Management of Acute Severe Colitis in Children With Ulcerative Colitis in the Biologics Era
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BACKGROUND AND OBJECTIVE: Approximately one-third of children with ulcerative colitis will experience at least 1 attack of acute severe colitis (ASC) before 15 years of age. Severe disease can be defined in children when Pediatric Ulcerative Colitis Activity Index is >65 and/or ≥6 bloody stools per day, and/or 1 of the following: tachycardia, fever, anemia, and elevated erythrocyte sedimentation rate with or without systemic toxicity. Our aim was to provide practical suggestions on the management of ASC in children. The goal of medical therapy is to avoid colectomy while preventing complications of disease, side effects of medications, and mortality.

METHODS: A systematic search was carried out through Medline via PubMed to identify all articles published in English to date, based on the following keywords “ulcerative colitis,” “pediatric ulcerative colitis,” “biological therapy,” and “acute severe colitis.” Multidisciplinary clinical evaluation is recommended to identify early nonresponders to conventional treatment with intravenous corticosteroids, and to start, if indicated, second-line therapy or “rescue therapy,” such as calcineurin inhibitors (cyclosporine, tacrolimus) and anti-tumor necrosis factor molecules (infliximab).

RESULTS: Pediatric Ulcerative Colitis Activity Index is a valid predictive tool that can guide clinicians in evaluating response to therapy. Surgery should be considered in the case of complications or rapid clinical deterioration during medical treatment.

CONCLUSIONS: Several pitfalls may be present in the management of ASC, and a correct clinical and therapeutic approach is recommended to reduce surgical risk.
therapy is recommended, with close collaboration between medical and surgical teams.\textsuperscript{8} The multidisciplinary approach (surgeon, pediatric gastroenterologist, infectious diseases physician, nutritionist) is an important issue for appropriate management. Adequate knowledge and proper use of the major categories of immunosuppressant medications (corticosteroids [CS], thiopurines, biologics, and calcineurin inhibitors) with details including indications, typical doses, and efficacy are essential. Often the risk of surgery or complications is related to the improper use of these agents, with mistakes in route of administration, timing, and dosages used. We present a review of current literature along with a synthesis on the ASC management in hospitalized pediatric patients.

**METHODS**

The aim of the current review is to present an update of the definition, clinical presentation, and therapy of ASC in hospitalized pediatric patients. A systematic search was carried out through Medline via PubMed (http://www.ncbi.nlm.nih.gov/pubmed) to identify all articles published in English, to date, on the basis of the following keywords: “ulcerative colitis,” “pediatric ulcerative colitis,” “biological therapy,” and “acute severe colitis.”

**RESULTS**

**Disease Definition**

By adapting the 1955 Truelove and Witts criteria,\textsuperscript{9} the European Crohn’s and Colitis Organization statement has defined ASC in adults as an exacerbation with at least 6 bloody daily stools and 1 of the following: tachycardia (>90 beats/min), temperature >37.8°C, anemia (hemoglobin <10.5 g/dL), or an elevated erythrocyte sedimentation rate (>30 mm/h).\textsuperscript{10} For pediatric patients, a new score of clinical disease, the Pediatric Ulcerative Colitis Activity Index (PUCAI) has recently been validated.\textsuperscript{11} An acute attack may manifest severely with onset of clinical relapse of disease,\textsuperscript{12} accompanied by local or systemic complications such as massive hemorrhage, toxic megacolon, and multiorgan failure; in some cases, this condition is defined as fulminant colitis.\textsuperscript{13} The presence of metabolic alkalosis, gaseous distension of the small intestine (signaling incumbent megacolon), and deep ulcers visible on endoscopy are poor prognostic factors.\textsuperscript{14} Finally, the persistence of elevated C-reactive protein (CRP) levels (>45 mg/L), and diarrhea (>3 evacuations/day) in the third day of an intensive regimen may be associated with a high risk (85%) of colectomy in the short-term.\textsuperscript{15} UC with ASC is defined in children as PUCAI score >65. Abdominal examination should include palpation for abdominal tenderness, organomegaly, rebound, or guarding. Rectal examination with investigation of the perianal region and/or the presence of blood in the rectum after digital examination is an important part of the initial evaluation. Common pitfalls in the initial workup of ASC include lack of evaluation for exclusion of acute infections or toxic megacolon before use of anti-inflammatory agents. *Clostridium difficile* infection is more common in inflammatory bowel disease (IBD) patients than in the normal population, with a reported increase in the incidence of infection in individuals with IBD.\textsuperscript{16} In a single-center study, Ananthakrishnan et al\textsuperscript{17} found an increase in the incidence of *C difficile* infection in hospitalized adult patients with UC (18.4/1000 in 1998 vs 57.6/1000 in 2004). Furthermore, in the setting of *C difficile* infection, there is a reported 6.6-fold increase in the risk of colectomy compared with those with *C difficile* infection but no IBD.\textsuperscript{18} Hence, it is crucial that stool samples be assayed for *C difficile* cytotoxin (both A and B) and cultured for bacterial pathogens.

The pathogenic role of the cytomegalovirus (CMV) in UC is unclear. The prevalence of CMV in intestinal tissue (ie, CMV disease) and not in blood (ie, CMV infection) varies in ASC from 5% to 81%, depending on the population being studied and the laboratory methods used for viral detection.\textsuperscript{19} Clinical suspicion of CMV viremia should be directly suspected when IBD patients present with prominent systemic symptoms, especially fever, lymphadenopathy, splenomegaly, leukopenia, and mild hepatitis.\textsuperscript{20} However, CMV colitis need not present such features. Criscuoli et al reported that CMV may be a cause of refractory UC in an adult population, with detection in histologic specimens of 11 patients (46%) with toxic megacolon compared with 2 (9%) severe UC matched controls ($P = .0078$) and 7 (14%) unmatched controls ($P = .003$).\textsuperscript{21} For instance, CMV infection does not need to be excluded in all children with ASC but only those with PUCAI >45 on the third day after presentation. Diagnosis requires demonstrating CMV in colonic tissue with processed biopsies for hematoxylin-eosin and immunohistochemistry and/or, if available, CMV DNA real-time polymerase chain reaction. The cutoff value for CMV DNA has yet to be identified, but values >250 copies/mg tissue seem to predict resistance to steroids. The treatment recommended is IV ganciclovir 5 mg/kg twice daily for 14 days, with remission rates from 67% to 100%.\textsuperscript{22} Therapy with appropriate antiviral drugs can be considered in addition to immunosuppressive therapy in ASC. Toxic megacolon is defined as the presence of symptoms such as severe pain, abdominal distention, altered level of consciousness, guarding or rigidity, fever, tachycardia, dehydration, electrolyte...
The increased risk is for thrombophlebitis, intracranial venous sinus thrombosis, Budd-Chiari syndrome, and portal vein thrombosis in patients with UC.23 Clinical monitoring in this first phase should include assessment of symptoms, frequency of bowel movements, presence of blood in stools, abdominal pain, temperature, pulse, abdominal tenderness, biochemical testing (blood count, inflammatory markers, biochemistry), and radiologic monitoring.24

Steroid Therapy

The use of CS for the induction of remission in UC was first described in 19559 and since then has been the mainstay for induction of remission in moderate to severe UC. Methylprednisolone is used more frequently than hydrocortisone for minor mineralocorticoid effects with a suggested dosage of 1 to 2 mg/kg, up to a maximum of 60 mg/day.25,26 Approximately one-third of patients with ASC are unresponsive to first-line therapy with IV CS; identifying predictive factors of nonresponse is still a diagnostic clinical challenge. Adult randomized controlled trials of IV steroids are lacking, but average colectomy rate is low.6,27 To date, 4 small retrospective studies (44 patients in total) and 1 large prospective study of 128 children have reported the short-term response rate to CS therapy in pediatric severe colitis.6,7 Similar to adults, in prospective studies, IV CS are also considered first-line therapy for ASC in the pediatric population.28 Despite the predominance of extensive disease in children with UC, data concerning severe pediatric UC are sparse. Turner et al reviewed rates and predictor factors of response to IV CS therapy in a single-center cohort with long-term follow-up. In their study, 99 children were evaluated for treatment of severe UC with measurement of associated clinical, laboratory, and radiographic data. Predictors of CS response were analyzed using univariate and multivariate analyses at days 3 and 5 of therapy. In this cohort of patients from the prebiologics era, 53% did not respond to therapy, with associated nocturnal stools and high PUCAI of >45 at 3-day follow-up. These were considered important predictors and were associated with CS failure.29 In clinical practice, patient response is assessed by improvement in symptoms (reduced bowel frequency, reduced urgency, improved stool constituency, reduced abdominal pain and rectal bleeding) and in blood test parameters (CRP, erythrocyte sedimentation rate, and platelet count). It was suggested that at day 5, careful assessment be made of the clinical response, and in cases of clear nonresponders, the decision should be made to consider step-up therapy.29 Steroids, especially in a pediatric population, carry a significant side-effect profile and can distort metabolic activity in a multitude of organ systems. While on high-dose steroid therapy, there is a high risk of developing opportunistic infections and other side effects; hypernatremia, hyperlipidemia, and metabolic bone disease have been reported.8 Common pitfalls in steroid therapy include the use of low doses (<1 mg/kg/day to induce remission, or giving prolonged therapy beyond 5 to 7 days, despite poor clinical response (PUCAI >70 at 5 days of therapy). In these cases, second-line therapy with immunomodulators should be started immediately. There is no evidence supporting bowel rest in patients with ASC nor regarding elimination diets. In a small adult study in UC patients, McIntyre et al showed no differences in clinical outcome between patients receiving parenteral or enteral nutrition.30

Second-Line or Rescue Therapy

In patients who are nonresponsive to IV CS, initiation of second-line/rescue therapy is indicated. This generally consists of various medical therapeutic options including calcineurin-inhibitors (cyclosporine, tacrolimus) and anti–tumor necrosis factor (TNF)-α (infliximab) agents. These therapies can induce a response in ~70% of patients.31 The increased use of second-line therapy is due not only to the effectiveness of these drugs but also to the fact that many surgeons prefer to control an acute attack of colitis with medical therapy and intervene at a later time.32 A child with a PUCAI >45 after 3 to 5 days from starting IV CS is defined as a nonresponder and should be prepared for second-line therapy. In this case, it is necessary to discuss treatment options with the family, have a surgical consultation and tuberculosis screening, perform sigmoidoscopy (on the third or fourth day) to exclude infection (CMV and C difficile), and search for chronic changes along with granulomatous inflammation. CRP values should be monitored because high values have some predictive value26 for disease outcome and poor treatment.
response. PUCAI >65 on day 5 of IV CS predicts nonresponse to therapy with a specificity of 94% and a positive predictive value of 100%, representing an indication to start second-line therapy.33 In patients with PUCAI scores between 35 and 64 on day 5 of treatment with IV CS, rescue therapy should always be considered; however, many clinicians wait another 2 to 3 days before assessing response to IV steroid therapy. Those with PUCAI <35 points on day 5 are unlikely to require second-line therapy by discharge26 (Fig 1).

**Infliximab**

Infliximab is a chimeric monoclonal antibody to human TNF-α that is known to play an important role in the inflammatory pathogenesis of UC. It is constructed by linking the variable regions of a mouse antihuman TNF monoclonal antibody to human immunoglobulin G1 with light k-chains.34 Six case series have reported the use of infliximab in children with ASC (126 in total), with pooled short- and long-term response rates of 75% and 64%, respectively. Short-term and 1-year colectomy rates have declined since the use of infliximab in children with ASC to 9% on discharge and 19% by 1 year.7 Initial infliximab dosage is 5 mg/kg over 2 to 4 hours; subsequent doses are given 2 and 6 weeks after the initial infusion. Some centers use higher doses (10 mg/kg) or infuse the second dose after 7 to 10 days (maintenance therapy can be given every 8 weeks after induction, if clinically indicated).26 Before treatment, it is important to perform infectious disease screening as follows: documentation of negative tuberculosis testing (via tuberculin skin testing or the QuantiFERON-TB Gold assay) and chest radiograph (if indicated by equivocal/positive results on tuberculosis testing), varicella immune status, and hepatitis B and C infection status via serology. It is necessary to evaluate vital signs frequently during the duration of infusion.24 If a patient has previously failed an adequate trial of thiopurine therapy, then infliximab may be preferred, as indicated in Fig 1, because it can be used as a maintenance regimen, unlike cyclosporine or tacrolimus, which are both typically given for 3 to 4 months to bridge therapy to thiopurines.

Eidelwein et al35 showed an initial short-term response to infliximab in pediatric UC: 75% had complete resolution of symptoms, and 25% improved after initial infusion; many of these patients continued to respond in the subsequent 6 months, but one-third of children underwent colectomy. The authors concluded that infliximab is a valid alternative therapy to cyclosporine or colectomy in patients requiring chronic CS therapy or not responding to 6-MP or azathioprine. In the pediatric population, time of response can be considered at the second week mark. One of the common pitfalls in the use of infliximab is starting anti-TNF-α therapy before excluding CMV, hepatitis B and C, tuberculosis infection, and toxic megacolon. Additionally, it is important to avoid underdosing of infliximab (initial recommended dose of at least 5 mg/kg) or improper use of infliximab therapeutic regimen during maintenance.

**Cyclosporine**

Cyclosporine acts mainly by binding to the cytosolic protein cyclophilin...
of T-lymphocytes, thereby inhibiting calcineurin, which is responsible for activating the transcription of interleukin-2. Pediatric cyclosporine data come from 8 retrospective case series (total of 94 children) in which the rate and adverse events were similar to those reported in adults.7,37 The pooled short-term response was 81%, but only 39% avoided colectomy in the long-term.7 Heterogeneity in the definition of disease activity, concomitant therapies, follow-up period (1–5 years), dose, and route of administration (half started with oral therapy) limit interpretation of these combined studies. The better oral therapy) limit interpretation of these combined studies. The better long-term success rates were, in part, related to the introduction of azathioprine. Treem et al18 evaluated 14 patients in a pediatric study with fulminant colitis treated with cyclosporine; short-term response was 78%, similar to adult studies, but for 7 of 11 patients initially responding to cyclosporine, colectomy was necessary after 1 year. Recommended initial dose is 2 mg/kg/day continuous IV infusion. Once remission is achieved, conversion to oral therapy 5 to 8 mg/kg/day is suggested, stopping the medication after 3 to 4 months.26 The trough levels used for monitoring range from 150 to 300 ng/mL. Before treatment, it is important to carry out the following: measure blood pressure; perform blood tests such as creatinine, glucose, electrolytes, liver profile; and test for and treat hyponatremia to decrease risk of neurotoxicity.26 Widespread use of cyclosporine has been tempered by potentially serious side effects, including nephrotoxicity, neurotoxicity (manifested as paresthesias, tremors, and seizures), serious infections (dose and hypocholesterolemia dependent), hypomagnesemia (if serum magnesium <1.5 mg/dL, the dose of cyclosporine should be reduced), hypertension (can be seen in up to 40% of subjects and usually responds to calcium channel blockers), hypertrichosis, headache, hyperkalemia, and, rarely, death.39 The use of cyclosporine or combination immunosuppressive agents is associated with reports of Pneumocystis jiroveci pneumonia, and therefore, routine use of trimethoprim-sulfamethoxazole for prophylaxis is recommended.40

The most adverse events secondary to cyclosporine use appear to be less frequent if oral administration is used.41 Monitoring should be carried out every second day during induction, weekly for the first month, and then monthly. This should consist of the following: drug levels (starting after the third dose), creatinine, glucose, electrolytes (including magnesium), lipid levels, blood pressure, and neurologic symptoms.26 Common problems in the administration of cyclosporine therapy in children with ASC include not using initial parenteral therapy (oral therapy can be started when remission is achieved) and failure to monitor and maintain therapeutic blood levels of cyclosporine.

Tacrolimus

There are few data available in the current literature on the use of oral tacrolimus in the short-term treatment of pediatric steroid-dependent/refractory UC. Watson et al retrospectively reviewed the results of 46 children with steroid-refractory colitis treated with tacrolimus. Oral tacrolimus was initiated at a dose of 0.1 mg/kg twice a day and titrated to yield trough levels of 10 to 15 ng/mL for induction and 5 to 10 ng/mL once in remission. Ninety-three percent of patients were discharged without undergoing surgery and the probability of avoiding colectomy after starting tacrolimus was 40% at 26 months.42 We report the published experience from our group of 6 pediatric steroid-refractory patients with moderate/severe UC who were treated with tacrolimus (0.1 mg/kg/dose twice daily) achieving blood levels between 7 and 10 ng/mL. Response was evaluated by using PUCAI scores, and all patients responded within 1 to 2 weeks. Subsequently, the patients were switched to thiopurine.43

Infliximab Versus Cyclosporine

No pediatric trials comparing cyclosporine and infliximab in ACS have been published to date. Adult data suggest that any therapeutic decision should be individualized.44 The CYcloSporine versus InFliximab (CYSIF) trial has randomized 111 thiopurine-naive patients with severe UC after 5 days of IV steroids to IV cyclosporin (2 mg/kg/day followed by 4 mg/kg/day orally) and infliximab (5 mg/kg IV infusion at 0, 2, and 6 weeks). Patients who responded at day 7 received oral azathioprine and tapered steroids from day 8. Response to treatment at day 7 was reported in ~85% patients in both groups. Colectomy rates at day 98 were also similar between cyclosporin and infliximab (18% vs 21%, P = .66). Treatment failure at day 98 was also similar, seen in 60% patients in the cyclosporin group versus 54% in the infliximab group. There was no clear evidence of superiority of either therapy over the other.45 We suggest that in patients naive to thiopurine therapy, initiation of IV cyclosporine should be followed by 3 months of oral therapy, with subsequent introduction of azathioprine. In patients who present with severe episodes of UC during azathioprine maintenance therapy, the use of infliximab may be considered as maintenance therapy. A recent retrospective, single-center study from Asia46 demonstrated, in an adult population, that infliximab seems to be more effective than cyclosporine in terms of colectomy rate in the univariate analysis. At 12 months, the rate of colectomy was 30% and 3% in cyclosporine and the infliximab groups, respectively (P = .034). The strategy of switching
Mechanism of action: Calcineurin inhibitor

Dose: IV 2 mg/kg/day. Once remission is achieved, convert to oral therapy 5–8 mg/kg/day. Stop medication after 3–4 mo.

Drug levels: Trough drug levels used for monitoring range from 150 to 800 ng/mL.

Toxicity/side effects: Nephrotoxicity, paresthesias, tremors, and seizures in the setting of hyponcholesterolemia (<120 mg/dL) and hypomagnesemia (<1.5 mg/dL), serious infections, hypertension, hypertrichosis, headache, hyperkalemia, and rarely, death.

Tests before and during treatment: Measure blood pressure and blood tests including creatinine, glucose, electrolytes, liver profile, lipid levels, and drug levels.

Table 1: Drugs Used in “Rescue Therapy” for Pediatric UC Patients With ASC

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcineurin inhibitor</td>
<td>IV 2 mg/kg/day. Once remission is achieved, convert to oral therapy 5–8 mg/kg/day. Stop medication after 3–4 mo.</td>
<td>Oral 0.1 mg/kg/day. Stop medication after 3–4 mo.</td>
<td>Anti-TNF-α</td>
</tr>
<tr>
<td>Dose</td>
<td>Calcineurin inhibitor</td>
<td>Initial trough drug levels of 10–15 ng/mL, and then 5–10 ng/mL once remission achieved.</td>
<td>Initial dosage is IV 5 mg/kg over 2–4 h; subsequent doses given 2 wk and 6 wk later. Maintenance therapy can be given every 8 wk after induction, if clinically indicated.</td>
</tr>
<tr>
<td>Drug levels</td>
<td>Trough drug levels used for monitoring range from 150 to 800 ng/mL.</td>
<td>Hyperglycemia, hypomagnesemia, neurotoxicity, and hypertension.</td>
<td>A cutoff value of 0.5 μg/mL was defined as clinically relevant. Less than 0.5 μg/mL was associated with a sensitivity of 86% and a specificity of 85% for identifying patients with a loss of response.</td>
</tr>
<tr>
<td>Toxicity/side effects</td>
<td>Nephrotoxicity, paresthesias, tremors, and seizures in the setting of hyponcholesterolemia (&lt;120 mg/dL) and hypomagnesemia (&lt;1.5 mg/dL), serious infections, hypertension, hypertrichosis, headache, hyperkalemia, and rarely, death.</td>
<td>Documentation of negative tuberculosis testing and chest radiograph and immunity against varicella and hepatitis B and C.</td>
<td></td>
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<td>Tests before and during treatment</td>
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Surgery and a Time-Limited Approach

A time-limited approach with assessment of predictors of response to therapies and close collaboration between gastroenterologists and surgeons is necessary to ensure optimal management with reduced risks of mortality. It is important to consider colectomy in patients with PUCAI scores >65 at 11 to 14 days after start of rescue therapy (Fig 1). Surgery is unavoidable in these patients, and time delay in nonresponders to medical therapy is associated with an increased risk of postoperative complications.35 Indications for surgery, other than ASC, include toxic megacolon, perforation, severe hemorrhage, or significant clinical deterioration during medical therapy. Although in general, medical rescue therapy should be considered as first-line treatment in steroid-refractory ASC, colectomy is still a cornerstone of any proposed management algorithm.48

The easiest classification scheme divides indications for surgery into 2 categories: emergency and elective surgery. Emergency surgery is performed in patients with toxic megacolon, perforation, massive hemorrhage, sepsis, or fulminant disease without adequate control with intense medical therapy.49 In emergency conditions, the primary surgical strategy is to address the complications of disease by removing the diseased colon and constructing an ileostomy while leaving the rectum in situ. This procedure is known as subtotal colectomy with end ileostomy. By leaving the rectum in situ, a future restorative procedure (ileal pouch-anal anastomosis) is required.50 A 3-stage procedure should be considered in a pediatric population with protective ileostomy, with anastomotic leaks being the most important short-term complications reported.26

CONCLUSIONS

Between 15% to 30% of pediatric UC patients will have an ASC attack, often at the time of disease onset. This condition requires hospital admission and standard intensive therapy. A lack of response to first-line therapy after 3 to 5 days should induce consideration of second-line/rescue medical therapy along with consideration of surgery if indicated. Management of ASC is multidisciplinary, with intensive steroid treatment being the mainstay of medical therapy (Table 1). The use of a specific salvage therapy in pediatric ASC still depends on many factors with no specific guidance currently reported. Delaying surgery, especially in early-onset UC (in children <3 years of age) is associated with increased mortality. Close collaboration between pediatric gastroenterologists and surgeons is needed to ensure the best management of patients with ASC.

ABBREVIATIONS

ASC: acute severe colitis
CMV: cytomegalovirus
CRP: C-reactive protein
CS: corticosteroid
IBD: inflammatory bowel disease
IV: intravenous
PUCAI: Pediatric Ulcerative Colitis Activity Index
TNF: tumor necrosis factor
UC: ulcerative colitis
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