Contemporary Medical Management of Acute Severe Ulcerative Colitis

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Acute severe ulcerative colitis is a medical emergency that requires prompt recognition, evaluation, and intervention. Patients require hospital admission with laboratory, radiographic, and endoscopic evaluation with initiation of corticosteroid treatment. Despite early intervention, many patients require salvage medical therapy, with some progressing to colectomy. Here we review important concepts and recent advances in the evaluation and medical management of adult and pediatric patients with acute severe ulcerative colitis.

Key Words: acute severe ulcerative colitis, salvage therapy, infliximab, medical management

INTRODUCTION

Acute severe ulcerative colitis (ASUC) is a life-threatening condition and medical emergency. Approximately 25% of adults and children with ulcerative colitis (UC) will develop ASUC requiring hospitalization.[1, 2] Despite available medical salvage therapies, colectomy rates remain high for patients with ASUC, as 14%–20% will require a colectomy by 1 year.[3,4] This statistic highlights the need for improvements in medical management. Between 2010 and 2017, a number of comprehensive consensus statements and systematic reviews have been published that provide guidance for the management of ASUC.[5–10] Our aim is to concisely review the practical aspects of the management of patients with ASUC and shed light on emerging data that may change our approach to these patients now and in the future.

DEFINITION

Acute severe ulcerative colitis was originally defined by Truelove and Witts as an exacerbation of UC with at least 6 daily bloody stools and 1 of the following: temperature > 37.8°C, anemia (hemoglobin < 10.5 g/dL), tachycardia (>90 beats per minute), or elevated erythrocyte sedimentation rate (ESR; >30 mm/h).[5] For pediatric patients, it has been defined as a Pediatric Ulcerative Colitis Activity Index (PUCAI) score of at least 65 points.[11] Once the diagnosis of ASUC is made, patients should be admitted to the hospital for monitoring, further evaluation, and management.

INITIAL MANAGEMENT

A practical checklist for the initial evaluation and management of patients with ASUC is provided in Figure 1.

Laboratory, Radiographic, and Endoscopic Evaluation

Upon admission, patients with ASUC should undergo both laboratory and radiologic evaluations to assess the disease severity, risk of complications, and concomitant infections. The initial laboratory evaluation should include complete blood count, electrolytes including magnesium, C-reactive protein (CRP), ESR, liver function panel including albumin, stool culture, and *Clostridium difficile* testing. In addition, an abdominal radiograph should be obtained to assess for toxic megacolon.[6] In anticipation of the potential need for salvage therapy with infliximab, also consider obtaining a tuberculosis interferon gamma release assay (which generally takes 48 hours for results), varicella zoster titer, and hepatitis B serologies at admission. If considering a calcineurin inhibitor, obtain a lipid profile and magnesium level, as there is an increased risk for neurologic adverse effects in patients with hypocholesterolemia or hypomagnesemia.[12] Each patient should have their vital signs, electrolytes, albumin, complete blood count, and CRP (±ESR) assessed regularly throughout their hospitalization to assess for disease progression and complications.[5]

Endoscopic evaluation is important to assess for superimposed cytomegalovirus (CMV) as a driver of disease exacerbation in patients with ASUC not responding to intravenous corticosteroids. Full colonoscopy is not recommended in

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Checklist for Initial Evaluation and Management of ASUC

Baseline disease activity assessment
- ☐ PUCAI score (pediatrics)

Initial laboratory evaluation
- ☐ CBC
- ☐ Electrolytes
- ☐ Hepatic Profile
- ☐ CRP/ESR
- ☐ Stool Culture
- ☐ Stool *C. difficile* PCR

Pre-salvage/maintenance therapy laboratory evaluation
- ☐ TB screen (if considering anti-TNF)
- ☐ Hepatitis B serology (if considering anti-TNF)
- ☐ Varicella Zoster titer (if considering anti-TNF)
- ☐ TPMT (if considering thiopurines)
- ☐ Lipid Profile (if considering calcineurin inhibitor)

Imaging evaluation
- ☐ Abdominal x-ray

Endoscopic evaluation
- ☐ Flexible sigmoidoscopy with CMV PCR if no response to 3 days of intravenous corticosteroids

Thromboembolism prophylaxis
- ☐ Heparin prophylaxis (adults and high-risk pediatric patients)
- ☐ Pneumatic compression device (low-risk pediatric patients)

Nutrition
- ☐ Assess status and establish nutrition plan

Corticosteroids
- ☐ Methylprednisolone 1-1.5 mg/kg IV to a maximum of 40-60 mg daily

FIGURE 1. Admission checklist for initial evaluation and management of hospitalized patients with ASUC.

patients with ASUC due to risk of perforation. For pediatric patients, a joint consensus statement by the European Crohn's and Colitis Organization (ECCO) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) specifically recommends an unprepped flexible sigmoidoscopy be performed on those without a clear clinical response to intravenous corticosteroids, as evidenced by a PUCAI score greater than 45 on day 3 of therapy.[5] The latest ECCO consensus statement for adult patients similarly states that an unprepped flexible sigmoidoscopy should be considered in addition to intravenous corticosteroids.[7] Diagnosis of CMV should be made through analysis of colon tissue, rather than peripheral blood, as peripheral CMV activation intermittently occurs in patients with UC without clear effects on disease course.[13, 14] Although histopathologic features of enlarged cells with intranuclear inclusion bodies may be detected on routine hematoxylin and eosin (H&E) staining, immunohistochemistry or in situ hybridization on paraffin-embedded tissues, or tissue polymerase chain reaction (PCR) for CMV DNA—is a more sensitive mode of detection. The best tissue test for CMV complicating ASUC has not been determined, and the relative merits of various assays have been reviewed in depth by others.[15–17] The ECCO consensus guidelines on opportunistic infections in IBD recommend assessment by either tissue PCR or immunohistochemistry.[17]

Toxic Megacolon

Toxic megacolon is a potentially life-threatening complication of ASUC. In the setting of acutely worsening pain, bleeding, fever, or new vital sign instability, an abdominal radiograph must be obtained to evaluate for toxic megacolon. In adults, a transverse colon dilated ≥55 mm and signs of systemic toxicity are indicative of toxic megacolon. In children younger than 10 years of age, 40 mm may be used as the criteria for colon diameter.[5] The signs of toxemia include fever, tachycardia, leukocytosis, anemia, worsening pain, abdominal distention, hypotension, dehydration, altered mental status, or electrolyte abnormalities.[18] An emergent surgical consultation should be obtained in the setting of toxic megacolon. Initial conservative treatment includes close monitoring, nil per os, intravenous fluids, correction of electrolyte abnormalities and anemia, and broad-spectrum antibiotics. Placement of a nasogastric tube for decompression should also be considered. If the patient is unable to be treated conservatively due to vital sign instability or toxicity, then emergent colectomy should be performed. Cyclosporine and anti–tumor necrosis factor (TNF) therapies should not be used in the setting of toxic megacolon.[5]

Thromboembolism Prophylaxis

ASUC is a pro-inflammatory state associated with increased risk of vascular thrombosis. Low–molecular weight heparin (LMWH) prophylaxis and graduated compression stockings are recommended for all adult patients hospitalized with ASUC without additional risk factors for bleeding.[6] This is true especially for older patients as there is a linear correlation with venous thromboembolism and age.[6, 19] In addition to heparin prophylaxis, it is important to avoid prolonged immobilization, prevent dehydration, minimize use of central venous catheters, and hold oral contraceptives and tobacco products.[18, 19]

According to the most recent pediatric consensus guidelines, there is not sufficient evidence to support the routine use of prophylactic LMWH for preventing thromboembolic complications in children with ASUC.[5] Although increased over baseline, the absolute risk of thromboembolic complications in children hospitalized with UC is 1%–1.9%.[20, 21] Additional risk factors for thrombosis in children with ASUC include presence of a central venous catheter, known hypercoagulable disorder, oral contraceptive drugs, and history of thromboembolism in a first-degree relative.[20, 21] The practice of the authors caring for children is to encourage pediatric patients to get out of bed if stable, use intermittent pneumatic compression devices, and start LMWH prophylaxis in patients with any of the aforementioned risk factors.

Nutrition

Nutrition is an important aspect of treatment for all hospitalized patients to support healing. Patients should be rehydrated and, unless there are concerns for toxicity, started on a regular diet upon admission. Three randomized controlled trials in the 1980s and 1990s did not show any benefit of bowel reset in the management of ASUC, and parental nutrition and bowel rest are associated with increased risk of infectious complications in this setting.[22–24] Only if patients are unable to tolerate a regular diet is enteral or parenteral nutrition recommended. The notable exception is in the setting of toxic megacolon, where the patient should be promptly made nil per os.[5]

Pain Control

Balancing patient comfort without exacerbating the disease process is a challenge in ASUC. Pain may be a symptom of the ongoing chronic inflammation or related to a more serious complication of ASUC.[5, 25] Physicians should examine patients and assess for toxic megacolon or colonic perforation in the setting of acute severe exacerbations of abdominal pain in ASUC. Thromboembolic complications should be considered in the setting of new chest or extremity pain. Hot compresses, relaxation techniques, and acetaminophen are often sufficient for pain control in ASUC.[5] Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided due to risk of further exacerbating disease.[26] Opioid pain medicines should be used sparingly and at a low dose because they are relatively ineffective for the intermittent colicky abdominal pain associated with UC, they decrease gut motility and increase risk of toxic megacolon with colonic dilatation, and they are associated with increased mortality in IBD.[27, 28] Consultation with a pain specialist and/or psychologist may be helpful in patients with inadequately controlled pain in whom disease complications have been excluded.[25]

Anemia

Throughout their admission, patients will have their hemoglobin monitored closely for signs of anemia in the setting of chronic inflammation and acute blood loss. Blood transfusions may be needed to maintain adequate hemoglobin. In the acute setting, oral iron should be avoided as it may cause increased inflammation and potentially produce free radicals.[29, 30]

Pregnancy

Pregnancy does not change the management of ASUC for patients. Pregnancy with active inflammatory bowel disease (IBD) is associated with adverse pregnancy outcomes including preterm birth, small for gestational age, and increased rates of cesarean section, stillborn, and neonatal death.[6] Therefore, it is recommended to treat pregnant patients effectively in an effort to prevent morbidity and mortality for neonates. Corticosteroids, calcineurin inhibitors, and infliximab may be used in the setting of ASUC exacerbation during pregnancy.[31] Methotrexate should be avoided during pregnancy due to its teratogenicity.

OPPORTUNISTIC INFECTIONS

Cytomegalovirus

It remains unclear whether CMV reactivation is the cause or consequence of ASUC exacerbations. Although CMV is typically a mild self-limited illness in immunocompetent individuals, in an immunocompromised individual, CMV has the potential to progress to a severe systemic disease or end-organ damage such as colitis.[32] In patients with UC, the catabolic state and impaired natural killer T-cell function also predisposes these patients to infection, especially when there is active inflammation.[33] Furthermore, steroid treatment has been shown to pose an increased risk for CMV reactivation.[34] The reported incidence of CMV detection in the tissue of patients with steroid-refractory UC by immunohistochemistry or PCR ranges between 25% and 57%.[35] CMV-positive patients are more likely to have steroid resistance and to require salvage therapy and colectomy in the setting of ASUC.[34] Although several observational studies have reported response rates of 60% to 80% (with and without continuation of immunosuppressive therapy depending on the study), meta-analyses report conflicting results. One meta-analysis reported an overall increased rate of colectomy in CMV-positive patients treated with antiviral therapy compared with those not treated, whereas another concluded that there was a reduced risk of colectomy with antiviral treatment only in those CMV-positive patients refractory to corticosteroids.[36, 37] Both groups of authors agreed that the quality of evidence to support antiviral treatment for CMV in UC is low. The ECCO guidelines on opporunisitic infections in IBD recommend that patients with corticosteroid-refractory ASUC and a positive tissue diagnosis of CMV be treated with intravenous ganciclovir (2–3 weeks) in consultation with an infectious disease specialist.[17] If patients respond to treatment with clinical improvement, transitioning to oral valganciclovir after 3–5 days may be considered.[17, 34] Although the ECCO guidelines recommend considering discontinuation of immunosuppressive therapy during antiviral treatment for CMV, a recent large multicenter retrospective study observed no difference in colectomy rates between those treated with infliximab and cyclosporine in addition to antiviral therapy compared with those treated with antiviral therapy alone.[38]

Clostridium difficile

Patients admitted for ASUC should be evaluated for *C. difficile* stool PCR upon admission.[5, 29] Patients with *C. difficile* in the setting of ASUC have a more severe disease course with increased morbidity and mortality, requiring longer

hospitalization.[39] Specifically, patients need to be monitored for toxic megacolon, colonic perforation, and venous thromboembolism, as there is increased risk in the setting of *C. difficile*.[39] Patients with *C. difficile*–complicating ASUC by definition have severe disease and are often on immunosuppressive medical therapy, and therefore should be treated initially with oral vancomycin.[17] A recent multicenter large retrospective cohort study, presented in abstract form, reported that initiation of corticosteroids or biologic medications after antibiotic treatment for *C. difficile* was not associated with an increased risk of *C. difficile* recurrence, and was actually associated with a reduced risk of death, sepsis, or colectomy.[40] This preliminary work suggests that escalation of immunosuppressive treatment in the setting of treated *C. difficile* infection may not worsen clinical outcomes.

Pneumocystis jiroveci

The risk of pneumonia from *P. Jiroveci* in patients with IBD on corticosteroids and/or immunosuppressive therapy is quite low.[41] ECCO guidelines recommend *P. Jiroveci* prophylactic treatment with trimethoprim-sulfamethoxazole in patients on triple immunosuppressive therapy, or dual immunosuppressive therapy that includes a calcineurin inhibitor.[17]

CORTICOSTEROIDS

Intravenous (IV) corticosteroids are firstline therapy for ASUC and should be initiated promptly upon admission to the hospital. Therapy should not be delayed pending completion of evaluation for superimposed infections. For pediatric patients, IV methylprednisolone 1–1.5 mg/kg/d to a maximum of 40–60 mg daily is the corticosteroid of choice due to fewer mineralocorticoid effects compared with hydrocortisone.[5] For adults, either 100 mg 4 times daily of IV hydrocortisone or 60 mg daily of IV methylprednisolone has been recommended.[42] Treatment with IV corticosteroids is not beneficial beyond 7–10 days of treatment.[43] Timing and indications for initiation of rescue therapy are discussed below. If a patient with established corticosteroid-dependent UC is admitted, infliximab may be considered at admission.[5, 44]

Between 50% and 67% of adult patients and 63% and 74% of pediatric patients will exhibit an initial response to IV corticosteroids.[3, 43, 45, 46] In fact, in the recent pediatric PROTECT trial, 21% of pediatric patients treated with IV steroids at diagnosis achieved week 12 corticosteroid-free remission on mesalamine maintenance therapy alone.[46] These data highlight the continued utility of intravenous corticosteroids as induction therapy in ASUC, before introduction of second-line rescue therapy.

INDICATION FOR RESCUE THERAPY

Several predictive indices have been developed that may allow determination of need for salvage therapy after 3–5 days of corticosteroid treatment. In one series, 85% of adult patients with >8 bowel movements per day or 3–7 per day and CRP >45 mg/L on day 3 of admission ultimately required colectomy.[47, 48] Another group determined that a score including stool frequency and CRP, calculated as bowel movements/d + (0.14*CRP mg/L) × 0.14, had a positive predictive value of 72% for colectomy.[49] Other scoring systems, one including stool frequency, blood, nocturnal stools, pain, and activity level, and another including stool frequency, colonic dilatation, and serum albumin, have been proposed with similar predictive accuracy.[45]

For pediatric patients, the PUCAI is a simple weighted score that has been prospectively validated for predicting response to corticosteroids in pediatric ASUC (Table 1).[11] A PUCAI score of greater than 45 points on day 3 of IV corticosteroids has a positive predictive value of 43% and negative predictive value of 94% for predicting need for rescue therapy. Therefore, patients with a PUCAI of ≤45 on day 3 are likely to respond to corticosteroids. Preparations for rescue therapy (required laboratory evaluation, flexible sigmoidoscopy with

TABLE 1. Pediatric Ulcerative Colitis Activity Index

Item	Points
1. Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
2. Rectal bleeding	
None	0
Small amount only, in <50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
3. Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
4. No. stools per 24 hours	
0–2	0
3–5	5
6–8	10
>8	15
5. Nocturnal stools (any episode causing wakening)	
No	0
Yes	10
6. Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of PUCAI	(0–85)

Turner et al.[10]

CMV testing) should be made for patients with a PUCAI >45 after 3 days of corticosteroids. On day 5, a PUCAI score greater than 65 has both a positive and negative predictive value of 82% for predicting need for rescue therapy. Therefore, it is reasonable to initiate rescue therapy in those patients with PUCAI scores >65 on day 5. A PUCAI between 60 and 35 on day 5 of corticosteroids warrants another 2–5 days of treatment to assess for delayed response. Finally, if a patient has a PUCAI of <35 on day 5 or later, they are unlikely to require salvage therapy before discharge.[5, 50]

Endoscopic indices and histopathologic features may also prove useful for predicting response to corticosteroids. In a retrospective study of 89 patients, the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) was identified as an independent predictor of rescue therapy or colectomy. Ninety-two percent of patients with a UCEIS greater than or equal to 7 required rescue therapy, colectomy, or subsequent readmission.[51] In the recent large pediatric PROTECT UC study of standardized 5-ASA and corticosteroid therapy for newly diagnosed pediatric UC, among the 141 patients treated with IV corticosteroids, total Mayo score, rectal biopsy peak eosinophil count ≤32 eosinophils per high-power field, and rectal biopsy surface villiform changes were independently associated with rescue therapy or colectomy by 12 weeks.[46]

SALVAGE THERAPY OPTIONS

Options for salvage therapy include the anti-TNF biologic drug infliximab or calcineurin inhibitors such as cyclosporine and tacrolimus. Adalimumab, vedolizumab, and golimumab have proven efficacy in ambulatory patients with moderate to severe ulcerative colitis; however, there are insufficient data to support their use as rescue therapy for ASUC.[52] Colectomy may also be considered after failure of intravenous corticosteroids depending on patient preference and comorbidities. Consultation with a surgeon at the time of salvage therapy initiation is recommended so that patients may start to become familiar and hopefully more comfortable with colectomy should the need arise.

In determining which salvage therapy to use, patient comorbidities, prior ineffective medications, and future maintenance therapy strategy should be considered. There is an increased risk of neurologic adverse effects with cyclosporine in patients with low magnesium or cholesterol; therefore, cyclosporine is not recommended in these patients.[7, 12] Calcineurin inhibitors are generally only appropriate as induction therapy, and bridging to maintenance therapy with a thiopurine (or potentially vedolizumab as more data emerge) should be planned. Alternatively, infliximab is appropriate for both induction and maintenance therapy. Two randomized controlled trials have now demonstrated similar short- and long-term efficacy and colectomy rates after treatment with infliximab or cyclosporine for ASUC.[53–55] Given its similar efficacy, fewer adverse effects (compared with calcineurin inhibitors), and suitability as maintenance therapy, infliximab has become the most commonly used salvage therapy.

Calcineurin Inhibitors

Before anti-TNF therapy, cyclosporine was firstline treatment for ASUC refractory to intravenous corticosteroids.[56] Randomized controlled trials demonstrated an early response rate of 82%–85% within a median of 4 days of IV cyclosporine treatment.[56–58] Long-term response rates after transition to maintenance therapy are 40%–66%.[59] Cyclosporine is initially administered as a continuous intravenous infusion at 2–4 mg/kg/d until serum trough levels of 150–300 ng/mL are obtained. After 7 days of treatment and clinical response, patients may be converted to oral cyclosporine at 5–8 mg/kg/d for at least 3 months, with goal trough levels of 100–200 ng/mL.[5, 60] Trough drug levels should be measured to improve treatment, optimize dosing, and minimize toxicity. Patients on cyclosporine must be monitored for potential serious adverse effects including neuropathy, hyperkalemia, infection, and hypertension.[34] After 3 months of oral cyclosporine treatment, maintenance therapy with a thiopurine drug is generally attempted. Recently, the use of IV cyclosporine as a bridge to vedolizumab in patients with ASUC was reported in abstract form.[61] In this retrospective study of 17 adult patients, those responding to intravenous cyclosporine after 8 days were started on standard induction and maintenance vedolizumab, and cyclosporine was discontinued after 8 weeks. Ten of 15 patients who responded to cyclosporine were in endoscopic remission at week 10, and 14 of 15 patients were in clincal remission at week 20. The future published report of this study and additional prospective studies are warranted before making broad recommendations about this approach.

Tacrolimus is a macrolide calcineurin inhibitor that has also been studied as salvage therapy for ASUC. Tacrolimus has better oral bioavailability, tolerability, and fewer serious adverse effects as compared with cyclosporine.[18] In a randomized controlled trial, oral tacrolimus resulted in a clinical response of 50%, compared with 13% in the placebo group.[62] In a small, multicenter, open-label pediatric trial, the short-term response rate to tacrolimus was 69%, but only 38% ultimately avoided colectomy after 1 year.[63] Trough levels should be monitored, with an initial goal of 10–15 ng/mL, then 5–10 ng/mL once remission is obtained.[5] In addition to trough drug levels, for all calcineurin inhibitors, magnesium, creatinine, and serum cholesterol need to be monitored closely to assess for toxicity. Intravenous cyclosporine may lead to nephrotoxicity and to a lowered seizure threshold in the setting of hypomagnesemia and hypocholesterolemia.[5, 10]

Infliximab

Anti–tumor necrosis factor therapy has become a mainstay of salvage therapy for ASUC in both pediatric and adult patients. Although the majority of patients will respond to

anti-TNF therapy, 30% of patients are primary nonresponders and will not achieve remission with treatment.[64] Another 20%–40% of patients will only demonstrate a partial response to anti-TNF treatment. Additionally, 30% of adults with ASUC will require a colectomy within 60 days and 24% of pediatric patients will require a colectomy before hospital discharge.[65] These statistics are generated from mostly observational studies where patients received the standard infliximab induction regimen of 5 mg/kg at times 0, 2, and 6 weeks, followed by maintenance therapy every 8 weeks.

Emerging evidence suggests that patients with severe colitis exhibit rapid infliximab clearance related to disease severity and resulting in reduced drug exposure. We and others have previously reviewed the likely mechanisms for rapid infliximab clearance in ASUC in detail.[65, 66] In brief, rapid clearance is likely mediated high-serum and mucosal TNF burden that saturates the therapeutic antibody, upregulation of reticuloendothelial system phagocytes with subsequent proteolytic degradation, accelerated reticuloendothelial clearance, direct leakage of infliximab through the diseased colonic mucosa, and degradation of infliximab by high levels of tissue matrix metalloproteinases.[44, 65, 67] Dosing of infliximab guided by an understanding of the underlying pharmacokinetics is important because infliximab exposure, as measured by serum levels, is associated with improved outcomes.[42, 44] Patients with more severe UC have detectable fecal loss of infliximab, which is associated with poor short-term outcomes.[68, 69] Furthermore, adult UC patients with absent response to infliximab in the first 5 days exhibit significantly lower early drug exposure.[70] Finally, infliximab levels during induction therapy are associated with short-term clinical remission, colectomy avoidance, and mucosal healing (Table 2).[71–74] Patients with ASUC are often hypoalbuminemic, and low serum albumin concentration has been consistently identified as the strongest predictor of rapid infliximab clearance in UC pharmacokinetic studies.[66, 70, 73, 75]

Given more rapid clearance of infliximab in severe disease, many patients with ASUC, especially those with hypoalbuminemia, will likely benefit from higher total infliximab dosing and subsequent drug level monitoring. Although randomized trials have proven the efficacy of the standard induction regimen and 5-mg/kg dosing for the average ambulatory patient with moderate to severe UC, patients hospitalized with ASUC were excluded from these studies.[76, 77] In a retrospective cohort study of 50 adult patients hospitalized with ASUC, patients treated with an accelerated infliximab induction regimen (3 doses within an average 24 days) had improved short-term colectomy-free survival compared with those treated with the standard induction regimen.[78] Although medium-term colectomy rates over 2 years were ultimately similar between the 2 groups, it should be noted that both groups received standard 5 mg/kg every-80-weeks maintenance infliximab dosing after the induction period.[78] In our retrospective cohort of pediatric patients hospitalized with severe colitis and treated with infliximab, 65% of patients required dose escalation within the first year of therapy, and dose escalation was associated with low albumin and high erythrocyte sedimentation rate.[79] A similar 70% incidence of dose escalation was observed in a retrospective national Irish pediatric cohort.[80] These studies support that patients with ASUC may require alternative infliximab dosing regimens.

Screening for tuberculosis and hepatitis B should be performed before initiation of infliximab therapy. The clinical practice of the authors for the use of infliximab as salvage

TABLE 2. Induction and Maintenance Infliximab Levels Associated With UC Outcomes

Study	Time Point, wk	Target IFX Level, µg/mL	Outcome	Sensitivity/Specificity, %
Kobayashi et al.[101]	2	>21.3	Clinical remission (wk14)	61/69
Papamichael et al.[102]	2	<16.5	Colectomy	80/70
Papamichael et al.[71]	2	≥28.3	Mucosal healing (wk10–14)	NR
Adedokun et al.[73]	6	>22	Clinical response (wk8)	60/62
Papamichael et al.[71]	6	≥15	Mucosal healing (wk10–14)	60/74
Brandse et al.[70]	6	>6.6	Endoscopic response (wk8)	88/73
Adedokun et al.[73]	8	>41.2	Clinical response (wk8)	63/62
Adedokun et al.[74]	8	>41.1	Mucosal healing	NR
Papamichael et al.[71]	14	≥2.1	Mucosal healing (wk10–14)	84/62
Adedokun et al.[73]	14	>5.1	Clinical response (wk30)	66/63
Adedokun et al.[73]	14	>3.5	Clinical response (wk54)	82/50
Arias et al.[103]	14	>2.5	Relapse-free survival (mo6)	81/75
Van Stappen et al.[104]	14	≥2.1	Mucosal healing (wk10–14)	100/50
Adedokun et al.[73]	30	>3.7	Clinical response (wk30)	65/71

Abbreviations: ATI, antibodies to infliximab; IFX, infliximab; NR, not reported.

therapy for pediatric patients and young adults with ASUC is detailed in Figure 2. We administer an infliximab starting dose of 10 mg/kg and will redose in 3–5 days if there is no clinical response. Absent clinical improvement after a second dose, we recommend colectomy. After discharge, we administer the first outpatient infliximab dose 2 weeks after the last inpatient dose, and the next dose 4 weeks later with a concurrent trough level measurement. We determine whether to spread out the dosing interval to every 8 weeks based on this trough level measurement 6 weeks after the last inpatient dose. Reported target infliximab trough levels at various time points are summarized in Table 2.

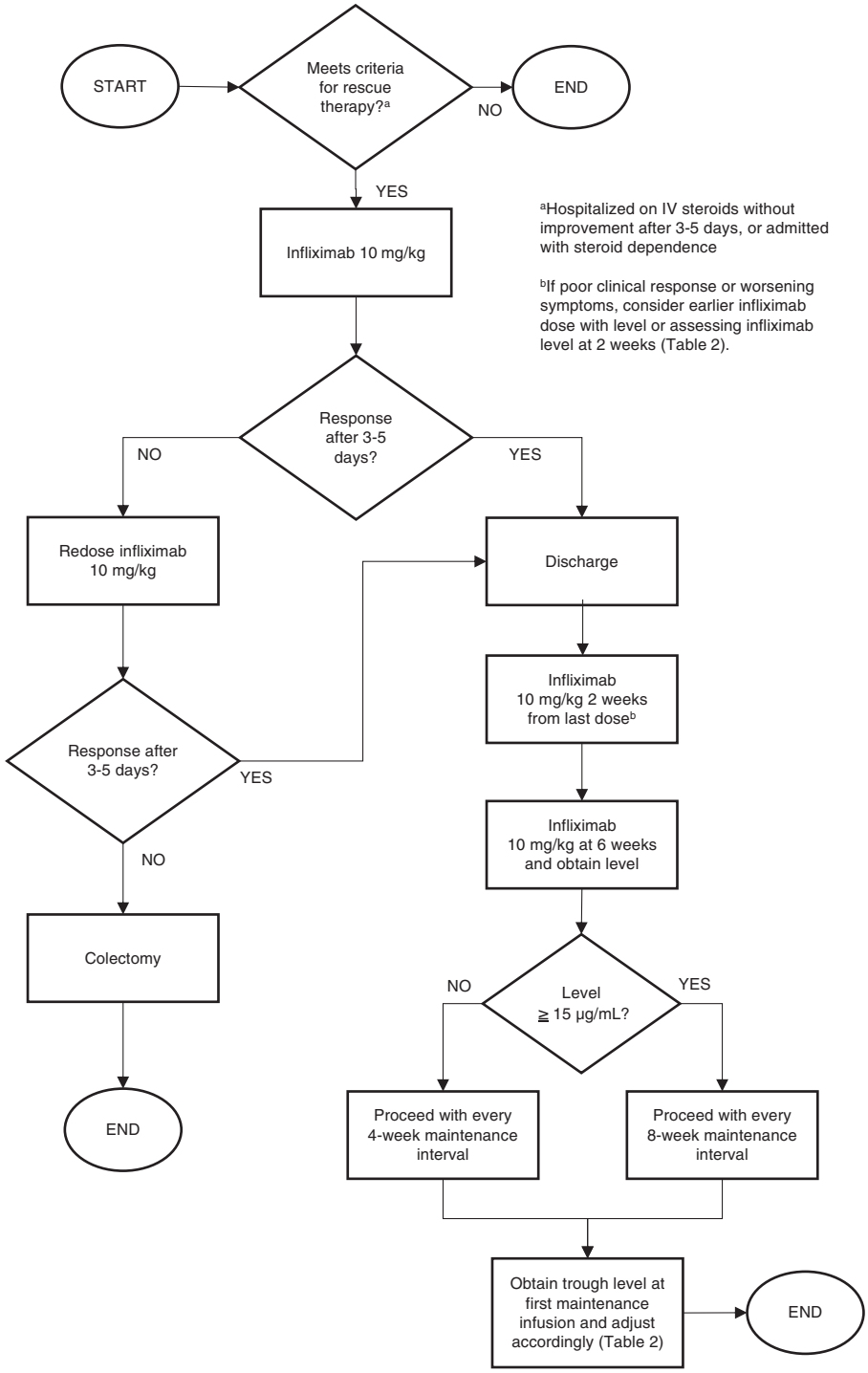

FIGURE 2. An algorithm for infliximab induction based on the authors' clinical practice.

Sequential Therapy

Current guidelines for both adult and pediatric patients do not support treating with sequential rescue therapy after initial salvage therapy has failed.[5, 6] This includes giving a calcineurin inhibitor first, followed by an anti-TNF treatment, and vice versa. In adults, reported responses to second salvage therapy ranged from 25% to 66% of patients.[81–83] However, the potential benefits must be weighed against grave potential risks. Serious adverse events reported with sequential therapy include herpetic esophagitis and pneumonia, pancreatitis with bacteremia, and sepsis leading to death.[81, 82]

SURGERY

The surgical management of ASUC has been reviewed in detail by others, and an extensive discussion is beyond the scope of this review.[6, 29, 67, 84, 85] Colectomy is recommended for those patients failed by medical salvage therapy and in the setting of toxic megacolon. Patients with ASUC often have risk factors for surgical complications, including severe disease, poor nutritional status, high-dose corticosteroid exposure, and hypoalbuminemia. Therefore, most patients will be best served by an initial abdominal (subtotal) colectomy and end ileostomy in preparation for future ileal pouch anal anastomosis.[86] Surgery should not be delayed to enhance nutrition or taper steroids. Venous thromboembolism prophylaxis should be continued after surgery.[5, 6]

EMERGING TREATMENTS

Antibiotics

There is now ample evidence for dysregulation of the intestinal microbiome in UC. Although the routine use of empiric antibiotics is not currently recommended in ASUC, several small studies have suggested the potential benefit of oral antibiotics. Randomized controlled trials in adults showed no benefit of IV antibiotics administered intravenously over placebo in addition to IV corticosteroids.[87–89] On the other hand, one controlled trial of oral vancomycin in addition to corticosteroids had a statistical trend toward reduction in colectomy in the vancomycin group.[90] Similarly, a small pilot trial of rifaximin showed a nonsignificant 25% absolute increase in clinical response.[91] In a recent retrospective uncontrolled study in pediatric patients with corticosteroid-refractory UC (two-thirds with ASUC, most also refractory to anti-TNF therapy), combination antibiotic therapy with oral metronidazole, amoxicillin, doxycycline, and vancomycin benefited half of patients.[92] A randomized controlled trial of this combination antibiotic regimen is currently underway.

Biosimilars

The infliximab biosimilar CT-P13 is now approved in Europe, Canada, and the United States for the treatment of UC. In a prospective observational study of CT-P13 for UC, 48% of patients achieved corticosteroid-free clinical remission and mucosal healing at 14 weeks. The subset treated as rescue therapy for ASUC (24 patients, 38% of the study population) achieved similar outcomes.[93] In another retrospective study, investigators compared the response of 55 patients rescued with CT-P13 for ASUC with 27 patients rescued with originator infliximab. Similar rates of clinical response, clinical remission, and mucosal healing were observed in both groups.[94]

Hyperbaric Oxygen

In patients with UC, underlying mucosal hypoxia triggers inflammation and edema. Hyperbaric oxygen therapy improves tissue oxygen delivery and therefore has been proposed as a potential treatment for UC.[95, 96] In a recent randomized controlled trial investigating hyperbaric oxygen for hospitalized patients with moderate to severe UC, 18 patients were randomized to daily hyperbaric oxygen or sham control in addition to IV corticosteroids.[97] Clinical remission at day 5 was achieved by 50% of patients in the hyperbaric oxygen group compared with no patients in the control group. There was also a trend toward less progression to second-line therapy in the hyperbaric oxygen group. Future larger studies need to be performed to confirm the efficacy of hyperbaric oxygen in this setting, but it appears to be relatively safe and well tolerated in IBD patients.[96]

Granulocyte/Monocyte Adsorbtive Apheresis

Granulocytes and monocytes infiltrate the colon mucosa in UC and are an important source of cytokines, reactive oxygen species, and proteases that induce tissue damage.[97] Granulocyte and monocyte adsorbtive apheresis (GMAA) is an extracorporeal procedure that removes activated granulocytes and monocytes from peripheral blood and has been studied for the treatment of UC. An open-label randomized trial comparing GMAA with intravenous corticosteroids in patients with ASUC showed a numerically but not statistically significantly higher response rate in patients treated with GMAA, with fewer adverse effects.[98] However, the results of this study must be interpreted with caution as randomization procedures were not reported, and there was no mention of investigator blinding. In fact, many studies of GMAA have similar methodologic limitations. In a systematic review of GMAA for UC, the authors did not undertake a formal meta-analysis because most of the elibible studies were deemed to be at high risk of bias due to study methodology.[99] In a multicenter, multinational, double-blind, sham-controlled study of GMAA for active ulcerative colitis, GMAA was not more efficacious than sham procedure for inducing remission in moderate to severe UC.[100] In a post hoc analysis of this study, a significantly higher response rate over sham procedure was observed in patients with the most severe histologic disease severity. Larger investigator-blinded randomized controlled trials in patients with

ASUC with high-quality methodology are needed before the role of GMAA in the treatment of ASUC can be determined.

OPPORTUNITIES FOR FURTHER INVESTIGATION

Although there are a number of detailed, evidence-based ASUC guidelines available to guide patient mangement,[6–8, 10, 17] there are many areas where stronger evidence is needed to support definitive consensus recommendations. For instance, it is still not clear whether CMV reactivation drives disease refractoriness or is simply a consequence of severe inflammation and/or immunosuppression. Moreover, the optimal test for detecting CMV in the tissue (immunohistochemistry, in situ hybridization, tissue qualitative or quantitatve PCR) is now known. Large randomized studies are required to determine if antiviral treatment of colon CMV reactivation improves response to therapy. With regard to thromboembolism prophylaxis, current pediatric guidelines state that there is not sufficient evidence to support the routine use of prophylactic LMWH in pediatric patients as is recommended for adults.[5] Large comparative effectiveness studies will be needed to determine whether the benefit of routine LMWH for reducing thromboembolic complications outweighs any risks in pediatric patients. In the area of anti-TNF salvage therapy, we need more research to determine whether early infliximab pharmacokinetics in ASUC affects outcomes, whether accelerated dosing strategies are more effective, and if so, what dosing strategy is most effective? Future research will also determine how alternative treatments such as antibiotic cocktails and hyperbaric oxygen, and newer therapies including vedolizumab and tofacitinib, may be incorporated into treatment algorithms for ASUC.

CONCLUSION

Although advances continue to be made in the medical management of ASUC, more research needs to be done to improve patient outcomes. ASUC is a medical emergency requiring hospital admission. The initial evaluation includes clinical, laboratory, radiologic, and endoscopic assessment to assess severity of disease, rule out toxic megacolon, and diagnosis superimposed infections. Treatment with IV corticosteroids should be initiated promptly, and various tools are available to determine which patients require salvage therapy after the first 3–5 days of corticosteroid treatment. Recent evidence supports that patients with ASUC have rapid clearance of infliximab. When infliximab is used as salvage therapy, higher total dose induction regimens with subsequent therapeutic drug monitoring may improve patient outcomes.

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