Treatment of Acute Severe Ulcerative Colitis

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Case

A 13-year-old boy was previously well until he acutely developed non-bloody diarrhea while on a skiing vacation. The following day he continued to have nausea, vomiting, and diarrhea, and started a clear liquid diet. On day 3 of this acute illness, he continued to pass 6–8 liquid stools daily and began to notice red blood in the stool. He was treated in the local emergency room with intravenous fluids and discharged. Stool cultures for enteric pathogens, including *Escherichia coli* 0157, ova, parasites, and *Clostridium difficile* were all negative. His white blood cell count (WBC) was 15,900, hemoglobin 13 g/dL, and hematocrit 37%. Liver function tests, amylase, and lipase were all normal. C-reactive protein (CRP) was elevated at 25 mg/dL.

On day 6 of the illness, he noted increased bloody diarrhea and was admitted to the local hospital. Despite being kept nil per os (NPO), he continued to pass 3–4 loose, grossly bloody stools daily. On the seventh day of the illness, he became febrile to 39 °C and continued to pass 5–6 bloody stools daily. His albumin was decreased at 2.2 g/dL. He was transferred to a tertiary care facility.

On transfer, his vital signs were stable and he was afebrile. His weight was 46 kg. He appeared pale but was resting comfortably. He had no oral ulcers. His chest and cardiac examinations were normal. His abdomen was soft with diffuse but mild tenderness without guarding or rebound tenderness. He had no organomegaly. Upon admission, an upper endoscopy was normal, but the ileocolonoscopy revealed pancolitis (Fig. 36.1) with normal-appearing terminal ileum, consistent with ulcerative colitis. His Pediatric Ulcerative Colitis Activity Index (PUCAI) score was 65. He was made NPO, given intravenous fluids at 1.5 times maintenance, and started on intravenous methylprednisolone sodium succinate 20 mg every 12 h. Repeat stool analysis was negative for enteric pathogens. Biopsies of the colon showed moderate-to-severe chronic pancolitis without evidence of granulomas, and biopsies of the terminal ileum were normal. Electrolytes were monitored daily and corrected as necessary; hematocrit was maintained over 30% with packed red blood cell transfusions; albumin was replaced with salt-poor albumin (1 g/kg) when below 3.0 g/dL. After 3 days of intravenous corticosteroids, his PUCAI was 55. Because of ongoing diarrhea and bleeding, a peripherally inserted central catheter (PICC) was placed for nutritional support and total parenteral nutrition was started. His PUCAI score on day 5 of intravenous corticosteroids was 60. Options for rescue therapy were discussed with the patient and family, and the pediatric surgery team was consulted. On hospital day 6, he was given 10 mg/kg of infliximab intravenously. Over the next 2 days, stool output decreased; he was restarted on oral feedings and was dis-

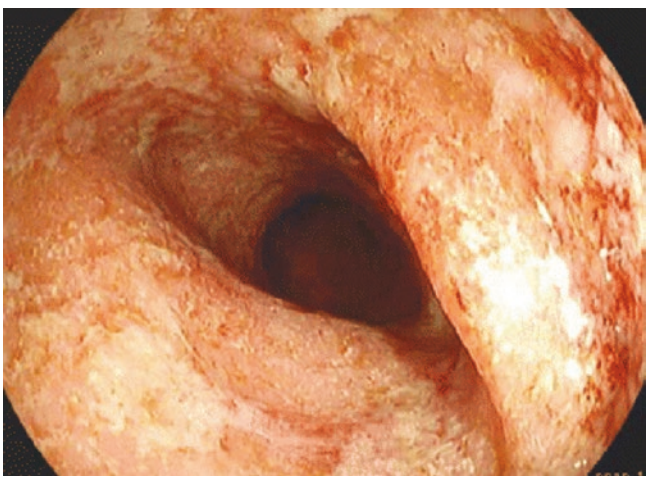

Fig. 36.1 Sigmoid colon: Diffuse inflammation with loss of vascular pattern and ulceration, typical of the pattern seen in ulcerative colitis

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charged on day 10. He returned in 2 weeks for his second infliximab infusion, passing formed stools without visible blood, and a prednisone taper was started.

He continued to do well, and maintenance infliximab therapy was continued after induction therapy was complete. Approximately 7 months later, hematochezia and abdominal cramping returned 6 weeks following an infliximab dose. The infliximab trough concentration was 9 μg/mL, and the presence of anti-infliximab antibodies could not be determined. Stool cultures were negative for enteric pathogens, and *Clostridium difficile* testing was also negative. Oral prednisone was started, but symptoms did not improve. He was passing 10–12 grossly bloody liquid stools daily, with three nocturnal stools with peridefecatory cramping and fecal urgency. He was admitted to the hospital, made NPO, and started on intravenous methylprednisolone sodium succinate 20 mg every 12 h. On day 3, his PUCAI score was 60. A sigmoidoscopy was performed that revealed severe proctitis. Rectal biopsy showed severely active chronic colitis without evidence of granulomas, and immunohistochemistry for cytomegalovirus (CMV) was negative. A 10 mg/kg dose of infliximab was given (6.5 weeks following the previous dose) without clinical improvement. He developed a fever of 38.5 °C, and intravenous ampicillin, gentamicin, and metronidazole were started. Total parenteral nutrition was started on day 4. On day 6 of intravenous steroids, his stool output was >2 L, and he required a blood transfusion for symptomatic anemia. His C-reactive protein was 10 times the upper limit of normal. On day 9 of the hospitalization, he underwent a total abdominal colectomy and ileostomy. He was discharged 6 days later and subsequently returned for completion of the colectomy, creation of a J-pouch with ileostomy reversal, and ileal pouch-anal anastomosis (IPAA).

Introduction

The clinical course of ulcerative colitis (UC) in children is unpredictable. Compared to patients with adult-onset disease, children with UC have more extensive disease and often a more severe course, characterized by higher rates of corticosteroid use and shorter time to surgery [1, 2].

Severe exacerbations of UC are common in both children and adults and cause significant morbidity. These exacerbations can occur both at disease onset and as relapse in patients with established disease.

In 2008, the European Crohn's and Colitis Organization (ECCO) defined acute severe colitis (ASC) in adults as an exacerbation with more than six bloody stools per day with at least one of the following: tachycardia (>90 b/min), temperature >37.8 °C, anemia (hemoglobin <10.5 g/dL), or an erythrocyte sedimentation rate (ESR) >30 mm/h [3]. In children, ASC is generally defined by a Pediatric Ulcerative Colitis Activity Index (PUCAI) score ≥ 65 [4], a cutoff that has been validated in independent cohorts and has predictive value with regard to response to intravenous corticosteroid (IVCS) therapy [5, 6] (see Chap. 46, Appendix 3.2 for more details regarding PUCAI scoring). In adults, fulminant colitis has been defined by >10 stools per day with continuous bleeding, abdominal tenderness and distension, systemic toxic symptoms such as fever and anorexia, and blood transfusion requirement; this can progress to toxic megacolon with severe colonic distension (>6 cm), hypotension, altered mental status, and high mortality [7]. While colonic dilation is a hallmark of current or impending toxic megacolon (TMC), precise criteria for TMC in children have not been established. One study showed that in children ≥10 years of age, a transverse colon diameter ≥ 5.6 cm was suggestive of TMC [8], while in children younger than 10 years of age, a diameter > 4 cm is concerning for toxic megacolon [9].

The frequency of ASC in children with UC is not fully known, but it is suggested that rates are as or even higher than the rates in adults. For example, over a 3-year period, in the greater Toronto area, it was estimated that 28% of all children with UC developed a severe exacerbation requiring hospitalization for intravenous corticosteroids before the age of 15 [10]. Colectomy rates have decreased significantly since the introduction of biological agents to treat ulcerative colitis [11]. A retrospective European and North American study of 5-year outcomes in children with ASC demonstrated that about one-third of patients had colectomy. Children with new-onset disease who had oral corticosteroids within 3 months of admission, elevated ESR and hypoalbuminemia were more likely to have a colectomy. These data were obtained prior to therapeutic drug monitoring which could change outcomes [12].

The remainder of this chapter addresses the management and ASC in children.

Initial Management

ASC is a serious and potentially life-threatening exacerbation of pediatric UC. As such, care for patients with ASC should be in the hospital setting so that frequent monitoring of clinical status, disease progression, and potential complications can take place. The goals of management are medical stabilization, treating exacerbating factors such as certain infections and implementing a stepwise active treatment approach typically beginning with intravenous corticosteroids (IVCS) in order to control gastrointestinal hemorrhage while avoiding/limiting complications from the disease and/or therapy. Response to therapy should be frequently reassessed by a multidisciplinary team of providers, including, in many cases surgeons with experience in IBD, in order to help guide plans for subsequent treatment.

The initial management of ASC includes a complete history and physical examination, beginning with the assessment of vital signs and general appearance which may reveal signs of systemic toxicity such as hypotension, fever, significant tachycardia, or altered mental status. Abdominal tenderness should be assessed, keeping in mind that tenderness and even colonic perforation and peritoneal signs may be masked in patients on high-dose corticosteroids. The absence of bowel sounds is an ominous prognostic indicator. Frequent reassessment is necessary as progression to fulminant disease may be rapid. A PUCAI score should be calculated at the onset of symptoms and then daily during the exacerbation until improvement and disposition. A PUCAI score over 65 correlates with severe disease. This validated scoring system not only gives the provider an idea of the general well-being of the child but also predicts response to IVCS and helps guide the timing of subsequent "rescue" therapy [6].

Hospitalized patients with ASC should have intravenous access and be fluid-resuscitated to assure adequate hydration. Laboratory studies including a complete blood count, serum electrolytes, albumin, ESR, and CRP should be obtained and repeated frequently. Despite the lack of randomized controlled clinical trials to provide evidence-based guidance for optimal therapy, expert opinion suggests that mucosal healing is best achieved by keeping the hematocrit over 30%, the albumin over 3 g/dL, and the electrolytes in the normal range. Although not evidence-based, in theory, avoiding anemia and hypoalbuminemia may enhance the delivery of oxygen to the intestinal tissues and improve mucosal blood flow. Hypoalbuminemia was identified as a predictor of long-term colectomy [12]. Normal electrolytes decrease the likelihood of stasis related to poor motility. Measurement of fecal calprotectin or lactoferrin may be a useful baseline as repeated assessment can help define response to medical therapy.

Patients with IBD are at higher risk of being diagnosed with *Clostridium difficile* infection (CDI). In one single-center study, 18.4% of children with UC had a positive polymerase chain reaction (PCR) for the toxin B gene of *C. difficile* [13]. The percentages may be even higher in hospitalized children with IBD [14]. CDI is implicated in disease exacerbation and increases the risk for complications such as colectomy in adults with UC [15, 16]. Although there is not yet direct evidence that treating CDI in children with ASC improves outcomes, testing for and treatment of CDI is current standard practice and was recommended in the joint ECCO/European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) ASC guidelines [9]. Stools should be screened for both toxins A and B. Stools should also be cultured for other potentially treatable bacterial pathogens.

Plain films of the abdomen are recommended as part of the initial evaluation of severe colitis if there are any signs of systemic toxicity that may suggest fulminant disease or TMC [9]. However, since examination findings can be masked by corticosteroid therapy, our practice is to obtain a baseline KUB on every hospitalized patient with ASC. As previously mentioned, transverse colon dilation ≥56 mm and ≥40 mm is suggestive of TMC in children ≥10 and <10 years of age, respectively. Colonic dilation has also been shown to predict response to IVCS therapy in this setting [17].

Although children with ASC may not wish to eat or drink due to their physical symptoms, unless surgery is imminent, they should be allowed to do so, since available evidence from the adult literature shows that while bowel rest may decrease stool frequency and volume, it does not improve outcomes and may worsen nutritional status [18]. If a regular diet cannot be tolerated by the third or fourth day, then enteral or parenteral nutrition should be considered, as malnutrition may impair healing and delay clinical improvement. The risks of parenteral nutrition, including complications from central venous catheters (e.g., infection, thrombus) and electrolyte abnormalities, need to be balanced with potential benefits. There is no evidence to support any particular oral diet or dietary restrictions in ASC.

Unlike in Crohn disease, antibiotics are generally not indicated in ulcerative colitis, unless there is evidence of toxicity or infection. Since bowel perforations may be silent in patients on high doses of corticosteroids, any clinical signs of infection should be investigated and treated. In well-controlled trials in adults with ASC, intravenous (IV) antibiotics including ciprofloxacin [19] and metronidazole [20] have not been shown to improve ASC outcomes when used as adjunctive therapy to corticosteroids. No large or controlled pediatric studies directly address the efficacy of antibiotics in ASC; however, the recommendations are to treat with IV antibiotics if the infection is suspected or while awaiting confirmatory testing [9]. ASC patients with fulminant disease or suspicion or diagnosis of TMC should be treated with IV antibiotics. The antibiotic agent(s) used should target enteric bacteria, including anaerobes.

In a small series of 28 children with ASC who were randomized to receive quadruple antibiotics (amoxicillin, vancomycin, metronidazole, doxycycline/ciprofloxacin) plus corticosteroids or corticosteroids alone for 14 days, the PUCAI on day 5 was lower in the antibiotic group, but five children underwent colectomy by 1 year—3 who received antibiotics and 2 who received only corticosteroids [21]. A group of adults with ASC were randomized to intravenous placebo or ceftriaxone and metronidazole along with standard care. Patients in the antibiotic group had similar CRP, partial Mayo score and fecal calprotectin and were as likely to have complete remission on day three as the placebo group. There were no differences in the likelihood of requiring a colectomy [22]. These studies, albeit with a small num-

ber of subjects raise doubts about the short-term and long-term benefit of antibiotic therapy in ASC.

Adults who are hospitalized with ASC are routinely treated with anticoagulants for venous thromboembolism (VTE) prophylaxis. Hospitalized children with IBD are also at increased risk for VTE [23]. The prothrombotic tendency in IBD is thought to be attributable to many different factors including an increase in procoagulants, a decrease in anticoagulants, thrombocytosis, as well as endothelial and immunologic factors [24]. VTE is more common in children with active IBD than in those who have the quiescent disease [25]. This risk may be augmented by the relative immobility of sick, hospitalized IBD patients. In one study, risk factors for VTE in hospitalized children with IBD included older age, central venous catheters, parenteral nutrition, and the presence of a hypercoagulable condition [23]. Children with colonic IBD appear to be at higher risk for VTE [26]. Despite this, the overall incidence of VTE in hospitalized children remains low (11.8/1000 hospitalizations) [23], and there have been no pediatric studies assessing the benefits and risks of prophylactic anticoagulation in ASC or in IBD in general. As such, the routine use of anticoagulation in children with ASC is not currently recommended [9]. However, non-invasive methods of VTE prophylaxis like frequent mobilization, adequate hydration, and pneumatic/mechanical devices are advised, as they are of low risk, even if not well supported by current evidence. It is reasonable to consider anticoagulation in patients with other risk factors for VTE, including known hereditary causes of thrombophilia, smoking, and the use of oral contraceptives. When used, anticoagulation does not seem to worsen bleeding during IBD flares.

Intravenous corticosteroids (IVCS) are the recommended first-line treatment for ASC in children. IVCS have been used for acute exacerbations of UC for more than 60 years and have been shown to reduce mortality in adults [27]. There are no randomized trials evaluating the comparative efficacy of various CS doses in children. The current recommendations for CS dosing are for 1–1.5 mg/kg/day of methylprednisolone up to 40–60 mg/day [9]. The daily dose is often divided over two daily doses. Doses above 60 mg/day have not been found to be more effective in adults with ASC [28]. More recently, a prospective pediatric cohort study which followed 283 children with ASC for 1 year concluded that an IVCS dose of 2 mg/kg/day was not more effective than doses of 1–1.25 mg/kg/day in preventing the need for salvage therapy during the hospitalization or by 1 year, although day 5 PUCAI scores were improved in the high-dose CS group before sensitivity analysis [29]. In this study, IVCS dosing was at the discretion of the provider (not randomized), but propensity matching was performed to limit bias. Interestingly, glucocorticoid bioactivity in serum did not predict response to IVCS in a study of children with ASC [30].

Not all children with ASC improve with IVCS. A systematic review found a 34% (range 9–47%) IVCS failure rate in a pooled analysis of five studies of children with ASC [31]. In the one prospective study included in the analysis, 37 of 128 children (29%) failed to respond to IVCS and required second-line treatment [6]. Multiple predictors for poor response to IVCS in children have been identified. A multicenter prospective study that followed 128 children with ASC found a response to IVCS less likely in older patients and in patients with the established disease [6]. The same study showed that after multivariate analysis, additional day 3 and day 5 predictors of IVCS failure included high stool frequency and a large amount of blood in the stool. A high CRP on day 5 also predicted CS failure. The PUCAI score outperformed other clinical indices in predicting IVCS failure on both days 3 and 5. A PUCAI score >45 on day 3 predicted CS failure with a sensitivity of 92% and a negative predictive value (NPV) of 94%, indicating a high likelihood of response if the PUCAI score is ≤45. On day 5, a PUCAI score of >70 had a specificity and positive predictive value (PPV) of 100% for CS failure, while a score of >65 has specificity and PPV of 96% and 82%, respectively. The addition of fecal calprotectin or CRP to the model did not improve the accuracy of the PUCAI score. The findings from this study and others have formed the basis of recommendations for disease monitoring and for the timing of second-line/rescue therapy in children with ASC. Additional predictors of poor response to IVCS have also been identified. A prior single-center study found that a high number of nocturnal stools and high CRP were predictive of CS failure on days 3 and 5 [10]. The presence of a megacolon, defined as a transverse colon diameter >40 mm and >60 mm in children <12 and >12 years of age, respectively, and ulceration on abdominal x-ray may also predict IVCS failure [17]. A separate study showed that day 3 interleukin (IL)-6 levels predicted IVCS failure, although this did not hold true after multivariate analysis [32]. Finally, there is limited evidence that IVCS nonresponders have decreased fecal microbial richness/diversity compared to responders, though this is not yet clinically applicable [33].

Monitoring Response to Corticosteroids

In general, monitoring for response to initial therapy begins with a careful and frequent reassessment of vital signs, stool frequency, volume, blood loss, and abdominal pain as well as changes in the abdominal examination. The validation of the PUCAI score in predicting IVCS failure has led to a suggested algorithm and the following recommendations for disease monitoring and for the timing of second-line, also referred to as "rescue" or "salvage", therapy [9]. A PUCAI score > 45 on day 3 of IVCS should initiate preparation for

second-line therapy, including discussion of potential risks and benefits with patients and families and inclusion of a surgeon with experience in IBD. A PUCAI score > 65 on day 5 should prompt initiation of second-line therapy. Patients with PUCAI scores between 35 and 65 on day 5 can continue IVCS for an additional 2–5 days, at which point further recommendations are based on the PUCAI score at that time. Patients who improve on IVCS and have a PUCAI score <35 on day 5 are unlikely to require rescue therapy before discharge [9]. Thiopurines can be considered in IVCS responders, particularly in those who were previously naive, but the therapeutic benefit is often delayed for 2–3 months; so, they have little role in the acute setting.

There is no current evidence to support the value of repeat colonoscopic evaluation in ASC patients who are improving on IVCS in the clinical setting. However, repeat sigmoidoscopy is suggested if the day 3 PUCAI score is >45 in order to search for evidence of Crohn disease such as granulomas and to exclude cytomegalovirus (CMV) colitis, which can complicate ASC and may alter therapy. While the prevalence of CMV colitis in children with ASC is not known, it is relatively common in adults with UC, particularly in those with steroid-refractory disease [34]. Mucosal biopsies should be obtained and evaluated for signs of CMV disease (deep ulcerations and viral inclusions) as well as immunohistochemistry [9]. CMV colitis should prompt an infectious disease consultation, and antiviral treatment should be considered [35]. In a small study pediatric patients who were found to be CMV-positive during hospitalization for ASC did not have an increased incidence of colectomy during admission when compared to children with ASC who were CMV-negative [36].

Medical Rescue Therapy

Patients with ASC with poor response to IVCS require rescue therapy. About one-third of children with ASC require rescue therapy before discharge from the hospital. In adults, the earlier use of rescue therapy appears to decrease mortality [37], and extending IVCS without rescue treatment beyond 14 days is unlikely to provide benefit and may increase the risk for complications, including, but not limited to, opportunistic infections, metabolic and electrolyte abnormalities, osteopenia/porosis, and psychiatric disturbance. The goals of rescue therapy are to improve symptoms and allow for the eventual discontinuation of CS. Current rescue therapy options for children with ASC include infliximab, calcineurin inhibitors (cyclosporine and tacrolimus), and colectomy. Although the data supporting these rescue therapies are primarily in CS refractory patients, these treatments are also used without IVCS in patients with contraindications or prior lack of response to CS.

Infliximab (IFX) is a monoclonal antibody against TNF-α that can induce and maintain remission in pediatric UC [37]. Pooled data from six pediatric case series (n = 126) of ASC patients treated with IFX showed a 75% (67–83%, 95% CI) response rate by the time of hospital discharge and a 64% colectomy-free rate during follow-up which ranged from a few months to a few years [31]. In one prospective study, 76% (25/33) of children with ASC refractory to IVCS had short-term responses to IFX [6]. The remaining 24% underwent colectomy. At 1 year, 55% had sustained response to IFX and 45% had CS-free sustained response, while an additional 28% required colectomy by 1 year. In a more recent retrospective study from a single center in Italy, 80% of ASC patients had short-term responses to IFX, but 50% of these patients went on to colectomy by 24 months [38]. Predictors of IFX failure may include shorter disease duration and more active disease at the time of admission and day 3 of IVCS [6]. IFX is typically dosed at 5 mg/kg at baseline and then repeated at 2 and 6 weeks following the initial dose. The pharmacokinetics of IFX in children with moderate-to-severe UC appears to be similar to that in adults [39]. However, many pediatric centers use higher doses (10 mg/kg) and/or shorter dosing intervals of IFX in ASC. The introduction of therapeutic drug monitoring has resulted in the clinical practice of adding additional doses if the IFX level is below 10. Since IFX is bound to albumin, patients who have serum protein loss in the stool are more likely to also lose IFX. While there is currently a lack of direct evidence to support this practice, some have suggested that IFX clearance may be higher in patients with acute severe disease leading to a requirement for higher dosing [40]. A recent retrospective study of children with IBD (CD and UC) showed that patients with a larger colonic inflammatory burden were more likely to require IFX dose escalation by 12 months than patients with limited or moderate disease and that 43% of patients who started at 5 mg/kg dosing did not improve with dose escalation [41]. Although this study was not limited to ASC patients, it does provide some indirect evidence that children with more extensive disease may benefit from higher IFX doses at the start of treatment. ECCO/ESPGHAN guidelines recommend IFX as the preferred rescue therapy in patients with previous thiopurine failure as IFX can also be effective as a maintenance agent in UC [9]. Prior to starting IFX, tuberculosis and Hepatitis B status should be documented.

Cyclosporine (CsA) is a calcineurin inhibitor that has been shown to be effective at inducing remission in adults with ASC [42, 43]. Support for the use of CsA in children with ASC comes from eight retrospective case series (n = 94) [31]. Pooled short-term response rates were 81% (76–86%, 95% CI), but long-term colectomy-free rates dropped to 39% (29–49%, 95% CI) in patients treated with CsA. There is heterogeneity in the eight studies with regard to CsA dose, route of administration, and duration of follow-up, which makes

interpretation difficult. CsA is generally used for 3–6 months as a bridge to maintenance therapy, often thiopurine treatment, which can take 2–3 months to become effective. CsA has not been studied as a long-term maintenance agent at UC. More prolonged use of CsA is limited by serious potential side effects such as hypertension, gingival hyperplasia, electrolyte disturbance, and renal and neurologic toxicity. Dosing is generally started intravenously and then transitioned to oral dosing (4–8 mg/kg/day) once the response is achieved [9]. Trough levels should be monitored frequently with preferred levels starting in the range of 150–300 ng/mL. Clinical response is generally seen in 5–7 days. Adult guidelines suggest that *Pneumocystis jiroveci* prophylaxis should be routinely given to patients treated with CsA, who are also treated with other immunosuppressive agents [44].

Tacrolimus, another calcineurin inhibitor, also appears effective as short-term rescue therapy for children with CS-resistant ASC. Retrospective studies report short-term response rates between 50 and 89% with long-term colectomy-free rates ranging from 0 to 40% [45–47]. The largest of these studies reported a 40% colectomy-free rate at 26 months, with most patients having been bridged to either thiopurines or IFX [45]. Hypertension (52%), tremor (46%), and hyperglycemia (35%) were common side effects of tacrolimus treatment. Initial dosing is typically 0.1 mg/kg/dose twice daily (0.2 mg/kg/day), and the dose is adjusted to reach levels of 10–15 ng/mL during induction and 5–10 ng/mL during maintenance therapy [45]. Tacrolimus may have more reliable oral absorption and may be better tolerated than CsA. Otherwise, time to response and side effects are similar to those of CsA, as is the need for *P. jiroveci* prophylaxis when used with other immunosuppressive agents.

There are no pediatric studies that directly compare the efficacy of medical rescue options in ASC. A prospective, multicenter, randomized open-label trial in adults with ASC refractory to IVCS found no difference in the efficacy of CsA and IFX [48]. A recent meta-analysis confirmed that these two treatments were equally successful in randomized trials but concluded that IFX appeared slightly more effective than CsA in nonrandomized trials [49]. Adverse events, postoperative complications, and mortality were similar with both treatments. Two small retrospective studies have compared tacrolimus and IFX rescue in adults with ACS [50, 51]. Neither study showed a difference in short-term efficacy, but the larger of the two studies showed that IFX was more effective than a tacrolimus bridge to thiopurine strategy in the longer term [51].

There is limited evidence from retrospective adult studies that a second medical rescue therapy (IFX following calcineurin inhibitor or vice versa) can prevent colectomy in ~30–70% of ASC patients following failure of a first rescue agent [52–54]. However, due to the high risk for serious toxicity with this approach, the use of a second rescue agent is not currently recommended for children with ASC until additional data on efficacy and safety can be obtained [9].

Surgery

The indications for surgical treatment in ASC are perforation, toxic megacolon, massive hemorrhage, or failure to respond to maximal medical management. However, in rare circumstances in which there are contraindications to medical rescue therapy, surgery may be considered first. The details of surgical options for UC are detailed in Chap. 41. The current surgical standard of care for UC is a restorative proctocolectomy consisting of a total colectomy, and rectal mucosectomy with ileal pouch-anal anastomosis (IPAA). This procedure can be done in one, two, or three steps. The first step in a three-step procedure includes a subtotal colectomy with ileostomy and Hartmann's pouch creation. This is followed by completion of the colectomy, rectal mucosectomy, and restorative IPAA with diverting ileostomy (step 2), and finally by ileostomy takedown reversal (step 3). In a typical two-step procedure, bowel continuity is immediately restored when the ileal pouch is formed (step 2), without a diverting ileostomy. Alternatively, the abdominal colectomy and mucosectomy may be performed with IPAA and diverting ileostomy in step 1 followed by ileostomy takedown (step 2). At some centers, abdominal colectomy and mucosectomy with IPAA may be done as a single operation [55]. The decision on which operation(s) to select is highly dependent on the experience and expertise of the surgical team.

High-dose corticosteroids have been shown to increase short-term complications such as postoperative infection [56]. Additionally, adult studies show a lower risk of IPAA leak in patients with a temporary protective ileostomy [57]. For these reasons, it is recommended that a two- or three-step procedure be considered in more complicated patients including those requiring emergent surgery, those treated with high-dose corticosteroids, or for those with significant malnutrition [9]. In a retrospective pediatric study, preoperative exposure to calcineurin inhibitors or thiopurines within 30 days of surgery or to IFX within 90 days of surgery was not associated with an increase in postoperative complications [58]. Whenever possible, efforts should be made to maximize nutritional status before surgery. Postoperative risks as well as typical outcomes should be discussed with patients and families to help form realistic goals. Additional issues that need to be discussed prior to surgery include the risk for pouchitis and potential issues with future fertility in female patients [59]. Patients also need to be aware that the risk for an eventual diagnosis of Crohn disease following restorative proctocolectomy for UC is 5–10% [60]. In addition to medical and surgical management, stress management and support for the patient and family are essential

components of the multidisciplinary approach needed to optimally care for children with ASC. Speaking with other patients/parents and a mental health evaluation should be part of the care of patients with ASC in whom surgical treatment is being considered.

Future Directions/Conclusions

Recommendations for the management of ASC in children are somewhat limited by the lack of pediatric data. Important questions remain unanswered and the rarity of ASC in children makes prospective interventional trials challenging to complete. Large, multicenter collaborative studies may be best positioned to answer some of these questions. Specific gaps in knowledge include longer-term outcomes of children with ASC, the most effective dosing regimens for rescue medications like IFX and calcineurin inhibitors, and the role of CMV in pediatric ASC. There needs to be an improved understanding of predictors of response to first-line rescue therapy which can help personalize care going forward. The role of established UC treatments like adalimumab, which has recently been approved by the FDA for ASC, and vedolizumab need to be elucidated. Despite recent improvements in medical treatment, many patients continue to require surgical intervention before discharge, and still more within the following 12 months.

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