency and also difficulties with evacuation).[85] Female infertility has also been reported,[86] although laparoscopic surgery has been associated with lower infertility rates likely from fewer adhesions.[87 88] It may be advisable for women to delay restorative IPAA until after childbearing years.[2] Pouchitis is arguably the most important complication of an IPAA and can occur in up to 50% of patients within 10 years. Pouch dysfunction and cuffitis are recognised complications following IPAA.[89]

## CONCLUSION

ASUC is a medical emergency that requires hospitalisation for intensive monitoring and therapy under a gastroenterologist with experience in managing IBD. Despite significant advances, the cornerstone of management is still the use of intravenous corticosteroids. Up to a third of patients will prove refractory to therapy and need a multidisciplinary approach with the patient, gastroenterologist, colorectal surgeon and stoma therapist. The critical decision for patients who have not responded to corticosteroids by day 3 is between medical rescue therapy and surgery. Both ciclosporin and IFX appear safe and effective when used appropriately and in experienced hands. Ciclosporin is an option in AZA-naïve patients who can be effectively bridged to purine immunomodulator maintenance therapy. In patients receiving rescue medical therapy, colectomy needs to be considered if there is no improvement by days 4–7 in discussion with the multidisciplinary team. Colectomy can treat acute colitis by excising diseased tissue and reduces future risk of recurrence and malignancy. However, it carries important functional and psychological implications, which deserve consideration. Evolving understanding of cytokine profiles and the inflammatory burden in ASUC along with the pathophysiology of gut permeability and potential for suboptimal drug delivery through altered pharmacokinetics of available treatments has seen cautious translation into medical territory and will shape our paradigms with medical treatment. Whether these evolving approaches will translate into timely and meaningful control of disease remains to be seen. Meanwhile, the clock starts ticking the moment a patient with ASUC is hospitalised, and, with investigation and treatment, timing is still everything.

## Main messages

► Intravenous corticosteroid therapy forms the cornerstone of treatment for patients admitted with acute severe ulcerative colitis.
► Early liaison with colorectal surgeons and for steroid non-responders by day 3—also a stoma therapist and psychologist—is appropriate in anticipation of the need for colectomy if required.
► A time-bound approach for steroid non-responders between days 3 and 5 assessing predictors of response is critical to favourable outcomes.
► Infliximab, ciclosporin or surgery are three rescue options.
► Delaying or denying colectomy to the patient 'failing' medical treatment may lead to adverse outcomes.

## Current research questions

► What is the efficacy of biosimilars in ASUC?
► What is the optimal pharmacokinetic based dosing of IFX for better response rate in ASUC?
► Controlled data from trials evaluating novel and experimental therapies are needed.
► Objective predictors of steroid failure are needed.
► What is the optimal timing for colectomy?

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## Self-assessment questions

1. In the assessment of acute severe UC, a colonoscopy is mandatory.
2. Patients failing intravenous corticosteroids between days 7 and 10 should be considered for pharmacological salvage therapy with infliximab or ciclosporin.
3. Ciclosporin therapy is the best option for steroid-refractory patients with acute severe UC already taking azathioprine.
4. Combination therapy with infliximab and ciclosporin A in acute severe UC is more effective and is associated with lower morbidity.
5. Despite the availability of modern and effective therapy for steroid-refractory acute severe UC, timely consideration of colectomy is appropriate.

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## Answers

1. False
2. False
3. False
4. False
5. True