ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Hospital Management of Acute Severe Ulcerative Colitis

Joseph Feuerstein, MD
Associate Clinical Chief, Gastroenterology
Center for Inflammatory Bowel Disease
Associate Professor of Medicine, Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

G&H When is hospitalization indicated for patients with ulcerative colitis?

JF Studies have found that up to 25% of patients with ulcerative colitis (UC) are hospitalized at some point for their disease. Some patients need to be hospitalized almost immediately at the time of diagnosis, whereas others have UC that evolves slowly over many years and then rapidly worsens. Predictors of more severe disease include diagnosis before the age of 40 years, more extensive disease involvement, severe endoscopic disease activity (eg, large or deep ulcers), corticosteroid dependence, and presence of extraintestinal manifestations of UC. Hospitalization is indicated when patients decline and show systemic signs and symptoms of worsening disease activity. Typically, Truelove and Witts' criteria can be used to define acute severe UC (ASUC). These criteria include 6 or more bloody bowel movements per day along with one marker of systemic toxicity (pulse >90 beats/min, temperature >37.8° C, hemoglobin <10.5 g/dL, or erythrocyte sedimentation rate >30 mm/h). Similarly, patients who are corticosteroid-dependent or -refractory and/or who have severe endoscopic disease activity according to the Mayo Clinic Score should also be considered to have ASUC. One of the more concerning systemic findings is weight loss, as it is not typically a sign of UC but may occur over time in more severe cases because patients are not eating. It is important that clinicians are aware when patients are not responsive to therapy and are showing these objective signs of worsening disease.

G&H Upon hospitalization, what tests and evaluations are needed?

JF A stepwise algorithmic approach to patients hospitalized with ASUC can be helpful to optimize management. When patients first arrive, it is important to obtain a thorough history that includes the involvement of the colitis, disease duration, and medication history (such as medication failure and primary or secondary nonresponse to biologic therapies). Medication history can help determine which drugs can be used later and whether there was a trigger for the patient's flare. For example, the patient may have had an infection recently or may have had significant use of nonsteroidal anti-inflammatory drugs, which can increase the risk of flare. Stool studies are often important as well to identify other infections, including those that can occur along with UC. An example is *Clostridioides difficile*, which can occur in the setting of a UC flare, but can also be its own disease process while UC is not active. Many experts advocate for extensive stool testing (including for *Escherichia coli*, Salmonella, Shigella, *Cryptosporidium*, and *Giardia*) to exclude any potential infectious causes, whereas other experts argue for a more focused approach based on potential patient exposures. Regardless, all patients should undergo a *C difficile* test on admission.

As for laboratory tests, a complete blood count should be obtained to look for signs of severe elevation in the white blood cell count, which may indicate the presence of an ongoing infection or severe inflammation.

Clinicians should also look for anemia with a hemoglobin test to assess the severity of the inflammation and bleeding. Platelet counts may be elevated owing to an acute phase reaction from inflammation. Often, clinicians also check the metabolic panel to make sure that electrolytes are normal. Liver function tests should also be checked to obtain a baseline prior to the initiation of any other drug therapies. Albumin is also important to check and may be low owing to overall poor nutritional status. Many drugs, such as those in the anti–tumor necrosis factor (TNF) class, are bound to albumin; thus, a low albumin may result in lower drug levels, leading to decreased drug efficacy.

Clinicians should also check C-reactive protein (CRP), which is a blood marker of inflammation. It is not the most accurate marker, as a normal CRP does not preclude ongoing inflammation, but it does provide at least some indication of the degree of systemic inflammation when it is elevated. Many clinicians also use fecal calprotectin to look for inflammation that is more specific to the gut. However, fecal calprotectin is elevated in both patients who have an enteric infection and those who have a UC flare. Therefore, it is important to differentiate between the two based on clinical assessment and overall stool testing.

When a patient has ASUC, he or she should be on a corticosteroid-sparing agent. If that is the case on the first day of hospitalization, I use QuantiFERON-TB Gold to screen for tuberculosis, as well as a hepatitis B panel to screen for hepatitis B, as many of the drugs that may be considered later require screening for both of these diseases. Because some patients do not mount an immune response to QuantiFERON-TB Gold, I also perform a quick screening for exposures to tuberculosis and obtain a chest radiograph to exclude undiagnosed pulmonary tuberculosis. If I think I may need to use cyclosporine, I also check total cholesterol as well as creatinine and magnesium.

As for imaging, I try to defer it on admission unless there are signs of toxic megacolon, abdominal tenderness, or distension on initial examination. Studies have shown that a computerized axial tomography (CAT) scan is not necessary in most situations. As a result, I typically start with an abdominal radiograph if there are any concerning signs of evolving megacolon. However, I obtain a CAT scan in a few circumstances, such as when CRP is extremely high.

In addition, I often perform a flexible sigmoidoscopy on the day of admission to obtain a sense of disease severity and to calculate an endoscopic Mayo Clinic Score. I frequently also send off biopsy samples for cytomegalovirus (CMV). If I am unable to perform the sigmoidoscopy right away, I sometimes perform a serum CMV test to receive an answer sooner, as CMV can cause concomitant infection and should be treated when present.

G&H How are these patients typically treated when first hospitalized?

JF When patients are admitted with ASUC, I always use intravenous (IV) methylprednisolone, typically at 20 mg 3 times daily. Most studies have shown that higher doses do not add much efficacy. In addition, side effects are increased with higher doses of corticosteroids.

Interestingly, two-thirds of patients respond to IV corticosteroids regardless of which treatment they were receiving previously. It is a little surprising that this is true even if patients fail oral corticosteroids, as most studies in other diseases have shown that patients have equal response to oral and IV corticosteroids because they are equally bioavailable. However, in UC, even though there is no absorption issue in the small bowel, patients do better with IV corticosteroids.

Additionally, I do not continue mesalamine when putting a patient on corticosteroids because it is unclear whether this is beneficial. I also do not make any notable dietary restrictions, as most studies have shown that diet changes do not provide mucosal improvement in UC. Withholding food may reduce the total number of bowel movements, but this is not a true improvement of disease activity.

G&H How is response to treatment assessed?

JF A number of different scoring systems can be used to assess overall responsiveness, typically on day 3 of hospitalization. The easiest and most frequently used is the Oxford score, which is based on the number of bowel movements per day, whether there is blood in them, and CRP. This prediction model has an 85% positive predictive value that a patient will need surgery if rescue therapy is not initiated. Another prediction rule is the Lindgren score (number of stools/day + 0.14 × CRP [mg/L]). A score of 8 or higher predicts a colectomy rate of 72%. A recent study by Bernardo and colleagues found that the Lindgren score was best at predicting IV corticosteroid failure, need for medical rescue therapy, and need for surgery.

Importantly, by using an objective measure, clinicians can decide on day 3 whether the patient needs therapy escalation. Without an objective measure, clinicians may see that there is some response to corticosteroids or that the CRP is slowly improving and may not escalate therapy as quickly as they should.

It should be noted that nowadays all patients who are hospitalized for ASUC should probably go on to biologic

treatment. The aforementioned scores help me know whether I should start biologic treatment in the hospital or whether I should discharge the patient on prednisone and then start biologic treatment later. With possible delays related to prior authorization and given the severity of the disease and the short window for patients to improve, I initiate most patients on a corticosteroid-sparing biologic in the hospital before discharge. Ideally, this should begin on day 3 without delay whenever possible.

G&H What are the options for rescue therapy?

JF Rescue therapy is typically infliximab or cyclosporine. Studies have compared these drugs and found that they have similar outcomes and are equally effective with similar side-effect profiles overall. Most practices select infliximab over cyclosporine owing to ease of dosing and the ability to use this medication for maintenance dosing as well. Some doctors have suggested that patients who are sicker with low albumin might do better with a continuous infusion of cyclosporine compared with infliximab, but there are very little data that support this.

It should also be noted that the ideal dose and frequency of infliximab in ASUC is not known. Studies have compared infliximab doses of 5 mg/kg and 10 mg/kg in patients with moderate to severe UC in the outpatient setting. Given that infliximab is bound to albumin and is excreted in stool, the sicker the patients, the more likely they are to excrete the drug faster. Many practices have switched to giving infliximab at the higher dose of 10 mg/kg and then often repeat the dose at 48 to 72 hours.

In patients who have already been on biologic therapy, previous exposure to an anti-TNF drug such as infliximab or adalimumab complicates matters because trying the same treatment is typically not successful, although it depends on the reason for the lack of response if there was primary or secondary nonresponse. If the anti-TNF drug can be optimized, that is often the safest option. However, in some situations, it might be more prudent to give cyclosporine after failure of an anti-TNF agent. Using third-line salvage therapy, though, is not without risk; increases in serious adverse events and mortality have been reported in the literature.

G&H When is surgery indicated?

JF Surgery is indicated early on if the patient develops toxic megacolon, perforates, or shows other signs of rapid decompensation. Some clinicians involve surgeons on the first day of admission. In our practice, my colleagues and I usually involve surgeons on day 3. When I talk to a patient about potentially escalating therapy, I always bring up surgery as one of the treatment options. Surgery should not be considered only in a case of failure of medical therapy. It is one of the therapeutic options along with infliximab or cyclosporine. In most cases, patients will not choose surgery as their first option, but it is an option that patients should feel is viable. I typically defer to my colorectal surgery colleagues to discuss the details involved in a 2- or 3-stage procedure.

G&H What other considerations should be kept in mind when managing these patients?

JF All patients should be on pharmacologic deep vein thrombosis (DVT) prophylaxis because ASUC is a hypercoagulable state. Patients with ASUC have a higher rate of DVT even if they are walking around and are relatively healthy. Not only is it important that this prophylaxis be ordered, but it also needs to be administered. Sometimes it is ordered, but the patient declines it. I typically remind patients about the importance of this prophylaxis every day and why they need to receive it.

In addition, several studies have shown that patients who are using narcotics for pain management in the setting of ASUC may have higher rates of both morbidity and mortality. Thus, none of these patients should have standing orders of narcotics. In my opinion, this should also include a sliding scale of narcotics because many of these patients have discomfort and will end up receiving narcotics if a sliding scale is used. If pain control is needed, acetaminophen and nonopiate medications should be used as much as possible.

Depression should be discussed with all patients with ASUC. Depression is known to be increased in this cohort, and often many patients struggle with their sudden worsening of disease and change in quality of life. Starting this dialogue with patients early on and offering support from social work and/or psychiatry is important.

Finally, the role of other biologics is evolving in ASUC. There is interest in their use, although most do not work as fast as infliximab and cyclosporine. However, given that some patients have been exposed to anti-TNF drugs already and ended up flaring, there is interest in trying other drugs to avoid sending these patients to surgery early on. Several case series have been published recently on using cyclosporine to transition to ustekinumab (Stelara, Janssen) or vedolizumab (Entyvio, Takeda); cyclosporine is used to get the disease under control, and then patients are managed with the corticosteroid-sparing biologic. There is also some interest in the use of tofacitinib (Xeljanz, Pfizer), which is one of the newer oral Janus kinase inhibitors. However, tofacitinib has a black box warning for an increased risk of pulmonary emboli as well as a small risk of death when using the high dose over a long period of time. Nevertheless, clinical trial data have

shown the efficacy of tofacitinib in patients who have failed anti-TNF therapy and have severe disease.

G&H When should patients be discharged from the hospital, and what monitoring is required afterward?

JF To be discharged, patients should have fewer than 4 bowel movements per day with no blood. Most studies have shown that if patients still have blood in their stool, they have a high likelihood of being readmitted and failing therapy because they are still too inflamed. Once patients have fewer than 4 bowel movements per day with no blood, I am much more willing to discharge them. Ideally, their CRP should also decrease. It is sometimes helpful to measure fecal calprotectin as well to obtain a baseline prior to discharge that can then be followed as an outpatient. Finally, patients should be stable on their corticosteroid-sparing drug.

When preparing patients for discharge, I typically start transitioning them by changing their IV corticosteroids to oral prednisone. I do not specifically keep them in the hospital for this, although some experts recommend trying oral prednisone before discharge. I tell my patients to stay on 40 mg of prednisone for at least a week when they leave the hospital and then to contact me because I want to know whether they are feeling better. A flare soon after discharge increases the risk of early readmission. If patients are still having symptoms, I may continue prednisone for another week at 40 mg before starting to taper down. Prednisone should not be tapered immediately upon discharge, as the taper should be designed for the individual patient based on his or her overall responsiveness to therapy.

Another consideration is whether a patient should be given a dose of infliximab 1 or 2 weeks after discharge. Data by Gibson and colleagues indicate that once a patient shows response to therapy, escalating dosing intervals may be more effective than typical induction dosing intervals. I often use all 3 outpatient induction doses approved by insurance and dose patients 1 week after discharge, 2 weeks later, and then 2 or 4 weeks later depending on their response to therapy. I often determine this based on the patient's initial symptoms over the first few days after discharge. If he or she is doing well and seems stable, I might wait 2 weeks, but more often, especially with more severe disease, I give a dose of infliximab 1 week after discharge.

Disclosures

Dr Feuerstein has no relevant conflicts of interest to disclose.

Suggested Reading

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