CASE STUDY SERIES IN IBD

Case Report: Medical Management of Acute Severe Ulcerative Colitis

Sudheer Kumar Vuyyuru, DM,[1,2] Vipul Jairath, MD, PhD,[1,2,3] Jurij Hanžel, MD, PhD,[2,4] Christopher Ma, MD, MPH,[2,5] and Brian G. Feagan, MD[1,2,3]

[1]Division of Gastroenterology, Department of Medicine, Western University, London, Ontario, Canada

[2]Alimentiv, London, Ontario, Canada

[3]Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada

[4]Faculty of Medicine, University of Ljubljana and Department of Gastroenterology, University Medical Center Ljubljana, Ljubljana, Slovenia

[5]Division of Gastroenterology and Hepatology, Departments of Medicine and Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

A 29-year-old female patient presented 5 years ago with bloody diarrhea, fecal urgency, and crampy abdominal pain. A colonoscopy was performed, which revealed diffuse loss of vascular pattern and superficial ulcers throughout the colon with a normal terminal ileum. Histopathologic examination of colonic biopsies showed chronic inflammatory changes with cryptitis, crypt abscesses, and architectural distortion of crypts. On this basis, the patient was diagnosed with ulcerative colitis (UC) and began receiving 5-aminosalicylic acid (4.8 g/day). After an initial period of remission, she experienced flare-ups requiring oral corticosteroids, azathioprine (2 mg/kg), and then vedolizumab (Entyvio, Takeda; 300 mg intravenously at weeks 0, 2, and 6, followed by every 8 weeks).

The patient was in clinical remission for 2 years and then presented to the emergency department with an acute exacerbation of UC, with 20 bloody bowel movements per day. On physical examination, there was tachycardia (120 beats per minute), fever (38.3 °C), and mild tenderness in the left lower quadrant of the abdomen. Laboratory findings revealed a markedly elevated C-reactive protein (CRP; 104 mg/L) and fecal calprotectin (3000 µg/g), anemia (hemoglobin 90 g/L), leukocytosis (14,000 cells/mm^3), and hypoalbuminemia (28 g/L). She was hospitalized and received intravenous methylprednisolone (60 mg/day) along with other supportive measures, including thromboprophylaxis.

Corresponding author:
Dr Vipul Jairath, Division of Gastroenterology,
Western University and London Health Sciences Centre,
339 Windermere Road, London, ON N6A 5A5, Canada;
Tel: (519) 685-8500 ext 33655; Fax: (519) 663-3658;
E-mail: vjairath@uwo.ca

Despite 48 hours of intravenous corticosteroids, the patient continued to have bloody stools (15 per day) and her CRP concentration remained elevated (98 mg/L). Flexible sigmoidoscopy showed deep ulcers and spontaneous mucosal bleeding (modified Mayo endoscopic score of 3), and histopathology indicated features of severe colitis. There was no evidence of cytomegalovirus (CMV) inclusion bodies on immunohistochemistry, and stool culture and toxin testing for *Clostridioides difficile* were negative. Abdominal radiograph did not demonstrate colonic dilatation.

Infliximab (10 mg/kg) was administered as rescue therapy, and surgical consultation was obtained. Two days after the first dose of infliximab, stool frequency was still 12 times per day with blood and the CRP level was persistently high (98 mg/L). A second infusion of infliximab was administered on day 8 of hospitalization. On day 10, the patient experienced worsening abdominal pain without clinical improvement, and subtotal colectomy with temporary end ileostomy was performed. Following surgery, the patient recovered well and without any postoperative complications, and corticosteroids were rapidly tapered. Subsequently, she underwent surgery for ileal pouch formation and ileostomy closure.

Discussion

Approximately one-fourth of patients diagnosed with UC will experience an acute exacerbation requiring hospital admission during their lifetime.[1] An episode of acute severe UC (ASUC) can be a life-threatening medical emergency with an overall mortality of 1%.[2] ASUC can lead to serious complications such as toxic megacolon and colonic perforation, and emergency colectomy may

Table 1. Modified Truelove and Witts Criteria for Ulcerative Colitis Severity[10,11]

Parameter	Mild	Moderate	Severe/ASUC
Bloody stools/day	<4 and all of the criteria below	≥4 and all of the criteria below	≥6 and at least 1 criterion below
Pulse	<90 bpm	≤90 bpm	>90 bpm
Temperature	<37.5 °C	<37.8 °C	>37.8 °C
Hemoglobin	>115 g/L	≥105 g/L	<105 g/L
CRP	Normal	≤30 mg/L	>30 mg/L
ESR	<20 mm/h	≤30 mm/h	>30 mm/h

ASUC, acute severe ulcerative colitis; bpm, beats per minute; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

be needed in medically refractory cases.[3] Up to 20% of patients admitted with ASUC require a colectomy on their first admission, and this risk increases to 40% after 2 admissions.[1,4]

Global hospitalization rates for UC have declined as a result of advanced biologic therapies, optimization of management algorithms, and shifting patterns in UC epidemiology.[5] Although hospitalization rates for UC are decreasing in Western nations, there has been an increase in hospitalizations in newly industrialized countries.[6] This could be attributed to increasing incidence of UC along with limited access to advanced therapies in developing countries.[7] Similarly, in a nationwide registry–based study, a declining trend in emergency colectomy rates was observed from 2000 to 2014 in the United States, while rates of elective ileoanal pouch surgery remained stable.[8] Rates of colectomy in patients with UC from 2007 to 2016 in the United States have decreased as the use of biologic drugs has increased, suggesting a potential association between advanced treatment and the reduction in need for colectomy.[9]

Risk Stratification

In 1955, Truelove and Witts conducted a randomized controlled trial (RCT) of cortisone in hospitalized patients with UC in which patients with severe disease experienced worse outcomes than patients with moderate or mild disease.[10] Nearly 70 years later, the criteria that they developed to define severe disease are still commonly used. According to the Truelove and Witts definition, ASUC is characterized by the presence of 6 or more bloody stools per day and at least one of the following signs of systemic toxicity: tachycardia (mean pulse rate >90 beats per minute), fever (>37.8 °C), anemia (hemoglobin <105 g/L), and/or a raised erythrocyte sedimentation rate (>30 mm/hr). These criteria were later modified to include elevated CRP (>30 mg/L) (Table 1).[11]

Initial Management

Patients with ASUC should be admitted urgently and treated according to a standardized management approach to prevent complications. Intravenous corticosteroids remain the gold standard for initial treatment. The pooled response rate following intravenous corticosteroids is reported to be 67% (95% CI, 65-69) with a colectomy rate of 27% (95% CI, 48-76).[12] In patients requiring nutritional support, enteral nutrition is preferred over parenteral nutrition because it is associated with fewer adverse events in ASUC.[13] All patients should receive thromboprophylaxis unless there is a clear contraindication.[14] Importantly, rectal bleeding associated with ASUC is generally not a contraindication to thromboprophylaxis. Stool cultures are essential to rule out *C difficile* and other bacterial infections. Although *C difficile* infection in patients with ASUC requires appropriate antibiotic therapy, routine antibiotics are not recommended in all patients. Colonic biopsy with immunohistochemistry should be performed to exclude active CMV infection, especially in patients with a history of corticosteroid dependency.[15] Performing CMV polymerase chain reaction analysis in peripheral blood and tissues is not routinely recommended, as sensitivity and specificity are suboptimal.[16]

Predictors of Response to Corticosteroids

Corticosteroids (methylprednisolone 60 mg or hydrocortisone 300-400 mg intravenously) are generally administered for at least 3 to 5 days before proceeding to salvage therapy, as a longer course of corticosteroids is associated with increased morbidity[17] and higher doses are not superior to standard doses.[12,18] Approximately 40% of patients fail to respond to intravenous corticosteroids and are at an increased risk of complications.[3] Therefore, early identification of these patients and instituting appropriate salvage therapy are crucial.

A number of prognostic indices comprised of clinical, endoscopic, and biochemical parameters have been developed to predict corticosteroid therapy failure and subsequent colectomy (Table 2). CRP is one of the commonly monitored biomarkers, and a persistently high CRP on day 3 of corticosteroids has been associated with corticosteroid failure.[19] Criteria developed by Travis and colleagues based on a retrospective case series of 48 patients with ASUC demonstrated that elevated stool

Table 2. Risk Prediction Scores for Corticosteroid Failure in Acute Severe Ulcerative Colitis

Name of score, year of first publication	Components of score	Day of assessment following IV corticosteroids	Accuracy in predicting corticosteroid failure/colectomy
Lindgren index,[19] 1998	Serum CRP (mg/L) × 0.14 + stool frequency (Cutoff >8)	Day 3	Sensitivity = 76.4% Specificity = 80.7% PPV = 72%
Oxford criteria,[20] 1996	Stool frequency >8/day or stool frequency 3-8/day with CRP >45 mg/L	Day 3	PPV = 85%
Seo index,[22] 2002	Stool frequency, blood, nocturnal stools, abdominal pain, activity level (Cutoff >200)	After 2 weeks of therapy	PPV = 83%
Ho index,[21] 2004	Stool frequency, colonic dilatation, serum albumin levels (Cutoff ≥4)	Day 3	Sensitivity = 85% Specificity = 75%
AIIMS index,[24] 2017	UCEIS >6 and fCal >1000 µg/g	On admission: UCEIS Day 3: fCal	Sensitivity = 29% Specificity = 100% PPV = 100%
ACE index,[58] 2020	CRP ≥50 mg/L (1 point), serum albumin ≤30 g/L (1 point), severe disease on endoscopic assessment (1 point) (Cutoff = 3)	On admission	Sensitivity = 73.5% Specificity = 89.7% PPV = 78.1% NPV = 87.1%
ADMIT-ASC score,[25] 2022	CRP ≥100 mg/L (1 point), serum albumin ≤25 g/L (1 point), UCEIS ≥4 (1 point) or ≥7 (2 points) (Cutoff ≥3)	On admission	Sensitivity = 32% Specificity = 96% PPV = 84%

ACE, Albumin, CRP, and Endoscopy; ADMIT-ASC, admission model for intensification of therapy in acute severe colitis; AIIMS, All India Institute of Medical Sciences; CRP, C-reactive protein; fCal, fecal calprotectin; IV, intravenous; NPV, negative predictive value; PPV, positive predictive value; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

frequency (>8 per day) or between 3 and 8 stools per day along with a CRP concentration of greater than 45 mg/L on day 3 of admission predicted an 85% likelihood of colectomy.[20] Ho and colleagues formulated a risk score using stool frequency, colonic dilatation, and serum albumin levels on day 3 as predictive variables in which patients with a score of 4 or greater had a corticosteroid failure rate of 85%.[21] Similarly, the Seo index predicted a colectomy rate of 60% and 83% after 1 and 2 weeks of corticosteroids, respectively, in patients with a score of greater than 200.[22] In the index developed by Lindgren and colleagues, CRP and stool frequency were considered predictive factors of corticosteroid response (CRP mg/L × 0.14 + number of bowel movements).[19] A score of greater than 8 on day 3 of intravenous corticosteroids was associated with colectomy in 72% of patients within 30 days.

Some markers have been shown to be useful in predicting outcomes as early as day 1 of hospitalization. Notably, the number of systemic Truelove and Witts criteria present on admission, in addition to at least 6 bloody stools per day, has been correlated with colectomy (1 criterion: 8.5%; ≥3 criteria: 48%).[1] The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) has been used to identify high-risk patients at the time of admission. A UCEIS score of 7 or greater was shown to be associated with the need for salvage therapy in 79% (n=11/14) of patients with ASUC.[23] In a subsequent study, 100% of patients with a UCEIS score of greater than 6 on admission day and a fecal calprotectin level greater than 1000 µg/g on day 3 did not respond to corticosteroid therapy.[24] Most recently, a predictive model composed of objective parameters (serum albumin, CRP, and UCEIS score) was developed in a patient cohort from Oxford, United Kingdom, and was externally validated in 2 additional cohorts. A score of 3 or greater on the day of admission had a predictive value of 84% for corticosteroid failure.[25]

Medical Salvage Therapy

Patients who fail intravenous corticosteroids require either medical or surgical salvage therapy. Cyclosporine and infliximab have been systematically investigated in clinical trials and are recommended as medical salvage therapy in ASUC. In the open-label CYSIF trial, 115 patients with corticosteroid-refractory ASUC were randomized 1:1 to infliximab (5 mg/kg intravenously on days 0, 14, and 42) and cyclosporine (2 mg/kg intravenously per day for 1

week followed by oral cyclosporine).[26] The primary outcome was treatment failure (absence of clinical response at day 7, relapse between day 7 and day 98, absence of corticosteroid-free remission at day 98, a severe adverse event leading to treatment interruption, colectomy, or death). There was no statistically significant difference between infliximab and cyclosporine in treatment failure, adverse events, and colectomy-free survival at 1 year and 5 years.[27] In the subsequent open-label, pragmatic RCT CONSTRUCT, 270 patients were randomly allocated 1:1 to receive infliximab (5 mg/kg intravenously at weeks 0, 2, and 6) or cyclosporine (2 mg/kg intravenously for 7 days, followed by 5.5 mg/kg orally per day for 12 weeks).[28] No significant differences were found between the 2 drugs with respect to the primary endpoint of quality-adjusted survival, or the secondary endpoints of colectomy rates, time to colectomy, serious adverse events, and death. A meta-analysis of RCTs that investigated infliximab and cyclosporine as salvage therapy in corticosteroid-refractory UC also found no significant differences between infliximab and cyclosporine.[29] Although consensus guidelines do not favor either agent, infliximab is generally preferred at regular or accelerated dosing regimens because of ease of administration and concerns of cyclosporine-related nephrotoxicity and neurotoxicity, especially when associated with hypercholesterolemia and hypomagnesemia. Therefore, long-term use of cyclosporine is not recommended, and patients who responded to intravenous cyclosporine should be bridged to an alternative maintenance therapy such as thiopurines.[30] Thus, cyclosporine is not advisable for patients who have previously failed thiopurine therapy.[30] However, recent evidence for the use of biologics as maintenance therapies, including vedolizumab, ustekinumab (Stelara, Janssen), and ozanimod (Zeposia, Bristol Myers Squibb), following cyclosporine rescue therapy has emerged.[31-35] Additionally, there have been reports of sequential rescue therapy after failure of initial salvage therapy, but it is not recommended owing to increased risk of adverse events.[36]

Accelerated Dosing of Infliximab

Increased clearance of infliximab in patients with ASUC, especially in those with high inflammatory burden, led to the hypothesis that higher induction doses of infliximab may be needed in this population. However, the data supporting this hypothesis are conflicting.

Several observational studies have assessed different accelerated induction regimens, including higher doses (10 mg/kg) and increased frequency of dosing than the standard dosing schedule (5 mg/kg intravenously at weeks 0, 2, and 6, followed by every 8 weeks). In a retrospective study by Kohn and colleagues, a statistically higher proportion of patients receiving a single infusion of infliximab underwent colectomy compared with patients who received more than 1 infusion (35% vs 5%; P=.001).[37] Gibson and colleagues significantly decreased colectomy rates with intensified infliximab dosing in patients with corticosteroid-refractory ASUC compared with historical controls (6.7% vs 40%; P=.039) during the induction period; however, longer-term colectomy rates were similar between standard and accelerated dosing regimens.[38] Conversely, a systematic review by Sebastian and colleagues that included 10 observational studies assessing a pooled population of 705 patients found no difference between accelerated and standard induction regimens associated with either short-term (17% vs 14.5%) or long-term (25% vs 30.7%) colectomy rates, and no significant difference in complication rates.[39] Although clinicians often use accelerated regimens as off-label therapy, the evidence supporting this practice is limited. RCTs exploring optimal dosing strategy for infliximab in ASUC (NCT02770040,[40] NCT03937609[41]) are underway.

Factors Influencing Response to Salvage Therapy

Despite improved management protocols and availability of biologics, short- and long-term colectomy rates with medical salvage therapy remain high (26%-47% and 36%-58% for cyclosporine, and 0%-50% and 35%-50% for infliximab, respectively).[42] To date, no validated scores exist to predict medical salvage therapy response. Age over 40 years, high CRP and low serum albumin at the time of infliximab initiation, and severe endoscopic lesions have been shown to be predictive of salvage therapy failure.[42] These factors indirectly suggest that high inflammatory burden is associated with poor response, especially for infliximab, and could be a result of increased clearance of infliximab by several mechanisms. High mucosal and systemic levels of tumor necrosis factor (TNF), which is associated with severe disease, neutralize anti-TNF antibodies, acting as an "antigen sink."[43] Intestinal losses owing to increased gut permeability secondary to mucosal ulceration also contribute to lower drug exposure. Last, observational studies have suggested that fecal loss of anti-TNF is associated with severe disease and lower serum drug concentrations.[44] These clearance mechanisms can result in subtherapeutic infliximab levels and may contribute to poor response.[45]

Tofacitinib Salvage Therapy

Tofacitinib (Xeljanz, Pfizer) is a Janus kinase (JAK) inhibitor that blocks predominantly JAK1 and JAK3 at therapeutic doses. Phase 3 pivotal studies from the OCTAVE clinical program demonstrated the efficacy and safety of tofacitinib in moderate to severe UC, leading to approval by the US Food and Drug Administration

(FDA) in 2018.[46] However, concerns were raised regarding an increased risk of major adverse cardiac events and thrombotic events in patients with rheumatoid arthritis exposed to tofacitinib.[47] Consequently, the FDA issued a black box warning for all currently approved JAK inhibitors, and guidelines now recommend tofacitinib as a second-line agent after failure of anti-TNF therapy in the United States.

Case reports and series have described off-label use of tofacitinib in patients with ASUC who did not respond to corticosteroid therapy.[48,49] Conceptually, several characteristics make tofacitinib an attractive candidate for inpatient induction therapy. First, the drug is readily absorbed and symptomatic improvement can be seen as early as day 3 in moderate to severe UC.[50] Second, as a small molecule, tofacitinib is less susceptible to intestinal loss than infliximab. Third, tofacitinib has been shown to be effective in patients with moderate to severe UC who have failed anti-TNF therapy.[51] Broad-spectrum immunosuppressive effects are important limitations among patients who are at substantial risk of life-threatening infections and thromboembolic disease.

A retrospective cohort study of tofacitinib in hospitalized pediatric patients with UC who had failed corticosteroids and infliximab demonstrated that 8 out of 11 (73%) patients were free of colectomy at 90 days and 6 (54%) were free of colectomy at 6 months.[52] In a case-control study, patients hospitalized with ASUC who received tofacitinib (n=40) were matched to controls with ASUC according to sex and date of admission (n=113).[53] The 90-day colectomy rate was significantly lower in patients managed with tofacitinib induction therapy in addition to intravenous corticosteroids (hazard ratio, 0.28; 95% CI, 0.10-0.81; *P*=.018) compared with patients in the control group when adjusted for disease severity covariables. Subgroup analyses showed that this benefit was statistically significant with tofacitinib doses of 10 mg 3 times daily, but not with twice-daily dosing. Although these data are interesting, they are largely limited to retrospective case series and should not be used to inform routine clinical practice. The efficacy and safety of tofacitinib for ASUC should be assessed rigorously in an RCT.

Colectomy

Patients who are refractory to medical therapy should be offered surgery. Subtotal colectomy is the surgery of choice in the emergent setting. Subsequently, ileal pouch–anal anastomosis performed in a staged manner is generally the preferred approach, although some patients choose completion proctectomy with permanent end ileostomy. Emergency colectomy is associated with higher morbidity and mortality rates than semi-elective procedures,[54] so controlling inflammation promptly with timely initiation of medical therapy is important.[55] Age, longer hospital stay, superimposed infections, prior admission owing to inflammatory bowel disease, and male sex are some of the factors associated with increased mortality after emergency colectomy.[56] However, delaying the decision for surgery can be associated with increased postoperative morbidity and mortality, especially in patients exposed to intravenous corticosteroids for longer than 7 days.[57] This underscores the importance of predicting response to medical therapy early in the course of ASUC and early decision-making.

Conclusion

ASUC is a potentially life-threatening condition that requires hospitalization and intensive medical and supportive management to prevent complications. Early identification of patients at a high risk for corticosteroid failure and timely initiation of salvage therapy are critical. The choice of therapy depends on several factors, including clinical, endoscopic, and laboratory parameters and prior treatment history, and should be a collective decision made by the patient and a multidisciplinary team of health care professionals comprised of the treating physician, gastroenterologists, and surgeons. Although a number of models have been developed to predict corticosteroid response in patients with ASUC, validated tools to predict the failure of medical salvage therapy are lacking.

Infliximab and cyclosporine are the only agents currently approved for medical salvage therapy, and off-label use of tofacitinib has been reported in case series. Although available data supporting use of tofacitinib in patients with ASUC are insufficient to make any recommendations, future clinical trials might shed light. Surgical decision-making should not be delayed while cycling through different agents; therefore, early prediction of response to medical therapy failure is crucial.

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References

1. Dinesen LC, Walsh AJ, Protic MN, et al. The pattern and outcome of acute severe colitis. *J Crohns Colitis*. 2010;4(4):431-437.
2. Dong C, Metzger M, Holsbø E, Perduca V, Carbonnel F. Systematic review with meta-analysis: mortality in acute severe ulcerative colitis. *Aliment Pharmacol Ther*. 2020;51(1):8-33.
3. Molnár T, Farkas K, Nyári T, Szepes Z, Nagy F, Wittmann T. Response to first intravenous steroid therapy determines the subsequent risk of colectomy in ulcerative colitis patients. *J Gastrointestin Liver Dis*. 2011;20(4):359-363.
4. Aratari A, Papi C, Clemente V, et al. Colectomy rate in acute severe ulcerative colitis in the infliximab era. *Dig Liver Dis*. 2008;40(10):821-826.
5. Tsai L, Nguyen NH, Ma C, Prokop LJ, Sandborn WJ, Singh S. Systematic review and meta-analysis: risk of hospitalization in patients with ulcerative colitis and Crohn's disease in population-based cohort studies. *Dig Dis Sci*. 2022;67(6):2451-2461.
6. Buie MJ, Quan J, Windsor JW, et al; Global IBD Visualization of Epidemiology Studies in the 21st Century (GIVES-21) Research Group. Global hospitalization trends for Crohn's disease and ulcerative colitis in the 21st century: a systematic review with temporal analyses. *Clin Gastroenterol Hepatol*. 2023;21(9):2211-2221.
7. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet*. 2017;390(10114):2769-2778.
8. Kayal M, Saha A, Poojary P, et al. Emergent colectomy rates decreased while elective ileal pouch rates were stable over time: a nationwide inpatient sample study. *Int J Colorectal Dis*. 2019;34(10):1771-1779.
9. Barnes EL, Jiang Y, Kappelman MD, et al. Decreasing colectomy rate for ulcerative colitis in the United States between 2007 and 2016: a time trend analysis. *Inflamm Bowel Dis*. 2020;26(8):1225-1231.
10. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *BMJ*. 1955;2(4947):1041-1048.
11. Magro F, Gionchetti P, Eliakim R, et al; European Crohn's and Colitis Organisation [ECCO]. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: Definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *J Crohns Colitis*. 2017;11(6):649-670.
12. Turner D, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol*. 2007;5(1):103-110.
13. González-Huix F, Fernández-Bañares F, Esteve-Comas M, et al. Enteral versus parenteral nutrition as adjunct therapy in acute ulcerative colitis. *Am J Gastroenterol*. 1993;88(2):227-232.
14. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. *Lancet*. 2010;375(9715):657-663.
15. Sager K, Alam S, Bond A, Chinnappan L, Probert CS. Review article: cytomegalovirus and inflammatory bowel disease. *Aliment Pharmacol Ther*. 2015;41(8):725-733.
16. Mourad FH, Hashash JG, Kariyawasam VC, Leong RW. Ulcerative colitis and cytomegalovirus infection: from A to Z. *J Crohns Colitis*. 2020;14(8):1162-1171.
17. Meyers S, Lerer PK, Feuer EJ, Johnson JW, Janowitz HD. Predicting the outcome of corticoid therapy for acute ulcerative colitis. Results of a prospective, randomized, double-blind clinical trial. *J Clin Gastroenterol*. 1987;9(1):50-54.
18. Rosenberg W, Ireland A, Jewell DP. High-dose methylprednisolone in the treatment of active ulcerative colitis. *J Clin Gastroenterol*. 1990;12(1):40-41.
19. Lindgren SC, Flood LM, Kilander AF, Löfberg R, Persson TB, Sjödahl RI. Early predictors of glucocorticosteroid treatment failure in severe and moderately severe attacks of ulcerative colitis. *Eur J Gastroenterol Hepatol*. 1998;10(10):831-835.
20. Travis SP, Farrant JM, Ricketts C, et al. Predicting outcome in severe ulcerative colitis. *Gut*. 1996;38(6):905-910.
21. Ho GT, Mowat C, Goddard CJR, et al. Predicting the outcome of severe ulcerative colitis: development of a novel risk score to aid early selection of patients for second-line medical therapy or surgery. *Aliment Pharmacol Ther*. 2004;19(10):1079-1087.
22. Seo M, Okada M, Yao T, Matake H, Maeda K. Evaluation of the clinical course of acute attacks in patients with ulcerative colitis through the use of an activity index. *J Gastroenterol*. 2002;37(1):29-34.
23. Corte C, Fernandopulle N, Catuneanu AM, et al. Association between the ulcerative colitis endoscopic index of severity (UCEIS) and outcomes in acute severe ulcerative colitis. *J Crohns Colitis*. 2015;9(5):376-381.
24. Jain S, Kedia S, Bopanna S, et al. Faecal calprotectin and UCEIS predict short-term outcomes in acute severe colitis: prospective cohort study. *J Crohns Colitis*. 2017;11(11):1309-1316.
25. Adams A, Gupta V, Mohsen W, et al. Early management of acute severe UC in the biologics era: development and international validation of a prognostic clinical index to predict steroid response. *Gut*. 2023;72(3):433-442.
26. Laharie D, Bourreille A, Branche J, et al; Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. *Lancet*. 2012;380(9857):1909-1915.
27. Laharie D, Bourreille A, Branche J, et al; Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. Long-term outcome of patients with steroid-refractory acute severe UC treated with ciclosporin or infliximab. *Gut*. 2018;67(2):237-243.

28. Williams JG, Alam MF, Alrubaiy L, et al. Infliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomised trial. *Lancet Gastroenterol Hepatol*. 2016;1(1):15-24.
29. Narula N, Marshall JK, Colombel JF, et al. Systematic review and meta-analysis: infliximab or cyclosporine as rescue therapy in patients with severe ulcerative colitis refractory to steroids. *Am J Gastroenterol*. 2016;111(4):477-491.
30. Lamb CA, Kennedy NA, Raine T, et al; IBD guidelines eDelphi consensus group. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*. 2019;68(suppl 3):s1-s106.
31. Tarabar D, El Jurdi K, Traboulsi C, et al. A prospective trial with long term follow-up of patients with severe, steroid-resistant ulcerative colitis who received induction therapy with cyclosporine and were maintained with vedolizumab. *Inflamm Bowel Dis*. 2022;28(10):1549-1554.
32. Shaffer SR, Traboulsi C, Krugliak Cleveland N, Rubin DT. Combining cyclosporine with ustekinumab in acute severe ulcerative colitis. *ACG Case Rep J*. 2021;8(5):e00604.
33. Cohen NA, Dalal SR, Choi D, Rubin DT. Ozanimod maintenance therapy after cyclosporine induction in acute severe ulcerative colitis. *ACG Case Rep J*. 2022;9(7):e00832.
34. Pellet G, Stefanescu C, Carbonnel F, et al; Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif. Efficacy and safety of induction therapy with calcineurin inhibitors in combination with vedolizumab in patients with refractory ulcerative colitis. *Clin Gastroenterol Hepatol*. 2019;17(3):494-501.
35. Ollech JE, Dwadasi S, Rai V, et al. Efficacy and safety of induction therapy with calcineurin inhibitors followed by vedolizumab maintenance in 71 patients with severe steroid-refractory ulcerative colitis. *Aliment Pharmacol Ther*. 2020;51(6):637-643.
36. Narula N, Fine M, Colombel J-F, Marshall JK, Reinisch W. Systematic review: sequential rescue therapy in severe ulcerative colitis: do the benefits outweigh the risks? *Inflamm Bowel Dis*. 2015;21(7):1683-1694.
37. Kohn A, Daperno M, Armuzzi A, et al. Infliximab in severe ulcerative colitis: short-term results of different infusion regimens and long-term follow-up. *Aliment Pharmacol Ther*. 2007;26(5):747-756.
38. Gibson DJ, Heetun ZS, Redmond CE, et al. An accelerated infliximab induction regimen reduces the need for early colectomy in patients with acute severe ulcerative colitis. *Clin Gastroenterol Hepatol*. 2015;13(2):330-335.e1.
39. Sebastian S, Myers S, Nadir S, Subramanian S. Systematic review: efficacy and safety of accelerated induction regimes in infliximab rescue therapy for hospitalized patients with acute severe colitis. *Dig Dis Sci*. 2019;64(5):1119-1128.
40. ClinicalTrials.gov. Optimising infliximab induction therapy for acute severe ulcerative colitis (PREDICT UC). https://classic.clinicaltrials.gov/show/NCT02770040. Identifier: NCT02770040. Accessed September 9, 2023.
41. ClinicalTrials.gov. TITRATE (inducTIon for acuTe ulceRATivE Colitis). https://classic.clinicaltrials.gov/show/NCT03937609. Identifier: NCT03937609. Accessed September 9, 2023.
42. Seah D, De Cruz P. Review article: the practical management of acute severe ulcerative colitis. *Aliment Pharmacol Ther*. 2016;43(4):482-513.
43. Yarur AJ, Jain A, Sussman DA, et al. The association of tissue anti-TNF drug levels with serological and endoscopic disease activity in inflammatory bowel disease: the ATLAS study. *Gut*. 2016;65(2):249-255.
44. Brandse JF, van den Brink GR, Wildenberg ME, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. *Gastroenterology*. 2015;149(2):350-355.e2.
45. Seow CH, Newman A, Irwin SP, Steinhart AH, Silverberg MS, Greenberg GR. Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. *Gut*. 2010;59(1):49-54.
46. Sandborn WJ, Su C, Sands BE, et al; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2017;376(18):1723-1736.
47. Ytterberg SR, Bhatt DL, Mikuls TR, et al; ORAL Surveillance Investigators. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med*. 2022;386(4):316-326.
48. Sedano R, Jairath V. High-dose rescue tofacitinib prevented inpatient colectomy in acute severe ulcerative colitis refractory to anti-TNF. *Inflamm Bowel Dis*. 2021;27(5):e59-e60.
49. Gilmore R, Hilley P, Srinivasan A, Choy M, De Cruz P. Sequential use of high-dose tofacitinib after infliximab salvage therapy in acute severe ulcerative colitis. *J Crohns Colitis*. 2022;16(1):166-168.
50. Hanauer S, Panaccione R, Danese S, et al. Tofacitinib induction therapy reduces symptoms within 3 days for patients with ulcerative colitis. *Clin Gastroenterol Hepatol*. 2019;17(1):139-147.
51. Sandborn WJ, Peyrin-Biroulet L, Sharara AI, et al. Efficacy and safety of tofacitinib in ulcerative colitis based on prior tumor necrosis factor inhibitor failure status. *Clin Gastroenterol Hepatol*. 2022;20(3):591-601.e8.
52. Constant BD, Baldassano R, Kirsch J, Mitchel EB, Stein R, Albenberg L. Tofacitinib salvage therapy for children hospitalized for corticosteroid- and biologic-refractory ulcerative colitis. *J Pediatr Gastroenterol Nutr*. 2022;75(6):724-730.
53. Berinstein JA, Sheehan JL, Dias M, et al. Tofacitinib for biologic-experienced hospitalized patients with acute severe ulcerative colitis: a retrospective case-control study. *Clin Gastroenterol Hepatol*. 2021;19(10):2112-2120.e1.
54. Nicholls RJ, Clark DN, Kelso L, et al. Nationwide linkage analysis in Scotland implicates age as the critical overall determinant of mortality in ulcerative colitis. *Aliment Pharmacol Ther*. 2010;31(12):1310-1321.
55. Singh S, Al-Darmaki A, Frolkis AD, et al. Postoperative mortality among patients with inflammatory bowel diseases: a systematic review and meta-analysis of population-based studies. *Gastroenterology*. 2015;149(4):928-937.
56. Bernstein CN, Ng SC, Lakatos PL, Moum B, Loftus EV Jr; Epidemiology and Natural History Task Force of the International Organization of the Study of Inflammatory Bowel Disease. A review of mortality and surgery in ulcerative colitis: milestones of the seriousness of the disease. *Inflamm Bowel Dis*. 2013;19(9):2001-2010.
57. Saha SK, Panwar R, Kumar A, et al. Early colectomy in steroid-refractory acute severe ulcerative colitis improves operative outcome. *Int J Colorectal Dis*. 2018;33(1):79-82.
58. Grant RK, Jones G-R, Plevris N, et al. The ACE (albumin, CRP and endoscopy) index in acute colitis: a simple clinical index on admission that predicts outcome in patients with acute ulcerative colitis. *Inflamm Bowel Dis*. 2021;27(4):451-457.