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ACUTE SEVERE ULCERATIVE COLITIS: REVIEW OF MANAGEMENT AND EMERGING TREATMENTS

Key Takeaways

- ASUC has a considerable risk of colectomy and complications, therefore decisions about medical vs surgical treatment should be made early on during hospitalisation to minimize morbidity.
- Emerging data supports Janus kinase (JAK) inhibitors as a new treatment opportunity for ASUC.
- There is still lack of randomized controlled data to fully understand optimal timing and sequencing of advanced therapies in ASUC.

Introduction

Acute severe ulcerative colitis (ASUC) is a medical emergency, with an overall mortality rate of 1%.[1] Patients with ulcerative colitis (UC) have a 20–25% rate of severe exacerbation requiring hospitalization for urgent medical treatment and surgical consideration.[2-4] The rate of re-hospitalization for recurrent ASUC is 34.4%, and it typically occurs within 24 months of the index admission.[5] Treatment requires a patient-centred multidisciplinary approach that includes gastroenterology, colorectal surgery, and nutrition support, with the goal of minimizing disease complications, adverse events of treatment, and healthcare costs.[6] Clinicians and patients have an increasing number of treatment options and additional safety issues to consider. We review the current approach to management and summarize emerging data on the use of novel agents to treat ASUC.

Initial management:

ASUC is largely defined by the Truelove and Witts criteria (Table 1), requiring six or more bowel movements, and at least one marker of systemic

illness.[4] The number of positive markers correlates with the risk of colectomy.[7] Less commonly used criteria include the modified Mayo classification and the Montreal classification.[2] A recent study conducted by Adams et al. validated threshold values for C-reactive protein (CRP) ≥100 mg/L, albumin ≤25 g/L, and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) ≥4 as predictors of steroid non-response.[8] Patients with ASUC require hospital admission and a comprehensive evaluation to identify triggers, such as NSAID use and disease complications. The physical exam assesses nutritional status and screens for signs of an acute abdomen. The initial investigations include a complete blood count (CBC), extended electrolyte levels, a liver panel, albumin levels, CRP levels, and stool studies to identify coexisting infections, including *Clostridioides difficile (C. difficile)* enteric pathogens. An abdominal radiograph establishes baseline bowel dilation and detects free air from a perforation. Computed tomography should be ordered sparingly to minimize the cumulative radiation exposure in a predominantly young cohort. Within 72 hours, and ideally 24 hours, an unprepped flexible sigmoidoscopy is performed to assess the degree of mucosal inflammation and to obtain sufficient number of biopsies from severely effected areas for cytomegalovirus (CMV). Minimal insufflation is required to limit perforation risk and prevent worsening of symptoms. A pre-biologic work-up is initiated, including a TB skin test or interferon-gamma release assays, chest radiograph, and hepatitis B serologies.

Initial management involves fluid resuscitation and either a clear fluid diet or low-residue enteral diet. Enteral feeding is preferred; however, parental nutrition may be required in severely malnourished patients. To induce remission, patients receive methylprednisolone 60 mg/day in divided dosing; higher doses do not confer a lower colectomy rate.[2] Based on recent data, immediately implementing advanced therapy, potentially avoiding corticosteroids may be reasonable in patients with a high risk of corticosteroid failure.[8] An early surgical consultation is suggested to discuss colectomy as both first-line and rescue treatment.[9,10] Venous thromboembolism (VTE) prophylaxis is required given the substantial VTE risk compared to that of the general population.[2,9,10]

Response to treatment is evaluated daily with stool charting, a physical exam, CBC, and CRP levels. Any clinical worsening, including abdominal distention, warrants an urgent abdominal radiograph to evaluate for complications, including megacolon and perforation. A high level of clinical suspicion and close monitoring is required as corticosteroids may mask abdominal pain severity.

A special note on opiates:

Opiate use in hospitalized inflammatory bowel disease (IBD) patients does not improve pain scores and is associated with an increased risk of infections, bowel obstruction, perforation, and mortality.[11] Concerningly, opiate-naïve IBD patients are often prescribed similar doses to regular opiate users and are frequently discharged with new opioid prescriptions.[11] Best practices include analgesia with acetaminophen and opiate avoidance when possible. A pain service consultation is recommended if analgesia requirements escalate.

Response to corticosteroids

On day 3 of admission, patients are risk stratified using the Oxford criteria: those with more than 8 stools per day; or more than 3 stools per day and a CRP level of >45 mg/L are likely refractory to corticosteroids, and have an 85% colectomy rate.[3] One-third of patients are unresponsive to corticosteroids and require rescue medical therapy or surgery.[3] Predictors of a corticosteroid-refractory course include an albumin level of <30 g/L, a CRP level of >30 mg/L and endoscopic severity.[7] A recent validated risk prediction model, that incorporates CRP ≥100 mg/L (1 point), albumin ≤25 g/L (1 point) and UCEIS ≥4 (1 point) and UCEIS ≥7 (2 points) was accurate in predicting CS non-response.[8] Tools such as these may help with early identification of patients who are in need of rescue therapy.

Corticosteroid-responsive patients complete 3–5 days of methylprednisolone therapy before transitioning to an oral prednisone dose of 40–60 mg/day. Maintenance therapy is typically initiated within two weeks of discharge, along with a corticosteroid taper.[2] Although corticosteroid-responsive patients have lower colectomy rates, re-hospitalization rates are similar to corticosteroid-refractory patients.[5]

Rescue medical therapy

Infliximab

Infliximab (IFX) is an anti-tumour necrosis factor alpha (TNFα) agent and an established rescue treatment for corticosteroid-refractory ASUC. The short-term colectomy rate for patients receiving IFX at a dose of 5 mg/kg on weeks 0, 2, and 6, is 29% compared to 67% for those receiving the placebo.[12] In ASUC, substantial fecal losses of IFX occur, and accelerated dosing strategies have been evaluated. Strategies include an initial 10 mg/kg dose of IFX, or shortened infusion intervals.[13] A recent meta-analysis found no significant difference in short or long-term colectomy rates between the accelerated and standard treatment groups; although a subgroup analysis demonstrated a trend toward lower colectomy rates with IFX at a dose of 10 mg/kg at 3, 12, and 24 month follow-ups.[13] As such, current guidelines do not make recommendations on accelerated IFX dosing.[9] From a pragmatic perspective, accelerated IFX dosing may be required for some patients. If surgery

is required despite IFX rescue therapy, recent data found no significant difference in infectious or surgical complications, reoperation, readmission, or mortality.[13]

Cyclosporine

Cyclosporine (CsA) is a calcineurin inhibitor that initially become a mainstay rescue treatment after Lichtiger et al. reported a significant clinical response with intravenous CsA at a dose of 4 mg/kg compared to placebo in corticosteroid-refractory severe ulcerative colitis (UC).[14] Similar response rates were observed with CsA at a dose of 2 mg/kg intravenous (IV) compared to CsA at a dose of 4 mg/kg IV.[9,10,15] A meta-analysis, which included the CYSIF and CONTRUCT trials, compared CsA (2 mg/kg IV) to IFX (5 mg/kg) as rescue therapy for ASUC. Among a subgroup analysis of randomized controlled trials (RCTs), the pooled rates of treatment response were not significantly different between treatments for short-term treatment response (IFX: 43.8% vs. CsA: 41.7%), 3 month (IFX:26.6% vs. CsA:26.4%), 12-month colectomy rates, and adverse events.[16] However, in the subgroup analysis of non-randomized trials, IFX was favoured over CsA for short-term treatment response (74.8% vs. 55.4% respectively) and the 12-month colectomy rate (20.7% vs. 36.8%, respectively).[16] Adverse events include infections, hypertension, renal impairment, seizures, and malignancy, which require close monitoring.[16] Owing to the safety profile, and requirement for dose-adjustments, CsA is less frequently used than IFX in the management of ASUC.[17] Following a response to CsA, patients are typically maintained on thiopurines; however, emerging evidence suggests vedolizumab and ustekinumab as maintenance therapy for ASUC.[18]

Tacrolimus

Tacrolimus is a calcineurin inhibitor that has been demonstrated to improve clinical outcomes in patients with steroid-refractory UC. However, tacrolimus has worse long-term outcomes compared to IFX in corticosteroid-refractory UC.[18] Limited data exists for its use as rescue therapy in ASUC. A recent ASUC cohort study reported higher rates of short-term colectomy, medication discontinuation, and rehospitalizations with tacrolimus treatment compared to IFX.[19] Tacrolimus is not currently recommended in treatment guidelines.[9,10]

Tofacitinib

Tofacitinib is a small molecule oral agent that selectively targets Janus kinase (JAK) 1-3 signalling. There is mounting interest and use of tofacitinib in ASUC given its quick onset and particularly for IFX-exposed patients. A systematic review of 148 ASUC cases, including the GETAID trial, evaluated tofacitinib as rescue therapy in IFX-exposed patients or as sequential treatment after failed IFX or CsA rescue therapy. Induction doses of tofacitinib were 10 mg twice a day or three times a day, and the pooled 30, 90, and 180-day colectomy-free survival was 85%, 86%, and 69%, respectively.[20] At follow-up, the rates of clinical and endoscopic remission were 35–69% and 55%, respectively.[20] A single-center observational study suggested that a short course of tofacitinib at a dose of 10 mg TID followed by tofacitinib at a dose of 10 mg PO BID may be more effective than tofacitinib at a dose of 10 mg PO BID.[21] Earlier concerns regarding the risk of VTE, malignancy, and cardiovascular events have not been observed in long-term, real-world safety data.[22] With the exception of an increased Herpes Zoster risk, rates of adverse events are similar to those of other UC treatments.[22]

Upadacitinib

Upadacitinib is a novel, selective JAK-1 inhibitor with a rapid onset of action and clinical efficacy in UC patients with prior biologic and tofacitinib exposure.[23] Although the data is limited to case reports and small studies, the use of upadacitinib in anti-TNF-exposed ASUC patients is promising.[24,25] In a study that included six patients who had previous IFX exposure and corticosteroid-refractory ASUC, upadacitinib was administered at a daily oral dose of 45 mg as rescue therapy.[26] By day 7, all of the patients demonstrated a clinical response and by week 16, five patients remained colectomy-free.[26] Further studies are needed before upadacitinib can be recommended as a rescue therapy.

Vedolizumab

Vedolizumab specifically targets the gut by selectively inhibiting the α4β7 integrin and is a first line therapy in moderate to severe UC. Vedolizumab is not suitable as rescue therapy in ASUC given its prolonged onset of action. However, it may be an alternative to thiopurine maintenance therapy following calcineurin inhibitor induction. A recent review of 156 ASUC patients, many of whom had previous anti-TNF exposure, showed a colectomy-free rate of 65-69% when combined with CsA or tacrolimus as bridge therapy.[18] The largest study involved 71 patients with severe UC in which 76% of them had ASUC. Vedolizumab was administered following CsA or tacrolimus rescue therapy, and the colectomy-free rates at 3, 12, and 24 months were 93%, 67%, and 55%, respectively.[18] Currently, there are no RCTs evaluating vedolizumab in ASUC.

Ustekinumab

Ustekinumab is an IL12/23 antibody approved for treating moderate to severe UC. Its use in ASUC has garnered interest as many patients are previously exposed to anti-TNFs, vedolizumab, and small molecules. The literature is limited to three retrospective studies in which the majority of patients had previously been exposed to anti-TNFs and vedolizumab. Ustekinumab was initiated following calcineurin inhibitor rescue therapy and at follow-up, all patients were colectomy-free.[18] Although the small

sample sizes limit extrapolation to clinical practice, the foundation is laid for further evaluation.

Surgery

Increasingly, surgical options are discussed as an alternative to chronic medication management in UC. These options include a subtotal colectomy and ileostomy with potential re-anastomosis and formation of an ileal-pouch anal anastomosis later. However, patients remain wary of having a stoma and potential complications, such as pouchitis. Urgent colectomy carries greater risks of morbidity and mortality compared to elective colectomy, and understanding prognostic factors facilitates discussion about treatment outcomes. Predictors of colectomy include albumin levels of <30 g/L, CRP levels of >30 mg/L, *C. difficile* infection, endoscopic severity, previous thiopurine or anti-TNFα treatment, and the risk correlates to the number of predictors present.[5,7,13] Patients who avoid colectomy within 3 months of the index attack have a colectomy-free survival of 93.5%, 81.5%, and 79.4% at 1, 3, and 5 years, respectively.[5] Toxic megacolon, perforation, and massive hemorrhage are complications of ASUC and are indications for urgent colectomy.[2] Initial retrospective studies reported increased post-operative complications, such as infection, sepsis, and leak in patients with recent biologic use.[27] However, recent meta-analyses have not found an increased risk of post-operative complications in UC and Crohn's disease (CD) patients with anti-TNF and vedolizumab exposure.[27] Furthermore, the time interval from the last anti-TNF dose to surgery does not impact the risk of postinfectious complications and detectable serum levels are not associated with increased infection risk.[27] The use of advanced therapy should not impact surgical decision making.

Sequential Rescue Therapy:

Sequential rescue therapy refers to the use of IFX therapy following CsA rescue therapy, or vice versa, to avoid colectomy in ASUC. Gisbert et al. have shown that the colectomy-free rate of sequential therapy with IFX following CsA was 58%, and 42% when CsA was administered after IFX.[18] However, the sample size was too small to make a comparison of efficacy, and the overall adverse event rate and mortality was 26% and 0.88%, respectively, which is similar to the findings in previous meta-analyses.[18] Risks of this strategy include delaying necessary surgery and additive immunosuppression leading to increased infections.[18]

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) may be a useful strategy for guiding anti-TNF therapy dosing in moderate to severe UC. Optimizing drug levels in ASUC can theoretically improve outcomes. ASUC patients who are refractory to corticosteroids have improved clinical and endoscopic remission rates and colectomy-free rates when IFX levels are detectable.[28] Lower IFX levels are common in ASUC given the significant inflammatory burden and increased fecal loss and clearance of IFX. The development of strategies to optimize drug dosing remain challenging due to drug pharmacokinetics and limited availability of point of care TDM.[28] Furthermore, limited data exists on the use of TDM with accelerated IFX dosing and the optimal target levels for ASUC remain unknown.[28]

Antibiotics

The literature does not support the use of antibiotics to induce remission in UC. A recent Cochrane review, which mostly included severe UC patients, found no difference between antibiotics and placebo for induction.[29] Data specific to ASUC is lacking. Based on earlier studies in this review, North American guidelines recommend against the use of antibiotics for the treatment of ASUC.[9,10]

Conclusion:

ASUC has a considerable risk of colectomy and complications. Patients require close monitoring and early recognition of a limited response to corticosteroids, prompting early rescue medical therapy or surgery. For patients who are refractory to corticosteroids, CsA and IFX are the mainstay treatments. However, the recent availability of small molecule therapies and newer biologics has sparked renewed interest in innovative strategies for ASUC management. Increasingly, patients are exposed to more than one advanced therapy prior to hospitalization; therefore, deciding whether to attempt further therapy in the setting of ASUC is not straightforward. We recommend that all patients with ASUC be managed or transferred to an expert centre, when possible, in which both colorectal surgeons and gastroenterologists collaborate closely to optimize safety outcomes for this potentially life-threating condition.

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Diagnosis of ASUC using Truelove & Witts Criteria:		
• ≥6 BMs/day AND • HR ≥90 bpm;	• Temp ≥37.8°C: • Hemoglobin <105 g/L; or	• ESR >30 mm/hr
Investigations:		
• Labs: CBC, electrolytes, creatinine, urea, liver panel, albumin, CRP • Stool studies: culture & sensitivity, C. diff, ova & parasite • Imaging: AXR or CXR • Endoscopy: Flexible sigmoidoscopy within 72 hours • Preparation for rescue therapy: TB skin test, IGRA, Hepatitis B serologies, Cholesterol		
Treatment:		
• Fluid rescustitation • Clear fluid diet or low residue diet • Methylprednisolone 60 mg/day in divided BID or TID dosing • VT prophylaxis		
Day 3 Assessment using the Oxford Criteria:		
• BMs >8 / day or • BMs >3/day & CRP >45 mg/L		

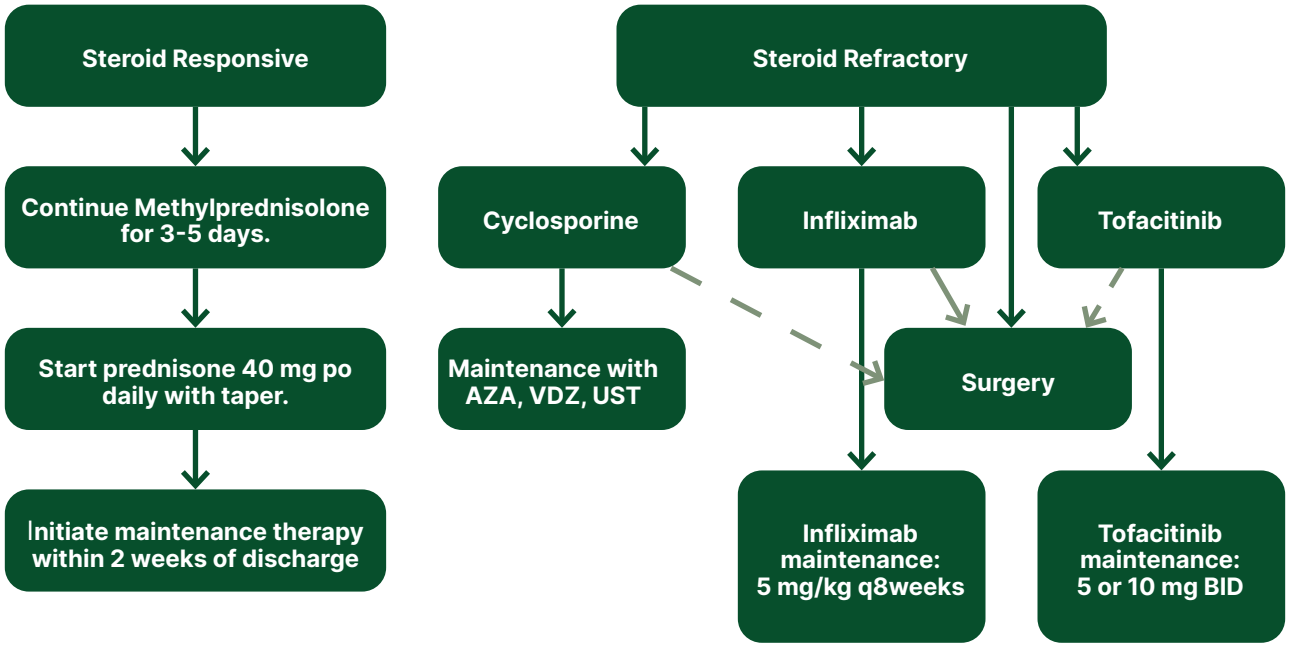

Table 1: Investigations & Management of ASUC; courtesy of Yvette Leung, MD and Natasha Klemm, MD

Clinical Pearls

- ASUC is a potentially life-threatening condition
- 1/3 of patients are steroid-refractory
- Predictors of a steroid-refractory course include: albumin <30 g/L; CRP >30 mg/L; and endoscopic severity
- Inflixmab & Cyclosporine are mainstay rescue medical therapy
- As patients become increasingly exposed to biologic therapies, newer agents are required as rescue medical therapy
- Newer agents, such as Tofacitinib, improve colectomy-free survival in steroid-refractory ASUC
- Predictors of colectomy after a steroid-refractory course include: albumin <30 g/L, CRP >30 mg/L, C. difficile infection, endoscopic severity, and previous thiopurine or anti-TNFa treatmentimproved colectomy-free
- Therapeutic Drug Monitoring may have a role in ASUC management, but further research is required before implementation in clinical practice

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