ABOUT THE AUTHORS

Thilini Delungahawatta, MD, MSc

Dr. Thilini Delungahawatta is a Gastroenterology resident at McMaster University. She earned a Master of Science degree from McMaster University, completed her medical degree at the University of Limerick (Limerick, Ireland), and subsequently trained in Internal Medicine at MedStar Health–Georgetown University (MD, USA), where she participated in the Health Equity Track. Her academic interests now focus on inflammatory bowel disease (IBD), with particular emphasis on health equity and improving clinical outcomes in IBD populations.

Affiliations: *Department of Internal Medicine / Division of Gastroenterology McMaster University, Hamilton, ON, Canada*

Neeraj Narula, MD

Dr. Neeraj Narula is an Associate Professor of Medicine at McMaster University and Staff Gastroenterologist at Hamilton Health Sciences, with a clinical and research focus in Inflammatory Bowel Diseases (IBD). He is the director of the IBD clinic and IBD fellowship program at McMaster University. He completed the Present-Levison Advanced Inflammatory Bowel Diseases Fellowship at Mount Sinai Hospital (New York, NY) in 2015 and a Masters of Public Health at Harvard TH Chan School of Public Health (Boston, MA) in 2018. He has over 190 peer-reviewed publications and 4 book chapters. He has been awarded over $4 million in research funding and grants. His research interests are predominantly in clinical epidemiology, nutrition, and pharmaceutical trials in IBD. He has held leadership roles in national organizations including Past-President of the Canadian IBD Research Consortium and VP-Treasurer for the Canadian Association of Gastroenterology (CAG). His recent awards include the CAG Early Career Investigator Award (2025), the Canadian IBD Research Consortium Distinguished Achievement Award (2025), Crohn's and Colitis 360 Research Award (2025) and the McMaster Mid-Career Research Award (2025).

Affiliations: *Department of Internal Medicine / Division of Gastroenterology McMaster University, Hamilton, ON, Canada*

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Recent Clinical Trials in Acute Severe Ulcerative Colitis:

Can We Improve the Chances of Success of Corticosteroids and Rescue Therapies?

Thilini Delungahawatta, MD, MSc
Neeraj Narula, MD

Key Takeaways

1. Don't withhold intravenous (IV) steroids waiting for the stool infectious workup to come back. Many patients with infectious etiologies for exacerbation will require antimicrobials plus steroids to manage severe relapses.

2. When considering infliximab rescue therapy, a 10 mg/kg dose likely leads to higher response rates among patients with hypoalbuminemia (<25 g/L) and elevated CRP (≥50 mg/L) than a 5 mg/kg dose

3. JAK inhibitors can be considered as an adjunct to IV steroids, or as rescue therapy in steroid-refractory patients with a history of anti-TNF failure.

Introduction

Worldwide, there are over 5 million individuals with ulcerative colitis (UC), a chronic inflammatory disease of the large intestine, with rising incidence in developing countries.[1] Acute severe ulcerative colitis (ASUC) represents a life-threatening disease flare associated with an overall mortality of approximately 1% and necessitates hospitalization to prevent complications and avoid colectomy.[1,2] The diagnostic criteria for ASUC were first defined by Truelove and Witts in 1955 and include ≥6 bloody stools per day with systemic toxicity, such as fever (>37.8°C), tachycardia (>90 beats/min), anemia (<105 g/L), or elevated inflammatory markers (erythrocyte sedimentation rate >30 mm/hour; later modified to use C-reactive protein (CRP) >30 mg/L).[1] Approximately 20% of UC patients will require hospitalization for ASUC during their disease course, and up to 15% will experience recurrent episodes.[2] With the emergence of quick onset medical rescue therapies, continuous refinement of ASUC management algorithms is warranted to reduce disease morbidity and mortality.

First-Line Therapy

Intravenous corticosteroids (IVCS) remain the first-line therapy for ASUC; however, approximately one-third of patients fail to respond.[1,2] In a meta-regression analysis by Turner et al.,[3] daily corticosteroid doses across studies ranged from the equivalent of 40–100 mg of methylprednisolone for an average adult body weight of 70 kg. Doses exceeding 60 mg/day of methylprednisolone showed no additional benefit in reducing colectomy risk. Clinical response to IVCS is typically observed within one week in approximately 70% of patients, thus, early identification of steroid non-response is critical to facilitate timely initiation of second-line therapy.[4] The Oxford criteria[5] remain the most widely validated tool for predicting steroid failure at day 3 of treatment. According to these criteria, 85% of patients with more than eight stools per day, or three to eight stools per day accompanied by a CRP level >45 mg/L, ultimately require colectomy.

Recent evidence suggests a role for Janus kinase (JAK) inhibitors with IVCS during the initial management of ASUC. In a retrospective

case-control study of 40 biologic-experienced ASUC patients, adjunctive tofacitinib administered with intravenous methylprednisolone was associated with a significantly lower 90-day colectomy rate compared with controls (15% vs 20.4%; hazard ratio [HR]: 0.28), with the greatest benefit observed using three-times-daily dosing (HR: 0.11).[6] The TACOS single-centre randomized controlled trial further demonstrated that adding tofacitinib (10 mg three-times-daily for 7 days) to intravenous hydrocortisone significantly improved the clinical response at day 7 compared with placebo (83.0% vs 58.8%; odds ratio [OR]: 3.42), reduced the need for rescue therapy (OR: 0.27), and conferred sustained benefit through day 90.[7] Another multicenter observational study of 25 ASUC patients treated with upadacitinib and IVCS reported a 90-day colectomy rate of 24%, with 83% of patients who avoided colectomy achieving steroid-free clinical remission.[8]

In contrast, other corticosteroid-based combination strategies have not demonstrated clinical benefit in the management of ASUC. In a multicentre randomized controlled trial comparing IVCS alone versus IVCS with mesalamine (4 g/day), no significant differences were observed in clinical response rates (72.6% vs 76.3%; OR: 0.82), length of hospitalization, or colectomy rates through day 90.[9] Similarly, a randomized controlled trial from the United Kingdom evaluating adjunctive anakinra, an interleukin-1 receptor antagonist, failed to reduce the need for rescue therapy within 10 days or colectomy rates by day 98 compared with IVCS alone.[10] Furthermore, three randomized controlled trials (n = 144) evaluated adjunctive antibiotics with IVCS versus placebo in ASUC and demonstrated no significant difference in colectomy rates at hospital discharge (relative risk [RR]: 1.00).[11] Lastly, although exclusive enteral nutrition (EEN) appears safe and well tolerated, with a signal toward improved corticosteroid responsiveness in ASUC (75% vs 57% with standard care, p = 0.051),[12] pooled evidence shows no significant benefit in remission induction (risk ratio [RR] 1.15, 95% CI 0.71–1.85), corticosteroid failure (RR 0.76, 95% CI 0.48–1.20), or colectomy rates (RR 0.88, 95% CI 0.51–1.51) compared with standard care.[13] Furthermore, an RCT evaluating EEN with adjunctive albumin versus EEN alone, along with standard therapy, demonstrated no differences in corticosteroid failure (33.3% vs 41.9%, p = 0.49), colectomy (10% vs 9.7%, p = 1), or response to salvage therapy (88.9% vs 76.9%, p = 0.62).[14]

Rescue Therapy

Intravenous cyclosporine, a calcineurin inhibitor that suppresses T-cell activation via inhibition of interleukin-2 transcription, was first reported in 1990 to be effective for treating ASUC at a dose of 4 mg/kg/day.[15] This finding was subsequently confirmed in a randomized controlled trial of 20 corticosteroid-refractory patients, in which cyclosporine (4 mg/kg/day) induced clinical response in 9 of 11 patients (82%) within a mean of 7 days, compared with 0 of 9 patients receiving placebo (P <0.001).[16] A subsequent randomized trial demonstrated comparable efficacy between cyclosporine doses of 2 mg/kg/day and 4 mg/kg/day, with evidence suggesting a potentially improved safety profile at the lower dose.[17]

The anti–tumour necrosis factor (TNF)-α monoclonal antibody infliximab represents another well-established rescue therapy.[18] In a pilot placebo-controlled study by Sands et al.,[18] 8 patients with severe steroid-refractory UC received a single infusion of infliximab (5–20 mg/kg), with 50% achieving treatment success at 2 weeks compared with no responders in the placebo group. Subsequently, the landmark randomized controlled trial by Järnerot et al.,[19] demonstrated that infliximab (5 mg/kg) significantly reduced colectomy rates compared with placebo (29% vs 67%; OR: 4.9).

In ASUC, disruption of the epithelial barrier and heightened inflammation lead to increased infliximab loss and accelerated drug clearance, resulting in low serum drug levels and providing a rationale for dose intensification of infliximab.[20] Interestingly, the PREDICT-UC study of steroid-refractory ASUC demonstrated similar clinical response rates at day 7 with infliximab dosed at 5 mg/kg and 10 mg/kg. Intensified or accelerated induction strategies did not improve outcomes at month 3 compared with standard dosing, despite earlier achievement of clinical and biochemical remission in post hoc analyses.[2] However, among patients with hypoalbuminemia (<25 g/L) and elevated CRP (≥50 mg/L) day-7 response rates were numerically higher with the 10 mg/kg dose compared with 5 mg/kg, suggesting a potential role for biomarker-guided dosing. Supporting this approach, a post-hoc analysis of PREDICT-UC demonstrated that lower infliximab concentrations on day 3 were

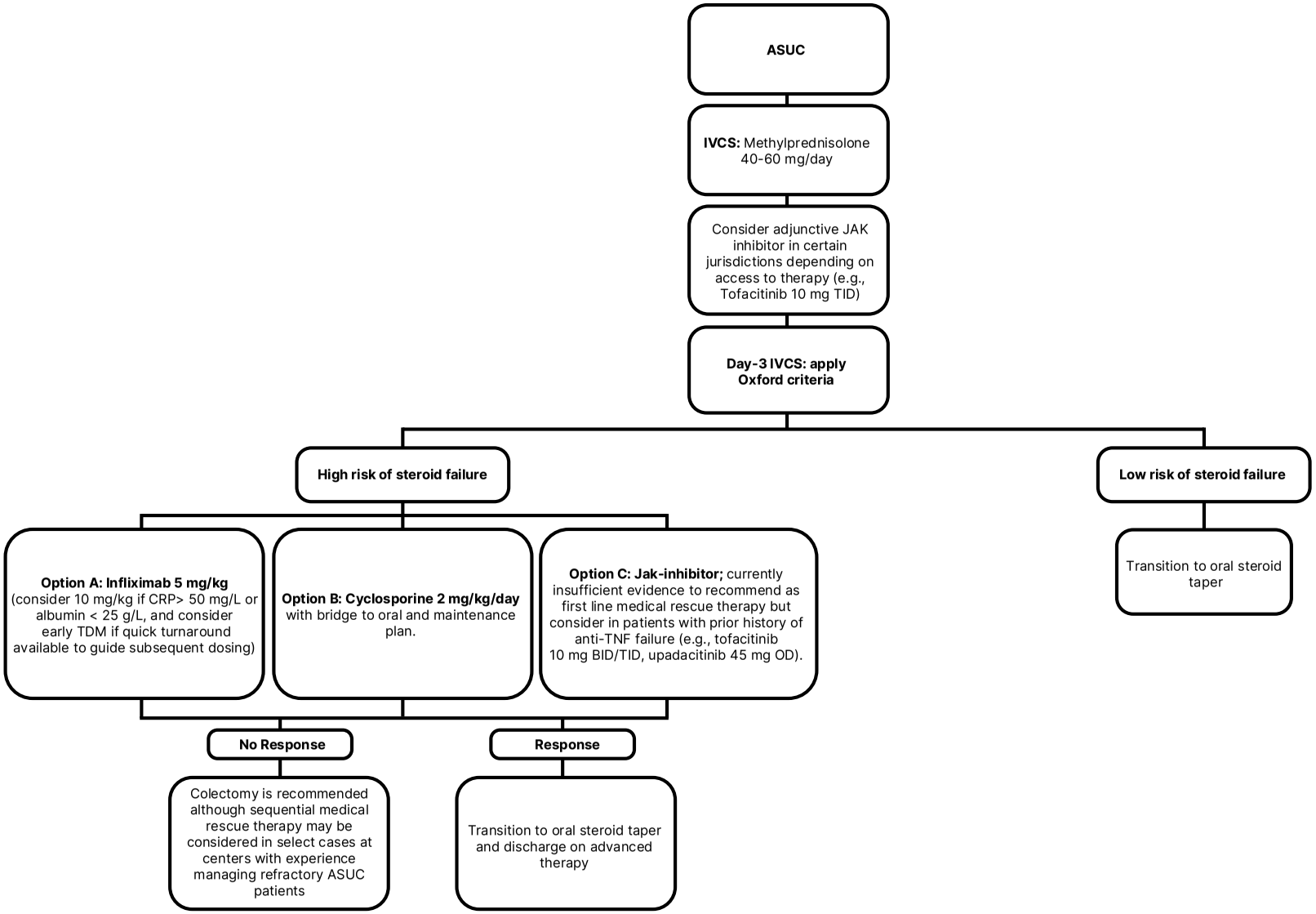

Figure 1. Treatment Algorithm for Hospitalized Patients with Acute Severe Ulcerative Colitis; *courtesy of Thilini Delungahawatta, MD and Neeraj Narula, MD.*

Abbreviations: ASUC: acute severe ulcerative colitis; **BID:** twice a day; **CRP:** C-reactive protein; **IVCS:** intravenous corticosteroids; **JAK inhibitor:** Janus kinase inhibitor; **OD:** once a day; TDM: therapeutic drug monitoring; **TID:** Three times a day; **TNF:** tumour necrosis factor

significantly associated with induction failure by day 14 and colectomy by month 3.[21] A day 3 infliximab level ≤53.6 µg/mL predicted induction failure (NPV 80.8%), while ≤57.9 µg/mL predicted colectomy (NPV 96.9%). Collectively, these findings suggest that early therapeutic drug monitoring or dosing strategies according to the individual patient's predicted drug clearance, may identify highrisk patients who could benefit from prompt dose intensification or early use of higher dosing. Indeed, patients with high early infliximab clearance showed higher day14 response rates when re-dosed early with 10 mg/kg compared with 5 mg/kg (38% vs 11%; RR: 3.43).[21] Nonetheless, data from a meta-analysis has shown no significant reduction in short-term colectomy risk with intensive infliximab dosing strategies compared with standard induction regimens (RR: 1.61; 95% confidence interval: 0.74–3.52).[22] Additionally, randomized trials summarized in recent meta-analyses have not shown a definitive difference between infliximab and cyclosporin, but the assessed observational studies suggest infliximab may be associated with improved treatment responses and a lower risk of colectomy at 12 months.[11,23,24]

JAK inhibitors such as tofacitinib and upadacitinib are approved for treating moderate to severe UC and possess several theoretical benefits that may support their use for ASUC, including rapid oral onset, efficacy irrespective of prior antiTNF exposure, and avoidance of the inflammationrelated colonic drug loss observed with biologics.[11] In a systematic review of 148 pooled cases of ASUC, tofacitinib was associated with colectomy-free survival of 86% at 90 days, clinical remission rates of up to 69%, and endoscopic remission in 55% of patients.[25] Additional prospective evidence comes from the multicenter, open-label TRIUMPH trial conducted across five Canadian hospitals, in which 24 hospitalized patients with steroid-refractory ASUC received tofacitinib 10 mg twice daily as rescue therapy; clinical response at day 7 was achieved in 58.3% of patients, with a mean time to response of 2.4 days.[26] Colectomy occurred in 25% of patients by 6 months, with no additional colectomies thereafter. Building on these results, the ongoing RESCUE-UC trial (**Clinicaltrials.gov** NCT06660693) is comparing an upadacitinib-first rescue strategy, with infliximab reserved for non-responders, to conventional infliximab-based rescue therapy in patients with steroid-refractory ASUC.

Conclusion

Despite major therapeutic advances, ASUC remains a highrisk clinical emergency requiring timely, evidencebased escalation of care. Intravenous corticosteroids remain the foundation of initial therapy; however, approximately onethird of patients fail to respond, underscoring the importance of early prognostic assessment and initiation of medical rescue therapy or surgery in non-responders. Adjunctive JAK inhibitors appear to enhance corticosteroid efficacy in ASUC, improving early clinical response and reducing need for rescue therapy, whereas other combination strategies including mesalamine, antibiotics, anakinra, and exclusive enteral nutrition (with or without albumin) have not demonstrated consistent benefit in corticosteroid response, remission rates, or colectomy outcomes. Recent clinical trials also highlight the growing role of JAK inhibitors as rescue options in those who are steroid-refractory, demonstrating rapid onset of action, encouraging remission rates, and potential synergy with corticosteroids. Among established rescue therapies, infliximab and cyclosporine show comparable short- and long-term efficacy, though emerging data suggest that personalized approaches, including biomarkerguided infliximab dosing and early therapeutic drug monitoring, may improve outcomes in selected highrisk patients. **Figure 1** provides a proposed algorithm for managing patients with ASUC based on the currently available evidence. Ongoing prospective trials will be essential for understanding how to position JAK inhibitors within treatment algorithms and in identifying strategies to maximize therapeutic success.

Correspondence

Neeraj Narula, MD
Email: neeraj.narula@medportal.ca

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