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Managing Severe Ulcerative Colitis in the Hospitalized Patient

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One of the true "emergencies" in inflammatory bowel disease (IBD) is the management of the patient with acute severe colitis. Natural history studies tell us that the first year after diagnosis of ulcerative colitis (UC) is associated with the highest colectomy rate. Ulcerative colitis severity can be defined by a combination of clinical and objective parameters. The Truelove and Witts Severity Index, developed over 60 years ago, still holds up as a good approximation of disease activity.[1] Patients with severe ulcerative colitis tend to have more than six bowel movements per day, frequent blood in stool, a body temperature >37.5 degrees Celsius, heart rate >90 beats per minute, hemoglobin that is <75% of normal (i.e., <9 g/dL for women, <10 g/dL for men) and erythrocyte sedimentation rate >30 mm per hour.[1]

On day one of hospitalization, abdominal film should be obtained to exclude toxic megacolon. Clostridium difficile superinfection should be excluded. The patient should be given intravenous fluids and corticosteroids. Patient expectations should be set. The colorectal surgeon should be consulted. Subcutaneous heparin should be administered for deep venous thrombosis prophylaxis, as patients have an elevated risk due to activation of the coagulation cascade due to systemic inflammation. Narcotics should be avoided as they can further slow gut motility and potentially precipitate toxic megacolon. In anticipation that the patient might require immunosuppression (either infliximab or a calcineurin inhibitor), thiopurine methyltransferase, interferon gamma release assay for tuberculous antigens and hepatitis B virus serologies should be obtained.

Numerous studies have documented the increasing prevalence and severity of Clostridium difficile infection, particularly in patients with inflammatory bowel disease.[2] These infections can lengthen hospital stay as well as increase in-hospital colectomy rates and mortality. Another superinfection to exclude is cytomegalovirus (CMV) infection, which is diagnosed by flexible sigmoidoscopy and biopsy, asking the pathologist to obtain CMV immunostains (this should be obtained within 48 hours of admission). The density of CMV inclusions in the biopsy fragments will help determine whether the CMV is an "innocent

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bystander" (generally <5 inclusions per biopsy) or an actual pathogen (generally >5 inclusions per biopsy).[3] Multiple studies have demonstrated that antiviral therapy with intravenous (IV) ganciclovir followed by oral valganciclovir can reduce colectomy rates in UC patients who are refractory to intravenous corticosteroids and who have CMV colitis.

Intravenous corticosteroid doses should be equivalent to methylprednisolone 60 mg daily. There is no evidence that steroid doses higher than the equivalent of methylprednisolone 60 mg daily are more efficacious—indeed, a meta-regression of multiple studies correlated colectomy rates with corticosteroid dose and found no reduction in colectomy rates beyond 60 mg daily.[4] The original "Oxford regimen" for acute severe colitis included not only intravenous fluids, electrolytes and corticosteroids, but also intravenous antibiotics, blood transfusion, bowel rest and corticosteroid enemas.[5] Although bowel rest is appealing (less antigenic stimulation, less luminal secretion, etc.) there are at least two controlled trials showing that total parenteral nutrition and bowel rest was no more effective in reducing colectomy rates compared to offering the patient a general diet. Therefore, routine bowel rest and total parenteral nutrition for acute severe colitis is not advocated; however, total parenteral nutrition (TPN) may be indicated for severe malnutrition. Similarly, several controlled trials have not demonstrated a benefit for intravenous antibiotics in acute severe colitis, but there may be a role for broad spectrum antibiotics in selected patients with fulminant colitis.

A number of studies have attempted to prognosticate risk of colectomy in patients with acute severe colitis.[6,7] The best indices seem to incorporate serum C-reactive protein concentration and stool frequency on the third day of hospitalization. For example, having >8 stools daily, or 3 to 8 stools daily in combination with a CRP >45 mg/L on day three, is approximately 85% predictive of requiring colectomy. Thus, by day three the provider has a good idea as to whether or not salvage therapy with infliximab or a calcineurin inhibitor will need to be implemented at day five.

The best study demonstrating the efficacy of infliximab in the setting of severe ulcerative colitis was a European study by Jarnerot and colleagues.[8] A total of 45 patients were randomized to infliximab 5 mg/kg versus placebo. Two thirds of the infliximab-treated patients were able to avoid colectomy as compared to only 29% in the placebo-treated group. A subgroup analysis of the Active Ulcerative Colitis Trials (ACT) showed that survival free of colectomy was significantly higher among patients randomized to the infliximab group compared to that of the placebo group.[9] Adverse events associated with anti-tumor necrosis factor (TNF) alpha agents have been well described over the past 20 years. These events include granulomatous and fungal infections, other serious infections, infusion reactions, drug-induced lupus, demyelination syndromes, congestive heart failure, hepatotoxicity and an increased risk of lymphoma and skin cancer.

The use of infliximab in the acute severe colitis setting is challenging in that infliximab is a protein and severe UC patients generally have a protein-losing colopathy (which in part explains their hypoalbuminemia). It has been shown that patients who are not experiencing clinical or endoscopic response in the acute severe colitis setting have higher levels of fecal infliximab than those responding.[10] Higher doses of infliximab, or an accelerated dosing regimen, might reduce the colectomy rate. However, this has been surprisingly difficult to prove. One retrospective study of 50 hospitalized UC patients who were steroid-refractory received either standard induction dosing or accelerated dosing (three doses within a median interval of 24 days).[11] In the short term, patients receiving accelerated dosing were significantly less likely to require colectomy during induction (6.7% versus 40%); however, by two years out, the colectomy rates were not significantly different. The experience with accelerated dosing of infliximab in severe UC by the IBD group at the University of Michigan has been published in preliminary form.[12] They instituted in 2013 a protocol whereby the second dose of infliximab 5 mg/kg was given early if the CRP level had not dropped by 7 mg/L. Surprisingly, the colectomy rate among the accelerated group was significantly higher (47.1%) than among the group receiving standard dosing (12.4%).[12] At this point in time, an accelerated dosing regimen would not be considered "standard of care."

The landmark trial demonstrating the short-term efficacy of intravenous cyclosporine in the acute severe colitis setting was published in 1994 (82% response rate with cyclosporine vs. 0% placebo, 18% vs. 44% colectomy rate).[13] Further randomized controlled trials showed that cyclosporine was at least as effective as corticosteroids,[14] and that a 2 mg/kg infusion was as effective as 4 mg/kg.[15] The long-term efficacy remains unclear. This appears to be a good option in a patient naïve to thiopurines, because one then can use cyclosporine as a bridge to thiopurines. Cyclosporine might make more sense in a patient with marked hypoalbuminemia/protein-losing colopathy. Serious infections including fatal infections (1.4%-2.8%) have been described with the use of cyclosporine.[16-18]

A randomized clinical trial comparing cyclosporine to infliximab in 110 patients with acute severe colitis refractory to steroids was performed by the GETAID group.[19] Treatment failure was defined as a composite of no clinical response at day seven, inability to achieve steroid-free remission by day 98, a clinical relapse between days 7 and 98, colectomy, or death. Rates of treatment failure were similar—54% for the infliximab group versus 60% for the cyclosporine arm.[19] The authors concluded that cyclosporine was not superior to infliximab. Colectomy rates at day 98 were very similar—18% in the cyclosporine group versus 21% in the infliximab-treated arm. Over the longer term, colectomy rates up to seven years out from initiation in the trials were similar.[20] Thus, it is reasonable to consider either option as salvage therapy in steroid-refractory severe ulcerative colitis patients. The sequential use of cyclosporine followed by infliximab or vice versa is generally not recommended, because such a strategy does not improve colectomy-free survival, and it appears to be associated with a high rate of serious adverse events including serious and sometimes fatal infections.[21]

Tacrolimus, which has better oral bioavailability than cyclosporine, may be a reasonable alternative to the aforementioned options. In a Japanese randomized trial comparing low-trough level tacrolimus (5-10 ng/mL) to high-trough level tacrolimus (10-15 ng/mL) and to placebo, the rates of clinical improvement, clinical remission, endoscopic improvement, and endoscopic remission were significantly higher for the treatment arm randomized to the high-trough level arm.[22]

Surgical options for ulcerative colitis include total proctocolectomy with Brooke ileostomy and total proctocolectomy with ileal pouch-anal anastomosis. In the acute severe colitis setting, the latter is typically offered as a 3-stage rather than 2-stage procedure. Such an approach is associated with reduced postoperative complications. Disappointingly, colectomy rates in the acute severe colitis setting have not changed over the past 40 years (since the advent of the Oxford regimen). A 2007 meta-regression of numerous studies of severe UC found that the mean weighted colectomy rate was 27% and there had been no change over time.[4] The mortality rate for acute severe colitis was 1%. A landmark study of the Nationwide Inpatient Sample by Kaplan and coworkers found that only about 30% of the colectomies performed in U.S. hospitals for ulcerative colitis were proctocolectomies with ileal pouch-anal anastomosis (IPAA), and this was most frequently performed at centers with the highest volume of colectomies.[23] In that same study, it was noted that there was an inverse relationship between postoperative mortality and colectomy volumes. Centers with the lowest volume of colectomies had a postoperative mortality of 4%, whereas the highest volume centers had a postoperative colectomy mortality of only 0.7%. Emergency or urgent colectomy had a postoperative mortality of 5.4%, while mortality associated with elective colectomy was 0.7%.[23]

We presented our experience at Mayo Rochester with severe ulcerative colitis in preliminary form.[24] Between 1997 and 2006, a total of 281 patients were hospitalized with acute severe colitis. The in-hospital colectomy rate was 44%. In multivariate analysis, predictors of colectomy included prior hospitalization for UC, previous need for steroids, a hemoglobin on admission of <12 g/dL, endoscopic severity with a Baron score of 3 or 4, and body mass index of <25 kg/m2.[24] Only 30% of those treated with cyclosporine were able to avoid colectomy, whereas 63% of those treated with infliximab could avoid in-hospital colectomy.

Putting this all together, one should exclude superinfections early on, get the colorectal

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surgeon involved early, treat with intravenous corticosteroids, assessing response at day three with a view to initiating salvage therapy or proceeding with colectomy if no clinical response by day five.[25,26] ■

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