Consensus for Managing Acute Severe Ulcerative Colitis in Children: A Systematic Review and Joint Statement From ECCO, ESPGHAN, and the Porto IBD Working Group of ESPGHAN

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OBJECTIVES: **Acute severe ulcerative colitis (ASC) is a potentially life-threatening disease. We aimed to formulate guidelines for managing ASC in children based on systematic review of the literature and robust consensus process. This manuscript is a product of a joint effort of the ECCO (European Crohn's and Colitis Organization), the Pediatric Porto Inflammatory Bowel Disease (IBD) Working group of ESPGHAN (European Society of Pediatric Gastroenterology, Hepatology, and Nutrition) and ESPGHAN.**

METHODS: **A group of 19 experts in pediatric IBD participated in an iterative consensus process including two face-to-face meetings. A total of 17 predefined questions were addressed by working subgroups based on a systematic review of the literature.**

RESULTS: **The recommendations and practice points were eventually endorsed with a consensus rate of at least 95% regarding: definitions, initial evaluation, standard therapy, timing of second-line therapy, the role of endoscopic evaluation and heparin prophylaxis, how to administer second-line medical therapy, how to assess response, surgical considerations, and discharge recommendations. A management flowchart is presented based on daily scoring of the Pediatric Ulcerative Colitis Activity Index (PUCAI), along with 28 formal recommendations and 34 practice points.**

CONCLUSIONS: **These guidelines provide clinically useful points to guide the management of ASC in children. Taken together, the recommendations offer a standardized protocol that allows effective monitoring of disease progress and timely treatment escalation when needed.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Acute severe exacerbations of ulcerative colitis (ASC) constitute a medical emergency in children and adults. The introduction of intravenous corticosteroid treatment by Truelove *et al.* (1) in 1955 dramatically reduced mortality in this otherwise life-threatening condition. Nevertheless, steroid refractoriness

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Table 1. Pediatric Ulcerative Colitis Activity Index (PUCAI)

Item	Points
(1) Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
(2) Rectal bleeding	
None	0
Small amount only, in <50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
(3) Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
(4) Number of stools per 24 h	
0–2	0
3–5	5
6–8	10
>8	15
(5) Nocturnal stools (any episode causing wakening)	
No	0
Yes	10
(6) Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of PUCAI (0–85)	

For User's guide and cutoff values for response, remission, mild, moderate, and severe disease activity, refer to the original study (37).

is common, making early recognition of ASC important, so that appropriate medical and, if necessary, surgical treatment can be provided in a timely fashion to minimize morbidity.

Adapting the 1955 Truelove and Witts' classification (1), an ECCO (European Crohn's and Colitis Organization) statement defined ASC in adults as an exacerbation with at least six bloody daily stools and one of the following: tachycardia (>90 b.p.m.), temperature >37.8 °C, anemia (hemoglobin <10.5 g/dl), or an elevated erythrocyte sedimentation rate (>30 mm/h) (2). With the validation of the Pediatric Ulcerative Colitis Activity Index (PUCAI), ASC was robustly defined in pediatric patients by a PUCAI of at least 65 points (3) (**Table 1**). This cutoff has been replicated in an independent cohort (4) and proven to predict clinically relevant outcomes of children admitted for intravenous corticosteroid therapy (5,6). The decision to admit a child with acute ulcerative colitis (UC) should follow clinical judgment on an individual basis. Some patients should be admitted with moderate–severe disease activity (i.e., PUCAI of at least 40 points) and some may be treated with a trial of oral prednisone as outpatients even with a PUCAI of >60 points. Nonetheless, the PUCAI score should be used as a general guidance for this decision, and strong consideration for immediate admission must be given when the definition of ASC is met (i.e., PUCAI of at least 65 points).

ASC in adults has been estimated to occur in 18–25% of all UC patients during ≥10 years of follow-up (7,8). The increased prevalence of extensive colitis in children makes ASC more likely. In a retrospective analysis of a population-based UC cohort, 28% of children <15 years of age required hospitalization during a period of just 3 years (5).

The pooled steroid-refractory rate in ASC across all pediatric studies has been found to be 34%, slightly higher than the pooled 29% adult rate (9,10). In the prebiological therapy era, the 1-year colectomy rate was as high as 50% in adults (11) and 61% in children (5).

The previously published pediatric guidelines on ASC are insufficiently detailed to allow the clinician to make rational decisions based on contemporary studies (12,13). We aimed to develop guidelines for managing ASC in children based on a systematic review of the literature and a robust consensus process of an international working group of specialists in pediatric inflammatory bowel disease (IBD). Selection of the working group was facilitated by an open call to all ECCO-registered members via e-mail. These guidelines have been created and endorsed by ECCO and the Pediatric Porto IBD working group of ESPGHAN (European Society of Pediatric Gastroenterology, Hepatology, and Nutrition).

METHODS

A list of 17 questions addressing management of ASC in children was developed by the steering committee and modified according to comments by the other members (**Appendix 1** online). Each question was appraised independently based on review of evidence by two group members, who then together developed a written recommendation with justification. Grading of evidence was assigned according to the Oxford Centre for Evidence-Based Medicine (**Appendix 2**). Review of evidence included both pediatric and adult data, given the paucity in some areas of specific pediatric studies (14). Electronic searches were performed in January 2010 using Medline, Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and the Cochrane Controlled Trials Register. The search strategies used are available upon request. Clinical guidelines, systematic reviews, clinical trials, cohort studies, case–control studies, diagnostic studies, surveys, letters, narrative reviews, and case series were retrieved.

Recommendations were discussed by the working group at two face-to-face meetings: during the ECCO annual meeting (Prague, February 2010) and during Digestive Disease Week (New Orleans, May 2010). The meetings were complimented by an e-mail Delphi process that together provided the forum for reformulation of recommendations until agreement was reached. All statements and practice points were supported by at least 95% of the group and in most cases reflect full consensus.

The guidelines that follow include recommendations (boxed in the text) and "practice points" that reflect common practice where evidence is lacking.

INITIAL DIAGNOSTIC EVALUATION

First, the diagnosis of UC should be confirmed, especially if ASC is the presentation of the disease, according to the accepted European and American pediatric criteria (15,16). Children who present with ASC without previous diagnosis of UC must undergo extensive workup including thorough history taking, complete stool workup, imaging of the small bowel, and sigmoidoscopic evaluation with biopsies (but not complete colonoscopy, in view of the high procedure-associated risk in this setup). Next, other contributing factors must be considered and in the appropriate clinical setting also ruled out, including enteric infection and medication-induced diarrhea (5-aminosalicylic acid (5-ASA) and antibiotics). Careful and daily evaluation of the severity of the disease is the mainstay of managing ASC, which should dictate decision making on nutrition and radiographic tests, as well as timing of treatment escalation and surgical consultation.

Associated infections

Clostridium difficile and stool evaluation (100% consensus).

1. Any child presenting with ASC should have stools screened for *C. difficile* toxins A and B and should be treated if found [Pediatric EL4, RG C; Adult EL2b, RG B]
2. Stools should also be sent for standard culture [EL4, RG C]

Practice points:

1. Four to five stool samples may have to be screened before excluding *C. difficile* infection.
2. Oral vancomycin may be the first-line choice in ASC associated with C. *difficile* because of its potential improved effectiveness. Intravenous metronidazole should be considered only if the oral route is not tolerated.
3. Stool virology testing may be performed in selected cases, such as in children with fever or vomiting as well as with non-bloody diarrhea.

The frequency and severity of *C. difficile* infection appears to be increasing, especially in patients with IBD, in both children and adults (17–19). Adults with both *C. difficile* and IBD were found to have lengthier hospitalization and a mortality rate 4 times greater than adults with either condition alone (20). *C. difficile* is the most common stool pathogen identified in adults with relapsing IBD, accounting for 6–19% of relapses (21,22). Of the 114 children hospitalized for ASC between 1991 and 2000, 15 were found to have an intercurrent infection, of whom 5 (4.4% of admissions) had infection due to *C. difficile* (5). Pascarella *et al.* (23) showed that 25% of children admitted with IBD had *C. difficile* compared with only 9% of non-IBD controls.

C. difficile infection can be identified by immunoassays or enzyme-linked immunosorbent assays for toxin A and toxin B, and by cytotoxicity assay. Assay for only one toxin fails to identify most *C. difficile* infections in pediatric IBD (24). Only ~50% of infected adults are diagnosed with a single stool sample assayed for both toxins, whereas 92% are ultimately identified by the fourth stool sample (18). Evaluation by endoscopic appearance of the colon is inadequate in IBD, in which typical pseudomembranes are commonly absent (18).

For severe cases, as in the case of ASC, a 10-day course of oral vancomycin is preferred (25). There is no clear evidence to support decreasing the dose of corticosteroids or immunomodulators, although in a retrospective survey, adults on immunomodulators with *C. difficile* appeared to have worse outcome (26). Other novel treatments recently proposed for *C. difficile* infection cannot yet be recommended for clinical practice (27).

Cytomegalovirus (CMV)(100% consensus).

Only children with steroid-resistant disease should undergo a sigmoidoscopic examination for biopsy to exclude CMV infection [Pediatric EL5, RG D; Adult EL 3b RG B]

Practice point

1. Colonic biopsies should be stained by immunohistochemistry for CMV and, if positive, appropriate antiviral therapy should be initiated in consultation with an infectious diseases specialist.

Most agree that only detection of CMV in the intestinal tissue by histopathology ("CMV disease"), and not blood ("CMV infection"), is clinically meaningful in UC. CMV infection is common in patients on steroids and associated with a high rate of steroid resistance (42–61% (28)). A case series in adults with moderate–severe colitis demonstrated frequent CMV infection during steroid therapy (as opposed to "CMV disease") that resolved spontaneously without antiviral therapy (29). There are case reports that have identified CMV also in the tissues of steroid-naive subjects (30,31). In all studies, immunohistochemistry was more sensitive than routine histological examination using hematoxylin and eosin. Therapy with appropriate antiviral therapy has been sporadically reported to improve colitis activity in infected patients (30–34).

Monitoring of disease activity during admission (100% consensus)

1. Assessment of vital signs should be performed frequently [EL2b, RG B]
2. The PUCAI score should be completed daily for predicting the clinical course during acute severe colitis [EL1b, RG B]
3. Blood tests for electrolytes, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin, liver enzymes, and complete blood count (CBC) should be measured upon admission and frequently thereafter as clinically indicated [EL2b, RG B]

Practice points

1. Endoscopic evaluation of the rectal mucosa in children should only be performed when the underlined diagnosis is unclear or to identify complications, most notably CMV colitis.
2. The risk of a full colonoscopy is too high in ASC and is not recommended.

Daily assessment of disease activity is the mainstay of managing ASC. The most significant predictor of failing medical therapy has consistently been found to be the severity of disease from the time of admission (5).

Clinical variables. Pulse rate and temperature have been shown to predict response to corticosteroids in adults with ASC (1,9). In a *post hoc* analysis on 227 children with acute severe UC, combining the data from the two largest pediatric cohorts to date (5,6), temperature on the third hospital day was statistically higher in nonresponders, but without clinical significance (36.9±0.6 vs. 37.2±0.64; $P=0.01$) and heart rate was similar (unpublished data of D.T.). On the other hand, the number of daily stools, nocturnal stools, and amount of blood have been shown to reflect disease severity, also in children (5,6,9,35,36). The PUCAI is a clinical index that incorporates these variables in one weighted score with good discriminant and predictive validity in ASC (5,6). It takes 1 to 2 min to complete and is very responsive to change (4,37) (**Appendix 1**). Its limitation is a "ceiling effect," in which once the highest score has been reached (i.e., 85 points), further discrimination in disease activity is impossible. Nonetheless it has been shown to perform well in children with ASC (5,6).

Laboratory markers. Albumin, C-reactive protein (CRP), hemoglobin, and erythrocyte sedimentation rate have been shown to have some predictive role in ASC by reflecting disease severity (1,9,35,38). Electrolytes do not have a predictive role, but form part of the definition of toxic megacolon (TMC; see section "TMC and radiography" below). If calcineurin inhibitors are given, magnesium, creatinine, and serum cholesterol should also be monitored during treatment to minimize toxicity. Fecal biomarkers (including calprotectin, lactoferrin, S100A12, and pyruvate kinase) currently have no role in monitoring disease progress of ASC, because of their low responsiveness (39). Although calprotectin, and particularly pyruvate kinase, have some predictive role in ASC, they do not add to the clinical variables outlined above (39,40).

Endoscopic evaluation. The degree of inflammation of the sigmoid colon has been correlated with treatment outcome in adults (41,42), but no similar data exist in children. Moreover, there are no data, even in adults, to suggest that the endoscopic appearance adds to the predictive value of the simple clinical variables. On the contrary, it had been shown that sigmoidoscopic appearance did not improve the validity of the Powell Tuck index (43) or the PUCAI score (3).

INITIAL TREATMENT

Corticosteroids (100% consensus)

Intravenous methylprednisolone, 1 to 1.5 mg/kg/day, is recommended to a maximum of 60 mg given in one or two divided daily doses [EL2, RG B]

Practice points:

1. Methylprednisolone is preferred over hydrocortisone because it has fewer mineralocorticoid effects.
2. Limited evidence exists to guide recommendations regarding rectal steroid treatment as adjuvant therapy in ASC. If the child tolerates enemas, they may be attempted, because a beneficial effect cannot be excluded.

Corticosteroids constitute the first-line therapy of ASC since the landmark trials of Truelove *et al.* (1,44). Intravenous steroids reduced the 1-year mortality rate from 22–75 to 7% in adults (1,45). No dose-ranging trials have been conducted in children. Two randomized, double-blind trials in adults with ASC have compared different corticosteroid regimens (46,47). Of the 31 patients without previous oral corticosteroid therapy, adrenocorticotropic hormone induced remission in 63 vs. 27% with hydrocortisone ($P=0.025$). However, in the 35 patients hospitalized after outpatient corticosteroid therapy, 53% responded in the hydrocortisone group and 25% in the adrenocorticotropic hormone group (46). Once-daily methylprednisolone 1 mg/kg was as effective as continuous infusion (47). Among adults with UC, 60 mg prednisolone once daily proved no more effective than 40 mg, but had greater toxicity (48). Similarly, 40 mg oral prednisolone as a once-daily dose was as effective as when given in divided doses (49). However, these studies were performed on ambulatory patients and the extrapolation to the acute severe setting may be inaccurate.

A meta-regression using data concerning 2,175 adult patients from 33 published studies demonstrated no variation in efficacy with dosing within the range of ≥60 mg intravenous methylprednisolone daily, whereas lower doses were seldom evaluated (9). Even high-dose pulse steroids (1 g methylprednisolone given once daily for 5 days) failed to achieve a greater than expected clinical remission rate (50), although the opposite has been recently proposed in a case series from Japan (51).

Most patients in a recent prospective multicenter pediatric cohort study of ASC received 1 to 1.5 mg/kg/day methylprednisolone up to 40–60 mg and achieved the expected response rate of 71% (95% confidence interval (CI) 63–78) without dose-response effect (6). Finally, glucocorticoid bioassay, reflecting the total steroid activity in the serum, did not predict the need for second-line therapy in children with ASC (52).

Antibiotic therapy (95% consensus)

Empiric antibiotics cannot be recommended in all children with ASC but should be considered when infection is suspected and in toxic megacolon [Pediatrics EL5, RG D; Adults EL2b, RG B]

Practice point:

1. As *C. difficile* infection is more common in ASC, a case can be made for empiric treatment pending toxin results, if *C. difficile* is locally common, especially if antibiotics have been recently prescribed.
2. Empiric antibiotic treatment should be strongly considered if the ASC is at disease presentation, pending stool *C. difficile* and culture results.

Of eight adult clinical trials (2,53), only three were explicitly in ASC (54–56), and these showed no difference in outcome when intravenous ciprofloxacin (55), metronidazole (56), or metronidazole and tobramycin (54) were used as an adjunct to steroid therapy. Of the remaining four studies of antibiotic usage in adult UC, only one showed evidence of benefit. Based on these studies, adult guidelines suggest that intravenous antibiotics should be used in ASC only if infection is considered likely (2,53). There are no publications on antibiotic usage in the treatment of pediatric ASC and thus we found no reason to diverge from the adult recommendations.

Heparin (100% consensus)

There is no specific evidence to support the use of prophylactic heparin for preventing thromboembolic complications in children with ASC [EL5, RG D]

Meta-analyses have shown that heparin treatment is not effective for inducing remission in ASC (57,58). Adult guidelines (2,59) recommend using heparin prophylactically (*not* as a therapeutic adjunct) for preventing venous thromboembolic events that are clearly increased in adults with ASC (60). Based on experience and case reports (61–63), the group acknowledged that there is likely to be an increased risk for thromboembolic events in children with UC including ASC. Even in adults, the risk seems to be age dependent. In a recent population-based case–control study, the risk of venous thromboembolic events in UC was increased across all age groups, but the absolute rate was much higher in the older population (27 deep vein thrombosis cases per 10,000 person-years in the 0–20-year-old group (odd ratio 10, 95% CI 3.4–29.3) vs. 207 per 10,000 in the >60-year-old group (64)). In a recent audit of current practice of 215 in-patient pediatric patients with UC, only 2% were given prophylactic heparin (http://ibdaudit.rcplondon.ac.uk/2008/). Therefore, the group agreed that routine heparin prophylaxis cannot be justified in children until better evidence is available to suggest that the benefit outweigh the risks.

5-ASA (100% consensus)

Interrupting 5-ASA (oral or rectal) in children with ASC is recommended upon admission. If patients are 5-ASA naive, introduction should be delayed until the recovery phase [EL5, RG D]

Oral 5-ASA preparations are effective for induction of remission in mild-to-moderate UC (65), including in children (66), but their role in ASC has not been studied. It was agreed that 5-ASA is likely to have little benefit when aggressive medical treatment is administered. Moreover, children (67) and adults (2) may rarely experience worsening diarrhea with their introduction.

Nutritional support (95% consensus)

1. Continuation of regular diet is recommended. If this cannot be tolerated, enteral, or occasionally parenteral nutrition, is appropriate [Pediatric EL4, RG C; Adults EL1b, RG A]
2. Oral feeding should be avoided when surgery appears imminent and is contraindicated in cases of toxic megacolon [EL5, RG D]

Practice points:

1. Continuous nutritional assessment, including measuring daily weight and calorie counts, is important.
2. If severe nausea and vomiting are present, or in the presence of severe abdominal pain, the patient may be unable to tolerate adequate nutrition enterally and would uncommonly require short-term parenteral nutrition.

Three clinical trials in adults showed no benefit of bowel rest in addition to corticosteroid therapy for ASC (68–70). The pooled response to medical therapy was comparable in cases and controls of the 96 adults in the three studies (22/48 (46%) vs. 27/48 (56%) respectively, $P = 0.22$).

In a small retrospective pediatric study (71), 5 of 15 children with ASC, who were treated with total parental nutrition and bowel rest, required colectomy, reflecting the expected 33% failure rate. In a pediatric prospective study, 74/128 (58%) were not on solid foods by the third admission day, but in a multivariate analysis this was not associated with improved outcome even after controlling for disease activity (unpublished data of D.T.). On the other hand, the complications of total parental nutrition, such as pneumothorax, electrolyte imbalance, and sepsis, are well recognized.

Pain management (95% consensus)

1. Children with severe or escalating abdominal pain should be investigated for bowel perforation and toxic megacolon [EL5, RG D]
2. Routine use of narcotics or nonsteroidal anti-inflammatory drugs (NSAIDs) is not recommended [Pediatrics EL5, RG D; Adults EL2b, RG B]

Practice points

1. Pain out of proportion with disease severity should be taken seriously and promptly lead to exclusion of TMC and bowel perforation.
2. Most patients with pain can be managed with relaxation techniques, hot packs, or oral acetaminophen (paracetamol).
3. Low-dose narcotics (equivalent to 0.1 mg/kg morphine), not frequently administered, are potentially safe, but should

be approached with caution and with close monitoring for complications in specialized centers; high or repeated doses should be avoided.
4. Experience with other agents, such as clonidine, naloxone (with opioids), and cannabinoids, have limited or no supporting evidence. A few case reports suggest that ketamine may be of use, but more evidence is required.

Opioids/narcotics. Older reports detail high rates of narcotic and anticholinergic use in adult patients with TMC (72,73). This has translated to dogmatic recommendations stating that opioids are contraindicated in ASC because of the associated decreased intestinal peristalsis (2,53). In a case–control study of pediatric patients with TMC, only 2/10 (20%) received narcotics before diagnosis of TMC (74). Narcotic use may be a marker of severe disease rather than a predisposing factor for TMC. Combined prolonged-release oxycodone and naloxone may prevent gastrointestinal complications while managing pain, but this has not been assessed in UC (75).

Nonsteroidal anti-inflammatory drugs. Nonsteroidal anti-inflammatory drugs have been associated with exacerbation of disease activity in adults with UC (76,77). A retrospective study found a 20-fold increase of IBD exacerbation or new-onset disease with nonsteroidal anti-inflammatory drug exposure, without a dose-effect relationship (76). Reports of selective COX-2 inhibition in adults with UC are mixed, with many showing increased risk of disease exacerbation or increased gastrointestinal symptoms (78–80).

Ketamine. Two case reports describe ketamine, an *N*-methyl-D-aspartate receptor antagonist, for use in the pain management of IBD (81,82). One of these (including two cases) suggests that ketamine as an infusion or patient/nurse-controlled administration is effective at reducing narcotic and nonsteroidal anti-inflammatory drug use in children with ASC (82). If clinicians choose to use ketamine, the authors suggest an infusion dose of up to 40 μg/kg/h or patient/nurse-controlled doses of 20–40 μg/kg with 10–30 min lockout periods.

Cannabinoids. Ample evidence from animal model indicates that cannabinoids modulate visceral sensation and pain, particularly in the inflamed gut (83–85). Our search revealed no related human studies.

MONITORING RESPONSE TO STEROID TREATMENT

When and on what grounds to introduce second-line therapy (100% consensus)

1. A child with a PUCAI of >45 points on day 3 should be prepared for second-line therapy [EL2b, RG B]
2. A PUCAI > 65 on day 5 should prompt initiation of second-line therapy [EL2b, RG B]
3. Corticosteroids may be continued for additional 2–5 days in a child with a PUCAI of ≤60 and ≥35 points on day 5, before a decision on second-line therapy is made; those with PUCAI <35 points on day 5 are unlikely to require second-line therapy by discharge [EL2b, RG B]

Practice points:
1. Preparations on day 3 for those with a PUCAI >45 best include discussing treatment options with the family, surgical consult, tuberculosis screening, and performing sigmoidoscopy (on the third or fourth day).
2. Sigmoidoscopy is important for excluding infection (CMV and *C. difficile*) and to search for chronic changes and granulomatous inflammation.
3. CRP values should be monitored, as high values have some predictive value.

Timely introduction of second-line therapy has reduced the mortality rate in adults with ASC from 7% with corticosteroid therapy to <1% (1,9). Clinical guidelines recommend that second-line therapy be initiated if no response to corticosteroids is noted within 3–10 days of initiating intravenous therapy (12,38,46,86–88). Predictive indices have utilized the third and the fifth day to determine whether escalation of therapy is required (5,6,35,38,89,90). The combination of a high stool frequency and elevated CRP on day 3 were found to predict colectomy in 75–85% of patients using either the Oxford (stool frequency of 8/day or 3–8/day and CRP >45 mg/l) (35) or Sweden indices (stool frequency/day + 0.14× CRP mg/l) (90,91); the Seo (89) and Edinburgh (38) scores may also have predictive ability in adult patients.

In children, Turner *et al.* (5) retrospectively evaluated 99 pediatric patients with ASC, of whom 46% were corticosteroid unresponsive. Comparing the PUCAI score to the Sweden, Oxford, and Seo indices, the authors concluded that the PUCAI, measured on the third and fifth day of steroid treatment, could be used to dictate introduction of second-line therapy. A prospective study in a larger cohort of 128 children with ASC found that the PUCAI was superior to all adult indices, CRP, and fecal calprotectin (6). Aiming for sensitivity on day 3 (screening day), a PUCAI >45 screened for patients likely to fail steroids (negative predictive value = 94%, positive predictive value = 43%; $P < 0.001$). The high negative predictive value indicates that complete response is likely in those with PUCAI score of 45 points. Aiming for specificity on day 5 (execution day), a PUCAI score of >70 optimally guided implementation of salvage therapy (positive predictive value = 100%, specificity = 100%, and negative predictive value = 76%; $P < 0.001$). A cutoff of >65 on the fifth day had a positive predictive value of 100%, specificity of 94%, and negative predictive value of = 78%.

Some of the children who have not responded to steroids within 5 days (i.e., PUCAI >65 and especially >70) may respond within the following weeks, but differing treatment escalation is associated with steroid and UC-associated morbidity. In a *post hoc* analysis of the two largest pediatric cohort studies combined ($n = 227$ children with ASC), 15/45 (33%) of children with a PUCAI score of 35–60 at day 5 required salvage therapy by discharge compared with 1/54 (2%) children with a mild disease activity (i.e., PUCAI score <35 points; Refs. 5, 6 and unpublished data of D.T.).

TMC and radiography (100% consensus)

1. Abdominal radiographs should be obtained in children with any sign of systemic toxicity, and subsequently as clinically indicated [EL4, RG D]
2. Diagnostic criteria for TMC should consist of radiographic evidence of transverse colonic dilatation (≥56 mm) plus signs of systemic toxicity [EL4, RG C]
3. Children with TMC should receive immediate surgical consultation, but they may be managed conservatively if vital signs are stable and there is no sepsis. If symptoms of toxicity worsen or do not resolve within 48–72 h, immediate colectomy should be performed [EL 4, RG C]
4. Cyclosporine and anti-tumor necrosis factors (anti-TNFs) are not recommended in TMC [EL5, RG D]

Practical points:

1. Systemic toxicity from TMC may be rarely masked by steroids.
2. A transverse colonic diameter of >40 mm with signs of systemic toxicity may be sufficient to diagnose TMC in children <10 years of age.
3. Intravenous antibiotics (such as ampicillin, gentamycin, and metronidazole), correction of electrolyte imbalance, food restriction, and preparation for surgery compose the mainstay of initial therapy for TMC. Although rectal decompression tube and positional changes have long been practiced, objective evidence of benefit is limited.

Abdominal radiography has helped predict steroid failure in several studies (9) but it is used primarily to screen for complications (i.e., TMC and perforation). As steroids can mask peritoneal signs, abdominal radiographs should be ordered on very low clinical suspicion. The distribution of transverse colonic dilatation in children >11 years of age generally follows that of adults, in which a width of >55–60 mm is associated with TMC in the appropriate clinical setting (5,92). In younger children, however, this upper width range is 40 mm (5).

The literature on TMC in children with IBD consists of case reports and small case series (93–101). The most widely used diagnostic criteria for TMC were reported in a series of 55 cases in adult IBD patients (**Table 2**) (102). Adolescents with TMC were more likely to have fever, tachycardia, dehydration, and electrolyte abnormalities compared with age-matched controls of hospitalized UC patients without TMC (74). Altered level of consciousness and hypotension were very rare in both groups. **Table 2** describes suggested pediatric criteria for the diagnosis of TMC based on this case–control study and experts' opinion.

In adults, mortality has been reported in 19–50% of patients with TMC (73,103). In the pediatric study, none died but 7/10 (70%) of children required colectomy by discharge (74). One case series demonstrated that positional changes combined with long tube insertion was associated with resolution of TMC (104). In a retrospective study of children with TMC due to Salmonella infection, tube placement was associated with a reduced risk of bowel perforation (105). A single case report describes the successful treatment of TMC with infliximab (106), but the potential associated risk in such very sick children should not be underestimated.

Table 2. Previously established adult and the currently suggested pediatric criteria for diagnosis of toxic megacolon

Adult criteria (from Jalan *et al.* (102))	Suggested pediatric criteria (based on ref. 92)
(A) Radiographic evidence of colonic distention	(A) Radiographic evidence of transverse colon diameter ≥56 mm (or >40 mm in those <10 years)
(B) At least three of the following: 1. Fever >38 °C 2. Heart rate >120/min 3. Neutrophilic leukocytosis >10.5×108/l 4. Anemia	PLUS (B) Evidence of systemic toxicity, such as: 1. Fever >38 °C 2. Tachycardia (heart rate >2 s.d. above mean for age) 3. Dehydration 4. Electrolyte disturbance (sodium, potassium, or chloride) 5. Altered level of consciousness or coma 6. Hypotension or shock
(C) In addition to the above, at least one of the following: 1. Dehydration 2. Altered level of consciousness 3. Electrolyte disturbances 4. Hypotension	

RESCUE THERAPIES

Medical rescue therapies (100% consensus)

1. Whenever discussing second-line therapy, surgery must always be seriously considered [EL4, RG C]
2. For pediatric patients failing intravenous corticosteroids, the use of either calcineurin inhibitors or infliximab is recommended [Pediatrics EL4, RG C; Adult EL1b, RG A]

Practice points:

1. If a patient has previously failed an adequate trial of thiopurine therapy, then infliximab may be preferred, as it can be used for maintenance, unlike cyclosporine (CsA) or tacrolimus that are typically given for 3 to 4 months to bridge to thiopurines. Infliximab may also be preferred in children with hypomagnesemia, hypocholesterolemia, hyperglycemia, azotemia, hypertension, or neurological abnormalities, all associated with increased calcineurin toxicity.
2. Children intolerant of corticosteroids who have a subsequent episode of ASC may be treated with calcineurin inhibitors or infliximab as initial therapy, without corticosteroids.
3. Parameters that can be used to determine short-term success to second-line therapies may be:
   -Calcineurin inhibitors: improvement of PUCAI (20 points) within 5–7 days.

Table 3. Medical rescue therapies in pediatric corticosteroid-refractory UC

	Cyclosporine	Tacrolimus	Infliximab
Initial dosing	2 mg/kg/day continuous intravenous infusion. Once remission is achieved, convert to oral 5–8 mg/kg/day divided b.i.d. Stop medication after 3 to 4 months.	0.1 mg/kg/dose orally b.i.d. Stop medication after 3 to 4 months.	5 mg/kg over 2–4 h; subsequent doses given 2 weeks and 6 weeks after the initial infusion. Some centers utilize higher doses (10 mg/kg), or infuse the second dose after 7–10 days[a]
Trough drug levels	Aim initially for 150–300 ng/ml, and 100–200 ng/ml, once remission achieved (for timing see below)	Aim initially for 10–15 ng/ml, and then 5–10 ng/ml, once remission achieved (for timing see below)	Not indicated
Tests before treatment	Measure blood pressure and blood tests: creatinine, glucose, electrolytes, liver profile; test and treat hypomagnesemia and hypocholesterolemia to decrease the risk of neurotoxicity (more with cyclosporine)		Documentation of negative tuberculosis testing and chest X-ray; consider varicella, hepatitis B and C serology in endemic areas
Main toxicity	Hypertension[b], hyperglycemia, hypomagnesemia, immune suppression, azotemia[c] (dose dependent), seizures[d] (dose and hypocholesterolemia dependent), hirsutism (more with cyclosporine), tremor (more with tacrolimus); erythromycin, ketoconazole, and grapefruit juice can increase cyclosporine and tacrolimus levels.		Infusion reactions, increased infection rate, rare opportunistic infections
Monitor toxicity	Monitor every other day during induction, weekly for the first month, and then monthly[e]: drug levels (starting after third dose), creatinine, glucose, electrolytes (including magnesium), lipid levels, blood pressure, and neurological symptoms. Consider: measure creatinine clearance at baseline and initiate Pneumocystis pneumonia prophylaxis		Frequent assessment of vital signs during infusion

[a]Maintenance therapy can be given every 8 weeks after induction, if clinically indicated.
[b]Hypertension can be seen in up to 40% of subjects and usually respond to calcium channel blockers (the latter, however, can increase cyclosporine levels).
[c]Serum creatinine >1.4 mg/dl or at least 33% over baseline (usually respond to cyclosporine dose adjustment).
[d]Neurotoxicity (manifested as paresthesias, tremors, and seizures) is promoted by hypocholesterolemia (<120 mg/dl) and hypomagnesemia (<1.5 mg/dl): if the latter occurs, dose of cyclosporine should be lowered.
[e]If oral drug dose has been changed, monitor levels 1 week later.

-Infliximab: no worsening of PUCAI at 7 days, and improvement of PUCAI (20 points) within 2 weeks after the first infliximab infusion.

4. For guidance on dosing, route of administration, and target therapeutic levels, see **Table 3**.

Approximately 30–40% of pediatric ASC patients will require treatment escalation; therapeutic options include surgery, calcineurin inhibitors (i.e., CsA and tacrolimus), and infliximab.

Cyclosporine. CsA acts mainly through binding to the cytosolic protein cyclophilin of T lymphocytes, thereby inhibiting calcineurin that is responsible for activating the transcription of interleukin-2 (107). Widespread use of CsA has been tempered by potentially serious side effects, including nephrotoxicity, serious infections, seizures, paresthesia, hypomagnesemia, hypertension, hypertrichosis, headache, hyperkalemia, and, rarely, death (108) (**Table 3**). These events seem less frequent if oral administration is used (109).

In addition to many open-labeled studies, results from two clinical trials in adults have confirmed the short-term effectiveness of CsA in ASC (110,111). When results from controlled and uncontrolled adult trials are pooled, 70–85% of patients initially respond to CsA, of whom 58–88% come to colectomy by 7 years (9,35,107,112). It is customary to initiate CsA intravenously, although oral preparations (Neoral) are reliably bioavailable (**Table 3**). While patients are on a triple immunosuppressive regimen (i.e., with thiopurines and steroids), prophylaxis against *Pneumocystis jiroveci* pneumonia is best considered and alertness for other opportunistic infections should be high.

Pediatric CsA data come from eight retrospective case series (total of 94 children), in which the rate and adverse events were similar to those reported in adults (10,113). The pooled short-term response was 81% (95% CI 76–86%) but only 39% (95% CI 29–49%) avoided colectomy in the long term (10). 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. Initial doses ranged from 0.7 to 7 mg/kg/day for intravenous and from 4 to 8 mg/kg/day for oral. The trough levels used for monitoring range from 150 to 600 ng/ml. The better long-term success rates were in part related to the introduction of azathioprine.

Tacrolimus. The potential advantages of tacrolimus over CsA include reliable oral absorption and apparently better tolerability. In a controlled trial of tacrolimus in 65 adults with moderate–severe UC (only 15 steroid resistant), response at 14 days was 68% in the high trough group (10–15 ng/ml), 38% in the low trough group (5–10 ng/ml), and 10% in the placebo group (114). Small, open-label case series in adults show response rates of 50–80% in ASC (115,116). Adverse events include hyperglycemia, hypomagnesemia, neurotoxicity, and hypertension (**Table 3**).

There are three small pediatric case series evaluating a total of 24 children with ASC treated with tacrolimus, of whom 16 (67%) showed good initial response, but only 0–22% sustained response in the long term (10). Other patients within these publications included steroid-dependent patients or those with Crohn's colitis (117–119).

Infliximab. Six case series have reported the use of infliximab in children with ASC (126 in total), with a pooled short- and long-term response rates of 75% (95% CI 67–83%) and 64% (95% CI 56–72%), respectively (6,10,120). The short-term and 1-year colectomy rates have declined since the use of infliximab in children with ASC to 9% by discharge and 19% by 1 year (6). In the only clinical trial in ASC, infliximab, administered to 45 adults as a single dose, reduced the number of patients undergoing colectomy within 3 months (7/24 (29%) in infliximab group vs. 14/21(67%) in placebo group) (91). Another study of 83 adults with ASC reported 12% requiring colectomy within 2 months (121). In this study two infusions appeared to be more effective than a single infusion. Positivity for anti-nuclear cytoplasmic antibody (pANCA) was found predictive of a suboptimal response to infliximab in one report of adult patients (122), but this was not replicated in children (120). The safety profile of infliximab given to children with ASC has been acceptable with no reported deaths.

How to determine treatment success of second-line medical therapy. The literature does not provide guidance on when treatment success or failure should be determined in children treated with salvage therapy. In adults, time to response is reported to be 5–7 days when using CsA and up to 2 weeks if tacrolimus or infliximab are used. Dealing with very sick children, it seems best not to wait more than a week after start of rescue treatment to determine treatment success or failure.

The role of third-line medical therapy (95% consensus)

Sequential therapy (calcineurin inhibitor following infliximab, or vice versa) is not recommended [Pediatric EL5, RG D; Adults EL4, RG C]

Sequential therapy of CsA/tacrolimus followed by infliximab or vice versa may be successful in ~25–40% of adult patients (123–126), but this has not been studied in children. In one series, in 19 patients with refractory ASC treated with infliximab after CsA or vice versa, the colectomy rate was 42% at 1 year and one patient died from sepsis (123). Another series from GETAID in France analyzed sequential treatment with infliximab in 86 UC patients after CsA failure, or vice versa, with a colectomy rate of 63% at 3 years (124). The associated risk of serious infections was high (16/86 patients), with one reported death from pulmonary embolism. Given the small number of patients, it is difficult to evaluate the real risk in patients receiving two powerful immunomodulators in sequence typically combined with corticosteroids. It seems that the risk is appreciable and it should be remembered that the mortality from emergency colectomy is close to zero in specialist centers. The aphorism that management of refractory ASC is about saving lives and not saving colons is best recalled.

Is there a preferred surgery in children? (100% consensus)

In the need for surgery in ASC, subtotal colectomy and ileostomy is recommended; subsequently, pouch formation may be preferred [EL2b, RG B]

Practice points:

1. The pouch procedures (i.e., ileoanal pouch or ileal pouch–anal anastomosis), also known as "restorative proctocolectomy," are likely superior to a straight pullthrough (i.e., ileoanal anastomosis) because they are associated with acceptable early complication rates, lower early stool frequency, and better long-term continence. Ileorectal anastomosis cannot be recommended for most children because of the high rate of failure, requiring removal of the remaining rectum. The advantages of the restorative proctocolectomy need to be balanced against the risk of chronic pouchitis and reduced fertility.
2. A three-stage approach should be considered in patients undergoing an emergency operation, those on high-dose steroids and/or suffering from malnutrition, and those in whom the possibility of a diagnosis of Crohn's disease is appreciable (e.g., children < 5 years of age).
3. Restorative proctocolectomy without protecting ileostomy may be safe in selected children without risk factors (e.g., high-dose steroids), and in whom the pouch procedure is completed smoothly.

In adults, restorative proctocolectomy has become the standard of care. The most important short-term complication is an anastomotic leak; the long-term complications include pouchitis, incontinence, and decreased fertility.

Should the surgery be done in one, two, or three steps?. The two questions are whether the reconstruction is best done at the same time as the colectomy, and whether there should be a protecting loop ileostomy. The decision is influenced by whether the patient is on high-dose steroids, as this is the primary predictor of anastomotic leaks. For a patient on high-dose steroids, 17% of adult surgeons would recommend a three-stage and 82% a two-stage operation (127,128). A meta-analysis of 17 studies and 1,486

patients showed a lower risk of leak with a protective ileostomy, although functional outcomes were similar (129). This was not replicated in children (130). Of the many published adult studies, two match patients with similar strata and documented a higher incidence of pouch-related complications in those undergoing a one-stage pouch, but similar long-term function (131,132).

Ileorectal anastomosis, straight ileoanal pullthrough, or restorative proctocolectomy?. A pediatric meta-analysis consisting of 5 studies and 306 patients suggested that the straight ileoanal pullthrough was associated with a higher risk of failure and perianal sepsis, as well as a higher stool frequency and incontinence than restorative proctocolectomy (133).

A multicenter study with 112 children with straight ileoanal pullthrough and 91 with a J-pouch showed that stool frequency was higher in the pullthrough group, although the difference became less with longer follow-up (134). One adult study documented less incontinence with ileorectal anastomosis but more urgency, and ultimately the need to resect the remaining rectum in 53% of patients because of refractory proctitis, dysplasia, or cancer (135).

Future fecundity is an important consideration in children undergoing pouch procedure. Adult data suggest that the risk of female infertility increases after restorative proctocolectomy from 12 to 26% and this should be seriously considered in the decision making (136). One long-term study of 52 children did not document any difference in fertility (137), but the authors did not compare the pullthrough to pouch with respect to this outcome. Fecundity is probably preserved after ileorectal anastomosis, as this avoids pelvic dissection (138). The final choice of surgery should be made by the patient, the gastroenterologist, and the specialist colorectal surgeon after a full and informed discussion of the options.

Ways to minimize surgical complications (100% consensus)

1. Delay in surgical intervention to enhance nutrition is not recommended [EL5 RG D]
2. Children undergoing colorectal surgery should be treated with antibiotic of appropriate spectrum starting an hour before the surgery and terminated within 24 h after surgery [EL5, RG D]
3. Preoperative steroid administration is associated with an increased risk of anastomotic leak and infectious complications [EL2b RG B]. However, surgery should not be delayed to taper steroids [EL5, RG D]

Practice points

1. A low serum albumin is a marker for an increased risk of postoperative infection; this emphasizes the importance of early decision making before inflammation severity suppresses albumin synthesis and also the role of nutritional support.
2. Prophylaxis against venous thromboembolism is best considered for all children undergoing surgery for ASC. It should be started before surgery and continued until the patient is walking.

Administration of steroids (≥20 mg methylprednisolone for ≥2 months) and severity of the patient's condition have consistently been associated with postoperative infections in retrospective studies in adults (139,140). In children, preoperative steroids, hemoglobin <10 g/dl, or albumin <30 g/l have been associated with greater rates of infection in a retrospective study of 51 children undergoing colectomy.

Treatment with azathioprine does not seem to increase the postoperative complication rate (141). Three of four studies in adults have concluded that infliximab given before elective colectomy does not increase the risk of postoperative complications (140,142–144). An increased surgical morbidity after sequential infliximab–CsA therapy (or vice versa) has been reported if colectomy is eventually indicated (145).

The use of perioperative antibiotics is a recommendation of the National Surgical Infection Prevention Project (146). Similarly, despite the lack of clinical trials, the efficacy of prophylactic heparin during the perioperative period is well established.

DISCHARGE CONSIDERATIONS

There are no studies that focused on hospital discharge in children. However, in a prospective pediatric multicenter cohort of ASC, 76 of the 128 children were discharged with mild disease activity scores that did not predict the need for treatment escalation during the subsequent year (unpublished data of D.T. from ref. 6). Reports describe the benefit of thiopurine maintenance therapy after an episode of ASC (147), but do not describe the optimal timing for starting therapy.

Practice points (100% consensus)

1. The following criteria should all be considered before discharging a child following treatment for ASC:
   (a) PUCAI < 35 points (i.e., no more than mild disease)
   (b) Afebrile and stable vital signs.
   (c) Sufficient oral intake and good hydration.
   (d) Off pain medications.
   (e) Stable hemoglobin without the need for transfusion for at least 2 days.
2. Once discharged, prednisone may be initiated at a dose 20% higher than the methylprednisolone dose given before discharge, to yield biologically equivalent dose (methylprednisolone is 20% more potent than prednisone).
3. If needed, starting azathioprine is best delayed for 2 weeks after discharge, until it is clear that the initial response has been sustained. If calcineurin inhibitors have been used during the admission, azathioprine is best delayed until prednisone is tapered to 20 mg daily, to reduce the toxicity of triple immunosuppression.
4. Whether to introduce dual therapy with azathioprine or 6-mercaptopurine, in case infliximab has been initiated, is based on local clinical practice and individual risk stratification.
5. Oral 5-ASA should be introduced or reintroduced on hospital discharge, if no intolerance is suspected.

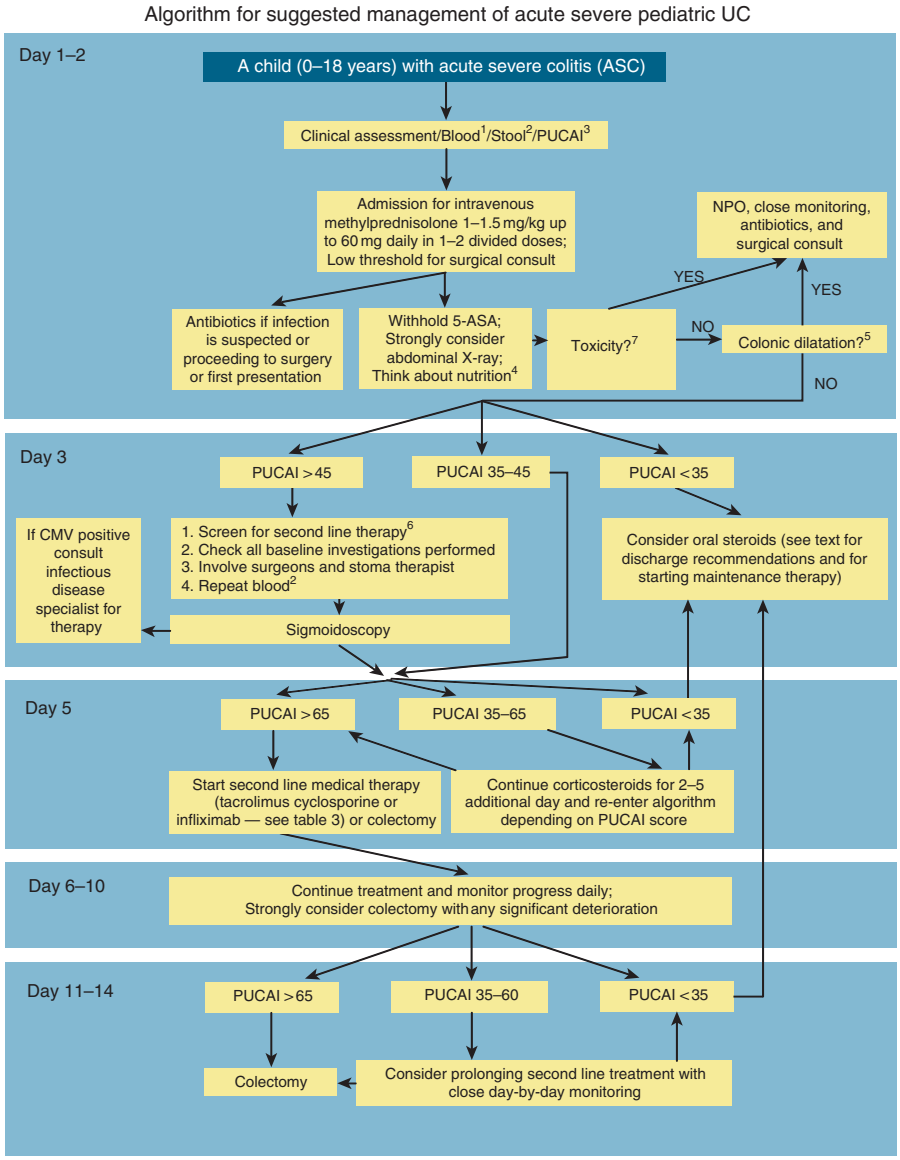

Figure 1. Algorithm for suggested management of acute severe pediatric UC. This is a guide to aid the clinician in the management of a pediatric patient with ASC for timely decision making. It acts as a guide only and does not replace clinical assessment for individual patients. It should be interpreted in conjunction with the text of the supporting guideline. [1]Complete blood count, urea, creatinine, electrolytes, liver enzymes, albumin, C-reactive protein, erythrocyte sedimentation rate, and blood culture (if febrile). [2]Stool cultures for enteric pathogens including *Salmonella, Shigella, Campylobacter*, and *Escherichia coli*. In addition, 3–5 stool samples for *Clostridium difficile* toxin should be collected. Stool virology in selected cases (see text). [3]See **Table 1**. [4]Continue normal diet if possible. If enough adequate oral intake is not tolerated, support with enteral tube feeding. If enteral tube feeding is not tolerated or in the presence of colonic dilatation or when surgery is imminent, then parenteral nutrition may be needed. [5]Dilatation on plain abdominal X-ray is suggested by colonic width of >56mm in children >10 years of age and >40 mm in younger children. Defined as toxic megacolon if associated with toxicity (see **Table 2**). [6]PUCAI >45 at day 3 warrants preparation for second-line therapy (see text and **Table 3**) and >65–70 points at the fifth day warrants execution of the planned therapy. Those not meeting these cutoff values may be slow responders and should be treated with corticosteroids for 2–5 more days until decision is made. [7]See **Table 2**. 5-ASA, 5-aminosalicylic acid; ASC, acute severe colitis; CMV, cytomegalovirus; NPO, nothing per os; PUCAI, pediatric ulcerative colitis activity index; UC, ulcerative colitis.

SUMMARY

This consensus process yielded 28 formal recommendations and 34 practice points along with practical tables, based on systematic review of the literature. Several of the recommendations are different than those published in adults, recognizing some unique considerations in children, including the use of a validated pediatric index to define ASC and guide treatment, performing sigmoidoscopy only in those failing steroids, lack of recommendation to treat with empiric heparin, and different criteria for TMC and radiographic appearance.

We have summarized the recommendations in a treatment algorithm; this must be used in conjunction with the supporting text (**Figure 1**). Although a significant effort was made to provide

Table 4. Suggested topics for future research in pediatric ASC

• Thrombotic complications in a pediatric cohort with ASC
• Dose-finding studies of corticosteroids in ASC in children
• A randomized controlled trial of infliximab vs. calcineurin inhibitors
• Further delineating the role of CMV in ASC and its diagnosis
• Elucidating the risk for TMC after treatment with narcotics

ASC, acute severe colitis; CMV, cytomegalovirus; TMC, toxic megacolon.

evidence-based guidelines, management decisions for ASC in children would be facilitated by further research (**Table 4**). These clinical management guidelines were developed to assist practitioners at all levels of health care, while recognizing that each patient is unique. The recommendations may, thus, be subject to local practice patterns, but serve as a general framework for the management of ASC in children. The development of the guidelines should now be followed by dissemination of the information to clinical practice.

QUALIFYING STATEMENTS

- These guidelines may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice.
- These guidelines are intended to be an educational device to provide information that may assist clinicians in providing care to patients. These guidelines are not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical decisions in any particular case involve a complex analysis of the patient's condition and available courses of action. Therefore, clinical considerations may require taking a course of action that varies from these guidelines.

CONFLICT OF INTEREST

Guarantor of the article: Dan Turner, MD, PhD.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Severe ulcerative colitis is a potentially life-threatening condition.
- ✓ Current pediatric guidelines were extrapolated from the adult literature.

WHAT IS NEW HERE

- ✓ These are up-to-date pediatric guidelines for the management of severe ulcerative colitis.
- ✓ Based on systematic review of the literature and consensus among international experts, a day-by-day decision-making flowchart is provided, based on daily scoring of the Pediatric Ulcerative Colitis Activity Index (PUCAI).

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