

EDUCATION PRACTICE

Poorly Responsive Ulcerative Colitis in the Hospital

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Clinical Scenario

A 20-year-old woman with a history of UC is referred for symptoms of frequent bloody stools, tenesmus, and the inability to taper off of corticosteroids. She was initially diagnosed with left-sided UC at the age of 8 and had an average of 1 moderate flare per year that responded to an oral steroid taper. She had a normal terminal ileum on previous colonoscopy and a normal small bowel follow-through. During the past 2 years, her disease has become refractory to medical therapies. During this time period, she has been on multiple medications including oral mesalamine, topical rectal corticosteroid and mesalamine preparations, and oral corticosteroids (10–60 mg prednisone). Infliximab was initiated 2 years prior at 5 mg/kg and titrated to 10 mg/kg during the past 18 months. Her last dose of infliximab was 4 months before this evaluation, when it was discontinued as a result of lack of response.

Her current symptoms consist of 10–15 stools per day associated with mucus and blood. She has intermittent moderate left lower quadrant abdominal pain. She has significant tenesmus. During the past 6 months, she has lost approximately 15 pounds. She denies any skin rashes or joint symptoms. She has not had any fevers or night sweats. Her current medications consist of prednisone 60 mg daily (for the past 12 days), mesalamine suppository 1 g per rectum at bedtime, oral mesalamine 3.6 g daily, and hydrocortisone 10% rectal foam. The patient is a nonsmoker; she is married and would like to start a family during the next 2–3 years.

She is 5 feet 4 inches tall and weighs 66 kg. Her heart rate is 98, with a blood pressure of 118/76 mm Hg. She is moderately tender to palpation in the left lower quadrant. There is no perianal disease. She has an elevated erythrocyte sedimentation rate (ESR) of 45 and hemoglobin of 10.2. Stool studies are negative for enteric pathogens, *Clostridium difficile* toxins A and B, and ova and parasites. A plain abdominal x-ray film shows no evidence of colonic dilatation. On flexible sigmoidoscopy, there is a contiguous area of severe erythema, granularity, friability, and contact bleeding from the rectum to the mid-transverse colon. After the mid-transverse colon, the mucosa appears normal. Biopsies from the involved area showed moderate to severe chronic active colitis without dysplasia. Biopsies were negative for cytomegalovirus. She is hospitalized and initiated on a continuous infusion of intravenous corticosteroids at 2 mg/hour (48 mg/day). During a period of 5 days, there is no change in her bowel movement frequency or bleeding.

The Problem

The lifetime risk of a severe exacerbation of UC requiring hospitalization is 15%.¹ Patients with extensive disease (macroscopic disease proximal to the splenic flexure) are more likely to develop acute severe colitis; however, it also occurs in patients with left-sided disease. Determination of disease activity in UC is based on clinical findings (both objective and subjective) and visual assessments of inflammation (endoscopy, imaging). Activity is described in terms of both severity and extent of the disease.^{2,3} Instruments for measuring disease activity include the Truelove and Witts Severity Index (Table 1), the Mayo Score (also called the Disease Activity Index), and the Lichtiger Index, which was developed specifically for severe UC.⁴

In a patient with hospitalized severe UC that is refractory to maximal therapy with intravenous corticosteroids, oral aminosalicylates, and topical medications, the question of “salvage” medical versus surgical therapy is paramount. Medical therapy in a hospitalized patient requires close monitoring and continual reassessment, because in a severely active patient, surgery might in fact be lifesaving. In patients with refractory hospitalized UC, it is difficult to know with certainty which patients will respond to intravenous corticosteroids. Certain characteristics have correlated with corticosteroid failure in previous studies. These include frequent bowel movements, low albumin level, and colonic dilatation on imaging in spite of treatment with intravenous steroids. After 3 days of intravenous steroids, 85% of patients with >8 stools per day or a stool frequency between 3 and 8 with a C-reactive protein >45 mg/L will require colectomy.⁵ Other prognostic indicators for corticosteroid failure include elevated maximum daily temperature, pulse, stool frequency >3, and low albumin level.⁶ These criteria are often used clinically to expedite escalation to more aggressive medical or surgical treatment earlier in the hospital course.

To decide on the appropriate course of therapy for this patient, the outcomes and complications of medical and surgical therapy for severe UC in a young woman need to be considered. Despite the introduction of new medications for the treatment of UC, the overall colectomy rate has remained stable at approximately 27% during the past 3 decades.⁷ However, these data do not consider the introduction of infliximab for

Abbreviations used in this paper: AZA, azathioprine; ESR, erythrocyte sedimentation rate; IPAA, ileal pouch–anal anastomosis; 6-MP, 6-mercaptopurine; TNF, tumor necrosis factor.

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Table 1. Measuring Disease Activity in UC: The Truelove and Witts Severity Index

	Mild	Moderate	Severe	Fulminant
Stool frequency	<4 stools daily (no blood)	>4 stools daily	>6 stools daily (with blood)	>10 stools daily (with continuous bleeding)
Toxicity	No signs of toxicity (heart rate >90, temperature >37.8°C, hemoglobin <10.5, ESR >30)	No/minimal signs of toxicity (heart rate >90, temperature >37.8°C, hemoglobin <10.5, ESR >30)	At least 1 sign of toxicity (heart rate >90, temperature >37.8°C, hemoglobin <10.5, ESR >30)	Abdominal tenderness
Imaging	No colonic dilatation	No colonic dilatation	No colonic dilatation	Colonic dilatation

UC, which shows promise for reducing colectomy rates. Issues particular to young women, including fecundity (the likelihood of conceiving as a function of duration of time), should also be considered in the discussion of medical versus surgical therapy.

Pathophysiology

IBD results from a genetic susceptibility to immune mediated bowel injury triggered by environmental stimuli. Intestinal inflammation is likely due to an overly aggressive immune response to luminal bacteria. Recent genetic findings highlight the important role of innate immunity against enteric microbes in disease pathogenesis. Ultimately, aberrant innate immune responses to enteric microbes initiate and perpetuate an exaggerated T-cell-driven adaptive immune response. Increased T-cell migration, retention, activation, and proliferation in the colon contribute to uncontrolled inflammation. Mechanisms of tissue injury are related to the secretion of inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-12/23, interferon- γ , interleukin-5, interleukin-13, and interleukin-17. In contemplating current and future therapeutic interventions in UC, clinically validated targets include inhibition of the activated T-cell response (for example, cyclosporine), blockade of trafficking of inflammatory cells to the intestine (for example, natalizumab), and inhibition of inflammatory cytokines released from activated cells like TNF (for example, infliximab).

In UC, there are no validated serologic or genetic markers that predict who will develop a severe exacerbation. Toll-like receptor-2⁸ genetic polymorphisms seem to be more common among patients with severe steroid-resistant UC. The discovery and validation of biomarkers that predict disease course and response to therapy in UC are an important priority for future research.

Management Strategies and Supporting Evidence

Corticosteroids and Conventional Adjunctive Therapies in Severe Ulcerative Colitis

An important medical treatment for severe UC that has failed outpatient management is intravenous corticosteroids. Adjunctive therapies might include oral mesalamine, topical mesalamine and corticosteroids, antibiotics, total parenteral nutrition, and immunosuppressants such as 6-mercaptopurine (6-MP) and azathioprine (AZA). There are few randomized placebo-controlled studies of these agents in severe UC. Intravenous corticosteroids have been used for the treatment of hospitalized UC patients since the 1950s.³ One study reported

a 73% remission rate (36/49) with a 5-day course of intravenous corticosteroids in patients with severe UC.⁹ There is no evidence that intermittent versus continuous intravenous steroid infusion changes outcomes.¹⁰ Antibiotics showed no additional benefit when combined with intravenous steroid administration.¹¹⁻¹³ Likewise, total parenteral nutrition and complete bowel rest in combination with corticosteroids showed no additional benefit.¹⁴⁻¹⁶ Because of delayed onset of action, 6-MP and AZA are not used in the acute management of severe UC. These medications can be used for long-term maintenance if remission can be achieved by other means. When a patient hospitalized with severe UC does not respond to 3-5 days of intravenous corticosteroids, salvage therapies such as cyclosporine, infliximab, and surgery become necessary. Clinical and laboratory criteria are often used to make decisions about defining early corticosteroid failure at day 3.^{5,17}

Cyclosporine in Severe Ulcerative Colitis

Cyclosporine is an inhibitor of the transcription factor nuclear factor of activated T cells and acts in part by attenuating production of interleukin-2 by activated T cells. Cyclosporine is effective in severe UC to induce rapid response during hospitalization. Initial response rates range from 62%-86%, defined as improvement in clinical symptoms and initial avoidance of colectomy.¹⁸⁻²³ Early studies used doses of cyclosporine of 4 mg/kg/day, but 2 mg/kg/day dosing is equally effective, with a better side effect profile.²⁴ Long-term clinical success with cyclosporine depends on initiation of 6-MP or AZA as a maintenance agent. Among those who initially responded to cyclosporine and were newly initiated on 6-MP, 20% required colectomy during a 5-year follow-up period. Those who were not initiated on 6-MP or previously failed 6-MP had a 45% colectomy rate.¹⁹ Likewise, in patients treated with cyclosporine and AZA, 80% were free of colectomy at 1 year, and 60% were colectomy-free at 7 years. In patients on cyclosporine alone, 47% were free of colectomy at 1 year, but only 15% were colectomy-free at 7 years.²⁰ These data show the importance of an exit strategy after initiation of cyclosporine as a result of short-term and long-term toxicities. Major adverse events that have been associated with cyclosporine use include nephrotoxicity (5.4%), serious infection (6.3%), seizures (3.6%), anaphylaxis (0.9%), and death (1.8%).²⁵ Other minor adverse events include paresthesias, hypomagnesemia, hypertension, hypertrichosis, headache, minor infections, hyperkalemia, and gingival swelling.²⁵

Cyclosporine is generally used as salvage treatment before colectomy. There is no increased operative mortality associated with presurgical cyclosporine in patients undergoing restorative

proctocolectomy. Overall, a 36% postoperative complication rate has been reported with cyclosporine,²⁶ similar to the historical complication rate for patients undergoing colectomy not treated with cyclosporine.

Practical considerations with cyclosporine include close monitoring of laboratory values and adjustment of the infusion rate. The initial dose is 2 mg/kg/day. The target cyclosporine level is between 150 and 250 ng/mL (by monoclonal assay; target levels will vary with polyclonal assays) for the intravenous dose.

Conversion to oral dosing is usually twice the intravenous dose (given every 12 hours), with a trough level adjusted between 100 and 200 ng/mL. An exit strategy with the initiation of 6-MP or AZA is necessary. Prophylaxis for *Pneumocystis carinii* should be initiated during hospitalization and continued as an outpatient. In summary, for severe UC, cyclosporine induces a prompt response and might result in prolonged response if 6-MP or AZA can be initiated.

Infliximab in Severe Ulcerative Colitis

Infliximab is a chimeric IgG1 monoclonal antibody that neutralizes the biologic activity of the inflammatory cytokine TNF. Infliximab is Food and Drug Administration–approved to induce and maintain remission in patients with moderate to severe UC. One study demonstrated a 50% clinical response rate to infliximab in a trial of hospitalized patients with UC (8 patients randomized to infliximab, 3 patients randomized to placebo) in whom intravenous steroids failed.²⁷ Another study randomized a cohort of 45 patients with severe hospitalized UC to rescue therapy with infliximab versus placebo after 3–8 days of intravenous steroids. The primary end point was colectomy within 3 months. The colectomy rate in the placebo group at 3 months was 67% versus 29% in the infliximab group (odds ratio, 4.9; 95% confidence interval, 1.4–17; *P* = .017).¹⁷ On entry, patients were classified as severe and fulminant. Fulminant patients were randomized on day 4 and severe patients on days 6–8. When the fulminant patients were separately analyzed, 69% (9/13) in the placebo group required colectomy compared with 47% (7/15) in the infliximab group (*P* = .3). Thus, there was a trend toward decreased colectomy rates in the most severe patients randomized to infliximab, but this was not statistically significant, possibly as a result of a small sample size and a type II error.

In patients who fail infliximab and progress to surgery, there are mixed data on associated complication rates. Another study also found no increase in postoperative complications associated with infliximab use.²⁸ However, there might be an increased rate of postoperative complications among infliximab-treated pa-

tients undergoing restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) compared with controls (odds ratio, 3.54; 95% confidence interval, 1.51–8.31 for early complications).²⁹ In a prospective series, although overall morbidity was similar between patients who received pre-IPAA infliximab and those who did not, anastomotic leaks (*P* = .02) and pouch-specific (*P* = .01) and infectious (*P* < .01) complications were more common in the infliximab group.³⁰

There is no role for the combination of cyclosporine and infliximab in steroid-refractory UC. The combination of these medications is associated with a higher morbidity. There is an 80% rate of surgical and infectious complications associated with concomitant use of both medications.³¹ In addition, when cyclosporine and infliximab are used as rescue therapy for patients failing the other modality, the risks likely outweigh the benefits. One study showed approximately one third of patients receiving salvage therapy by crossing over to the alternate medication were in remission at 1 year; however, serious side effects (including 1 death) occurred in 16% of patients.³² An overview of the differences between cyclosporine and infliximab in the treatment of severe UC is shown in Table 2.

Colectomy for Severe Ulcerative Colitis

Emergency indications for surgical intervention in severe UC include free perforation, hemorrhage, or systemic instability. An urgent indication for colectomy is a severe attack that is unresponsive to medical therapy. Unresponsive to medical therapy is a subjective term that is not precisely delineated in the literature for severe UC. However, the important point is that delaying surgery in an unstable or clinically deteriorating patient can lead to dire consequences. In our practice, the development of medical instability, worsening symptoms, or the lack of partial improvement during the first 3–5 days of salvage therapy should lead to serious consideration of immediate surgical intervention.

In the setting of severe UC, the procedure of choice is subtotal colectomy and ileostomy. The residual rectal disease is controllable in most patients. In general, there are advantages to the subtotal colectomy approach, including a lower morbidity if pelvic dissection is not performed, preservation of the rectum so that reconstructive procedures can be performed later, and allowing the definitive procedure to be deferred to an optimal situation when the patient is off immunosuppressive medications and has improved nutritional status. Usually the staged reconstruction with IPAA or definitive total proctocolectomy is performed several months later.

There can be surgical morbidity associated with colectomy, although these risks are minimal compared with the risks

Table 2. Cyclosporine and Infliximab in Severe UC

	Cyclosporine	Infliximab
Efficacy	62%–86%	50%
Time to response	3–7 days	2–3 weeks (median)
Avoidance of colectomy (3–5 y)	19%–60%, higher if AZA/6MP	47%
Postoperative complications	No increase	No to small increase associated with restorative surgery
Long-term therapy	No, must bridge to AZA/6MP	Yes
Long-term side effects	Infections, renal dysfunction, HTN	Infections, lymphoma
Ease of use	Harder: monitoring of levels, titrating dose	Easier: weight-based dosing algorithm

HTN, hypertension.

associated with continuing futile medical therapy in an unstable patient. One study evaluated outcomes after colectomy in a large population of patients with UC ($n = 25,586$).³³ During the 180 days after colectomy, 54% of patients required a second operative procedure (including planned staged operations; 15.3% of patients had unplanned operations). Complications occurring after colectomy included abscess (11.6% early, 16.3% late), fistulas (4.2% early, 6.0% late), and bacteremia/sepsis (7.9% early, 9.3% late). A retrospective cohort study ($n = 184$) found a 27% early postoperative complication rate for patients with UC undergoing colectomy.³⁴ During a median follow-up of 6.5 years, 35% of patients developed septic and/or obstructive complications.

Generally, patients have good outcomes after restorative IPAA. Median bowel frequency is 6 stools per day. Postprocedure symptoms can include intermittent urgency (23% of patients), evacuation difficulties (12% of patients), and intermittent soiling at night (52% of male and 32% of female patients). Overall, more than 90% of patients are satisfied with their pouch.³⁵ There is a small rate (6.2%) of pouch failure over time.³⁶ For women, there is an additional concern of reduced fecundity after IPAA. After colectomy and restorative IPAA, the fecundity ratio is significantly impaired (fecundity ratio, 0.25 [0.17–0.37]) compared with the reference population.³⁷ These effects are likely related to the surgery itself and are seen in other populations undergoing IPAA.³⁸ For this reason in women of childbearing age, it might be reasonable to delay restorative IPAA until after childbearing years.

Areas of Uncertainty

There are currently no reliable clinical markers or biomarkers that can be used to determine the likelihood of success for cyclosporine versus infliximab for an individual patient. Reliable predictors of response to these medications are needed to better avoid complications associated with delaying colectomy. There are 2 controlled trials in progress in Europe comparing cyclosporine with infliximab as rescue therapy in severe UC. These data will help to guide our choice of therapies in the future.

As this case illustrates, the decision of whether to use infliximab or cyclosporine for severe UC in the hospitalized patient is perhaps no longer the most relevant clinical scenario. Often these patients have already been exposed to infliximab in the outpatient setting. The most appropriate use of infliximab might in fact be to avoid hospitalization, intravenous corticosteroids, and surgery in the medically refractory outpatient. There are major gaps in clinical information on how to proceed in the setting of prior infliximab exposure as an outpatient in hospitalized UC patients. There are no data about response to intravenous corticosteroids or cyclosporine in UC patients who are exposed (and did not respond) to infliximab as an outpatient. In the authors' practice, intravenous steroids and cyclosporine are contemplated in patients if they had not been previously refractory to 6-MP/AZA. In patients who have previously failed 6-MP/AZA, surgery must be considered before intravenous steroids and cyclosporine because these patients are less likely to maintain remission long-term.

Published Guidelines

The only published United States guidelines for the management of severe UC are from the American College of Gastroenterology. The Ulcerative Colitis Practice Guidelines in Adults (ACG 2004) recommend hospitalization for a course of intravenous steroids in those refractory to oral treatment with prednisone, mesalamine, and topical medications or in the patient who presents with toxicity. These guidelines were formulated before the published experiences with infliximab in severe UC and need to be updated to reflect this medical option. Stool samples should be evaluated for superimposed infection with enteric pathogens and *C difficile*. There is no role for treatment with antibiotics, although these are used in patients with signs of toxicity. There is no benefit to total parenteral nutrition as a primary therapy for UC. Improved nutrition with total parenteral nutrition might be beneficial as an adjunct to enteral nutrition in patients with significant nutritional depletion. A flexible sigmoidoscopy with biopsies to exclude superimposed cytomegalovirus should be considered in patients not responding to maximal immunosuppressive therapy. Failure to exhibit significant improvement within 3–5 days is an indication for colectomy or intravenous cyclosporine. Long-term remission is enhanced in patients initiated on cyclosporine with 6-MP or AZA as a maintenance strategy.

Recently, the Association of Coloproctology of Great Britain and Ireland published a position statement on the management of acute severe colitis.³⁹ Recommendations about diagnosis, monitoring, and treatment are consistent with the 2004 ACG recommendations, but they also account for the use of infliximab. The necessity of joint care between an experienced gastroenterologist and a colorectal surgeon to ensure optimal outcome is emphasized. Intravenous corticosteroids remain the first line medical approach in acute severe colitis, and 3–5 days of treatment are recommended before initiation of other options. A single attempt at rescue therapy with cyclosporine or infliximab could be considered in selected patients before colectomy, but the choice of agent is limited by the absence of adequately powered randomized controlled trials. For patients with toxic megacolon, 24 hours of intensive medical therapy is recommended and continued only if there is radiologic and clinical evidence of improvement. Unresponsiveness to medical therapy is the most common indication for surgery but is difficult to precisely define. As a general guideline for those without evidence of toxic megacolon, after 5–7 days of rescue therapy, if there is no clinical improvement, surgical treatment is indicated. The most problematic patients are those who respond partially to medical therapy, because there are no data to adequately weigh the risks of continued medical therapy versus surgical intervention. On the basis of these guidelines and the present literature review, an outline for management of poorly responsive UC in the hospital is depicted in Figure 1.

Recommendations for This Patient

The patient initially failed to respond to high-dose oral prednisone during a 1- to 2-week period. Appropriate medical decisions at this juncture would be an outpatient trial of infliximab or admission to the hospital for intravenous steroids and other treatment modalities. There is no clear medical evidence to guide when within this 2-week window a patient should be considered an oral corticosteroid failure, but severe

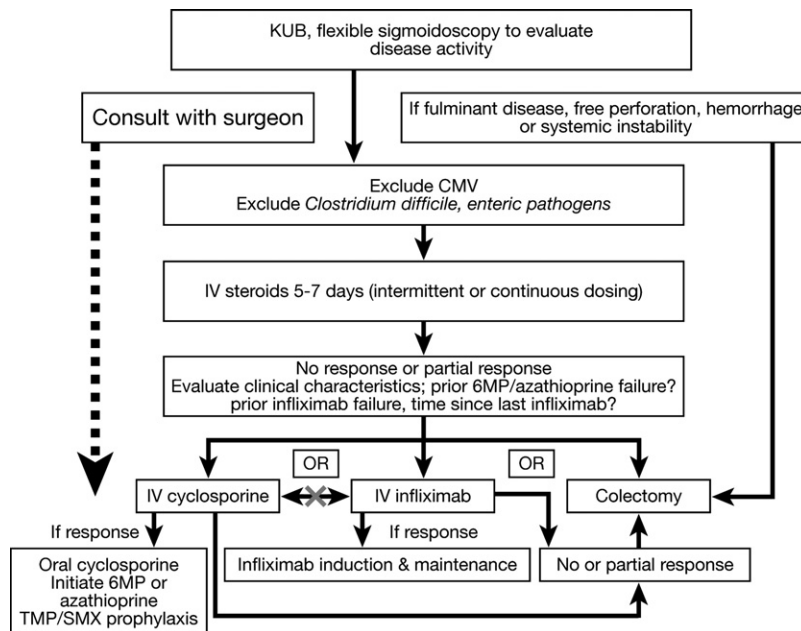


Figure 1. Algorithm for the treatment of severe hospitalized UC.

symptoms, systemic symptoms, and progression of disease activity might prompt an earlier decision to escalate therapy, whereas a partial response to oral prednisone might be an indication to exercise patience clinically.

The patient then did not respond to intravenous steroids during a course of 5 days. Serial abdominal exams remained benign, and abdominal x-rays did not show colonic dilatation. She was initiated on cyclosporine and underwent a 5-day course, with dramatic improvement in her stool frequency, pain, and ESR. Thiopurine s-methyltransferase activity was normal. She was initiated on 6-MP at a dose of 1.5 mg/kg at discharge from the hospital. Before discharge, she was transitioned to oral cyclosporine at a dose of 150 mg twice daily (approximately twice the intravenous dose she was receiving). At discharge, she had 2–3 bowel movements per day without blood. She was placed on an oral prednisone taper and maintained on topical and oral mesalamine medications. She was also started on sulfamethoxazole and trimethoprim 3 times weekly for *Pneumocystis* pneumonia prophylaxis. At follow-up 8 weeks after discharge, the patient was still doing well, in remission with 2–3 formed bowel movements daily. She had completely tapered off of oral prednisone. After 12 weeks, she was tapered off her cyclosporine and is currently doing well 10 months later on 6-MP and oral and topical mesalamine.

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Reprint requests

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Conflicts of interest

The authors disclose the following: Dr Plevy has financial relationships with Centocor Inc (Advisory Boards, Speakers Bureau, Grant support), Abbott Laboratories (Advisory Boards, Speakers Bureau, Grant support), UCB Biopharma (Advisory Boards, Speakers Bureau), Elan Pharmaceuticals (Advisory Boards, Speakers Bureau). Dr Long discloses no conflicts.