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Acute Severe Ulcerative Colitis

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Acute severe ulcerative colitis (ASUC) will affect at least one in four patients with ulcerative colitis, requiring hospitalization and induction therapy to achieve remission. The initial assessment should include measurement of inflammation, testing for infection, and evaluating for toxic megacolon. All patients will need prophylaxis against venous thromboembolism, and most will require significant IV hydration. Early endoscopy with biopsies will rule out cytomegalovirus (CMV) and herpes simplex virus (HSV) and help assess severity. First line therapy with intravenous corticosteroids is effective in 2/3rds of patients, while rescue therapy with cyclosporine or infliximab is effective in 80% of the remaining 1/3rd. Roughly 10% will require colectomy in the initial hospitalization, and another 5% will need a colectomy in the next 90 days. Close monitoring after discharge and timely adjustment of maintenance therapy to maintain remission is essential in these high-risk patients. First line small molecule therapies in high-risk patients may help reduce colectomy rates.

How is severe UC defined?

Severe ulcerative colitis was defined by Truelove and Witts in 1955[1] which reported on the use of cortisone in severe UC. Severe UC was defined as six or more bowel movements per day with visible blood in stools, and one or more of the following: fever > 100F/37.8C, tachycardia > 90 bpm, anemia (hemoglobin<= 10.5), or an ESR >= 30 mm per hour. Neither C-reactive protein (CRP) nor fecal calprotectin (FCP) were standard measurements in 1955. Kedia, et al.[2] used the Truelove and Witts criteria to validate a laboratory definition of severe UC and found that an FCP > 782 mcg/g of stool could identify severe UC with a sensitivity of 84% and a specificity of 88%. CRP is often elevated in severe UC, and when positive, can be followed daily as a marker of response to therapy. FCP and ESR change more slowly than CRP and are less helpful as rapid dynamic markers of response to therapy.

What is acute severe UC?

In theory, acute severe UC indicates a flare of rapid onset, but the rapidity is not defined. As a practical

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Table 1. Prediction of Colectomy Risk in ASUC with Additional Truelove & Witts Criteria

Number of positive additional T & W criteria (HR, T, Anemia, ESR)	Colectomy Rate (n =294)
+1	9% (11/129)
+2	31% (29/94)
+3 or 4	48% (34/71)

Increasing numbers of positive additional criteria for severe UC (up to 3) correlate with increasing risk of colectomy during the index hospital admission.

Dinesen, L, et al. JCC 2010; 4: 431-37.

definition, we generally define patients hospitalized for severe flares as having acute severe UC. In practice, this may include some patients with more chronic, ongoing flares, who have not responded to outpatient steroids or previous inpatient therapy with IV corticosteroids. These patients who have failed prior steroids (and/or prior biologics) are at particularly high risk for colectomy.

Admission and initial assessment

The initial assessment should include measurement of inflammation with CRP and FCP, testing for infection, usually including *Clostroides difficile* testing and a stool polymerase chain reaction (PCR) panel for enteric infection, and evaluating for toxic megacolon with abdominal x-ray, a complete blood count and differential, chemistries to detect baseline electrolyte and liver problems, and physical exam for toxic megacolon and dehydration.

Infection with *C. diff* can be detected with PCR and antigen testing for toxin, though detected *C. diff* may be merely colonization, may activate a UC flare, or may be the primary driver of diarrhea. Decisions about when to treat *C. diff* and hold corticosteroid therapy can be difficult. In general, mild inflammation and a positive toxin antigen test should favor treatment with vancomycin for *C. diff* without starting steroids. A sigmoidoscopy more consistent with UC rather than *C. diff*, and a lack of substantial improvement on vancomycin after 48 hours should trigger initiation of corticosteroids. The absence of toxin antigen, more severe inflammation, and a scope consistent with active UC should favor early initiation of corticosteroids, even if this means co-treatment with vancomycin to cover *Clostroides difficile*.

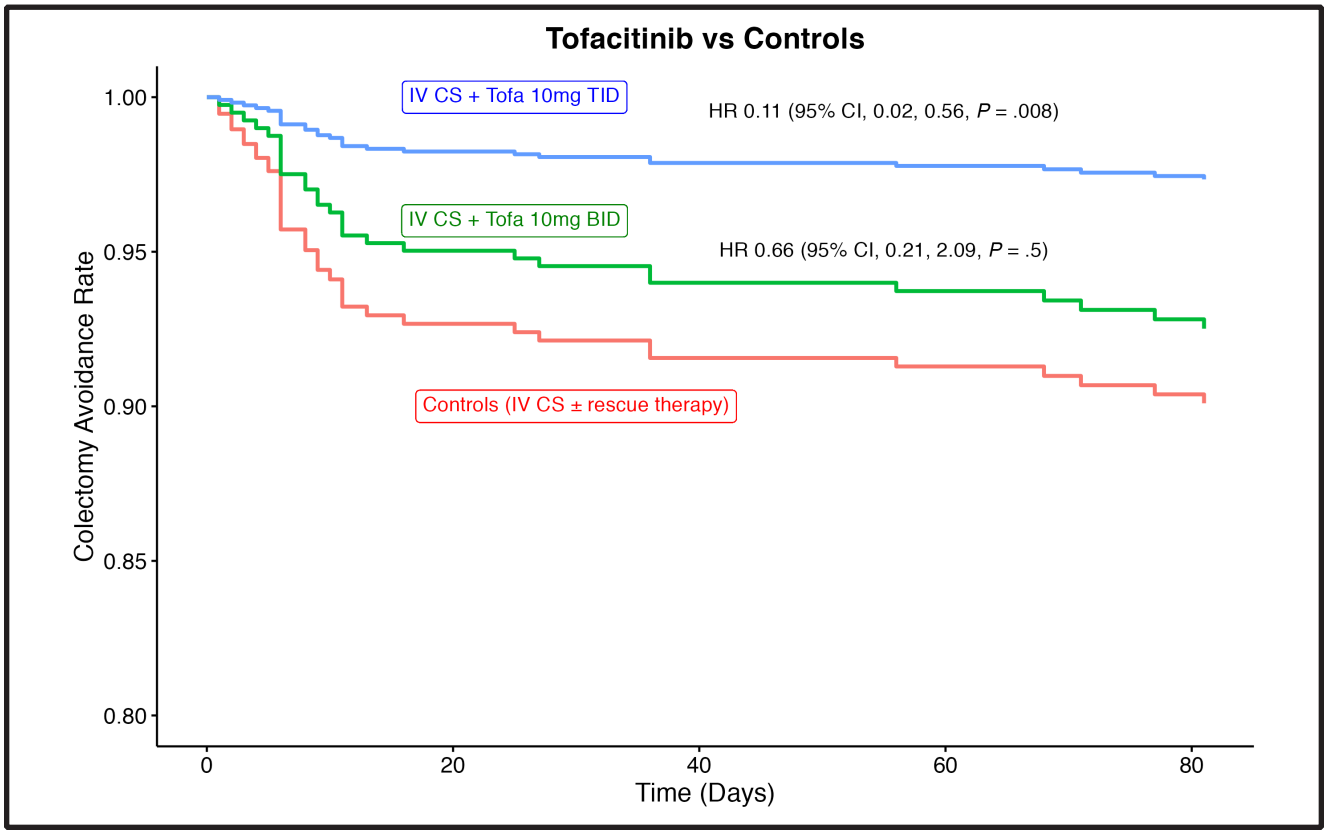
Stool PCR testing for other enteric infections and PCR for CMV are controversial, as many of the positive tests will be "red herrings" in the setting of a UC flare and may not be driving the clinical presentation. The presence of nausea or vomiting in the setting of a positive norovirus test suggests that this is a real infection, and occasional E. coli infections do occur in UC, particularly with recent steroid exposure. Very high CMV titers confirmed on biopsy can be primary CMV infections, especially after an extended course of corticosteroids. *C. diff* remains the most common colonic infection in UC and should be suspected as the primary driver when diffuse abdominal pain and fever are present and minimal or no blood in stool is seen.

The initial abdominal film should be evaluated for colonic thumbprinting and the presence of free air under the diaphragm. Ideally these should be rare when patients present early in a flare, but the risk of perforation rises over time in patients who have failed outpatient or inpatient steroid therapy, and this is especially important in readmissions or hospital transfers. An abdominal exam suspicious for rebound, or a very high (or surprisingly low) white blood cell count with thumbprinting should precipitate an early call to your surgical colleagues to get them on board.

Risk assessment

Patients with ASUC are at increased risk of colectomy if they have failed prior steroids or

Figure 1. First Line Tofacitinib + IV Corticosteroids –10 TID was associated with a lower colectomy rate



Berinstein, JA, et al. CGH. 2021;19:2112.

biologics, are younger or former smokers, require early admission after diagnosis, have extensive colitis or deep ulcerations, have high CRP and ESR, or have low hemoglobin or albumin. The number of positive Truelove and Witts additional criteria (anemia, fever, tachycardia, ESR) have also been shown to be predictive of colectomy (Table 1).[3] Early endoscopy (usually a flexible sigmoidoscopy with biopsies in the first 12 hours) can help prognosticate severity, and biopsies can help rule out CMV and HSV as infectious causes of colitis.

Empiric therapy and prevention of complication

All acute severe UC patients should receive empiric therapy to improve their symptoms and prevent complications. All patients should receive medical prophylaxis for venous thromboembolism, as both active severe UC and the use of corticosteroids increase the risk of venous thromboembolism (VTE). Patient mobility should not be a reason to avoid therapy with enoxaparin or unfractionated heparin, as these risk factors are unchanged by mobility. Confirm daily dosing with the patient, the responsible, nurse, and the medication administration record.

Nearly all patients will be dehydrated upon admission, due to self-restriction of food and fluids to reduce bowel moments, in addition to many watery bowel movements. This should be ameliorated with infusion of IV fluids initially at 1 L per hour until thirst is no longer present, and urine output is frequent and clear. Patients with heart failure, renal failure, or other contraindications to volume infusion should be started at a lower rate and monitored closely.

Most patients will have a limited appetite at the time of admission and should not force food intake. Many will be able to tolerate small amounts of high protein liquid nutrition, e.g., Boost or Ensure, until their appetite returns. When able to tolerate food, patients should start slowly with a high protein, low residue diet, often provided as a high protein breakfast at each meal and advance to full diet as tolerated. Many patients have severe urgency at the

initial presentation, and can benefit from a bedside commode, and twice daily 5-ASA suppositories to reduce this symptom. Patients in the hospital benefit from protected sleep time. Consider providing night quiet hours, limiting vitals and blood draws when possible, and dosing intravenous steroids early in the day (e.g., 6 AM and 2 PM for bid dosing) to reduce sleep disturbance. Discuss with each patient the common side effects of steroids and their effects on sleep, anxiety, depression, and PTSD. Each inpatient stay is also an opportunity for education, particularly on therapies for UC and surgical options for UC. Encourage patients to keep a pad and pen nearby to write down questions during the day. I often use the IBD School videos on YouTube to address particular education topics tailored to each patient.

First line therapy

When patients are first admitted to the hospital, and infection testing is pending, first line therapy with methylprednisolone, a corticosteroid, at a standard dose of 30 mg bid, is recommended. There is no evidence that doses higher than 1 mg per kilogram per day add any benefit. Alternative dosing schedules of once daily, three times daily, four times daily, or continuous dosing do not seem to have any additional benefit, though more frequent dosing may interfere with sleep.

Over time, an increasing number of ASUC patients are presenting with prior biologic (usually anti-TNF) failure. Recent case-control data in high-risk patients with prior biologic failure treated with first line tofacitinib 10 mg three times daily in combination with intravenous solumedrol suggest a significant reduction of colectomy rates (Figure 1) with aggressive first line therapy.[4]

All patients should be advised that colectomy is a reasonable option even at first line, as some patients will choose a one-time colectomy over lifelong maintenance medication. It is important for all patients to meet the local colorectal surgeons, usually on day two of admission, and to meet the wound care ostomy nurse, who will mark a site for optimal ostomy placement. A key part of patient education is to establish that colectomy is a reasonable therapeutic option, and to re-emphasize this regularly during the course of the hospital stay.

Reassessment at 72 hours

Patients should be monitored closely during their first 72 hours on steroids, including daily measurements of CRP, and tracking of bowel movements. The patient should be counseled on the options of colectomy and rescue therapy and should be prepared to make a decision on the next step if needed at 72 hours. There are three indices developed to estimate the likelihood of success of intravenous, steroids, and 72 hours. The CRP should be collected at 72h on steroids, and the most recent 24-hour bowel movement count used to calculate the Travis, Lindgren, and Ho prognostic indices, as described in the Michigan Severe UC Protocol.[5] If these all indicate low risk of colectomy, you should plan a transition to oral corticosteroids, advance to full diet, and plan for a maintenance therapy. If any one of these indices indicates high risk, the patient should be prepared to choose between colectomy and rescue therapy, so that either option can be started in a timely fashion.

Rescue therapy options

The two best studied rescue therapies after corticosteroids have failed in ASUC are cyclosporine and infliximab, which had equivalent 98-day outcomes in the CYSIF trial. One of the challenges of starting any biologic medication in ASUC is the protein leak across the damaged colon. Infliximab has been shown to leak into stool effluent at a high rate, lowering drug levels in ASUC patients. Small molecules (methylprednisolone, cyclosporine, Jak inhibitors), in contrast, bind to receptors inside of cells. This lowers their serum

level, and the amount of drug available to leak out of the colon. This makes the small molecules more attractive for induction of remission in ASUC. Limited data from a GETAID study suggest a high (79% at 3 months) success rate with tofacitinib after prior corticosteroid and biologic failure.[6]

A second problem with using biologics for induction of remission in ASUC is the low trough levels that frequently result with a leaky colon. Particularly for older biologics prone to formation of anti-drug antibodies like infliximab, this increases the risk of forming blocking antibodies, making it more attractive to achieve induction with small molecules, and start biologics after the colon leak has been slowed.

The third limitation of using a biologic for rescue therapy is that these drugs have a long half-life and tend to stay around for weeks at a time. If one is considering salvage therapy with a different medication, this compounds immunosuppression from steroids, the biologic rescue drug, and the addition of a 3rd salvage drug. It is usually wiser to use small molecules with more rapid washout for first and second line therapy if a 3rd line salvage therapy is being considered.

Assessing rescue therapy

The outcome from rescue therapy should be assessed between 72 and 108 hours after initiation. Daily CRP and a repeat FCP will be helpful, as these should continue to trend downward and enter the normal range. Bleeding in bowel movements should cease, and the number of bowel movements should be reduced. If bowel symptoms plateau, and CRP and/or FCP rise, these are bad prognostic signs, and generally mean colectomy in the very near future. In patients who have been on corticosteroids for some time and have a worsening of inflammation, it can be worth rechecking for CMV and/or rescoping with a flexible sigmoidoscopy to help inform the decision about colectomy.

Should you salvage?

Some patients, especially those new to ulcerative colitis, may resist the idea of colectomy, even after failure of corticosteroids and rescue therapy. The plan for next option should be an ongoing discussion during rescue therapy, with clear recommendation of colectomy as the standard of care. Salvage therapy entails significant risks, with multiple immunosuppressive medications that increase the risk of both infection and death. There are very limited data on salvage therapy with a 3rd immunosuppressive medication and some case series have documented high rates of infection, and occasional deaths. These risks may be decreased by the rapid washout of prior small molecules and may be increased by prior biologic therapies with long half-lives.

Patients need to be aware of the risks of multiple immunosuppression, and there must be a clear plan for an exit to a long-term maintenance therapy that is acceptable to the patient before any salvage therapy is attempted. It must be clear to both the patient and the provider colectomy is the standard of care after failure of rescue therapy, as the data on salvage therapy is very limited, and includes significant negative outcomes.

Preparing for colectomy

Preparing a patient for a colectomy is an ongoing process during each admission for ASUC. Colostomy must be presented as a viable therapeutic option, and a good ostomy site should be marked early in the stay by a wound ostomy care nurse. If there has been no previous imaging of the small bowel, CT or MRI should be done to evaluate for Crohn's disease rather than ulcerative colitis. An ongoing discussion with the surgeons should begin on day two of admission, and patient education about surgical options should be ongoing. When a decision is made to proceed to colectomy, immunosuppressive medications (including corticosteroids) should be stopped, and if possible, given time to wash out before surgery. When possible, nutritional status should be optimized, and an elective colectomy is always preferred over toxic megacolon, perforation, or an emergent colectomy.

Preparing for discharge

For the patient who achieves induction of remission during the hospitalization, planning for a successful discharge should begin as soon as the patient turns the corner. You should expect no blood in the stool and a CRP below 10 mg/L. Patient should be able to advance to a full diet without recurrence of symptoms. The patient should be

able to stop all intravenous therapy and transition to oral therapy. Note that switching from 60 mg daily methylprednisolone to 60 mg prednisone is a drop of 20% in efficacy, while a transition to 40 mg prednisone is an 88% drop in efficacy. The patient should be able to walk around and maintain normal activity levels as if they were at home for 24 hours before discharge. After 24 hours on oral therapy, there should not be a sudden rise in CRP, and you should obtain a new FCP to establish a new baseline. Note that while CRP often rapidly normalizes, FCP (along with mucosal healing) may take months to normalize. Some practitioners will obtain a repeat flexible sigmoidoscopy, especially in high-risk patients, to establish a new baseline and to estimate the time to complete mucosal healing. It is important to obtain insurance approvals of all maintenance therapies, and schedule infusions if needed, before the patient leaves the hospital.

After discharge

After induction of remission and discharge, it is important to monitor patients closely, as there is a high rate of recurrence and readmission. We typically monitor CRP, FCP, and symptoms for any recurrence at 1, 3, and 6 weeks. We standardize our symptom collection with the UC-PRO instrument in Epic. The typical discharge plan will start the patient on prednisone at a dose of 40 or 60 mg (for more severe cases) daily, with tapering by 5 mg per week. There is sone data suggesting that effective induction of remission with cyclosporine may not need a prednisone taper,[7] though this needs further study to determine if this is generalizable and whether this applies to other small molecules like JAK inhibitors. It is also important to check in on the patient after discharge to make sure that they have actually started their maintenance medication on schedule, without any insurance hiccups, and that they are tolerating this well. Readmissions and subsequent ASUC admissions increase the risk of colectomy, as documented by Dinesen.[3] ■

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