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Management of paediatric ulcerative colitis, Part 2: acute severe colitis; an evidence-based consensus guideline from ECCO and ESPGHAN

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ABSTRACT

Background and aim: Acute severe colitis (ASC) is one of the few emergencies in paediatric gastroenterology. Tight monitoring and timely medical and surgical interventions may improve outcomes and minimize morbidity and mortality. We aimed to standardize daily treatment of ASC in children through detailed recommendations and practice points which are based on a systematic review of the literature and consensus of experts.

Methods: These guidelines are a joint effort of the European Crohn's and Colitis Organization (ECCO) and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). Fifteen predefined questions were addressed by working subgroups. An iterative consensus process, including two face-to-face meetings, was followed by voting by the national representatives of ECCO and all members of the Paediatric Inflammatory Bowel Disease (IBD) Porto group of ESPGHAN (43 voting experts).

Results: A total of 24 recommendations and 43 practice points were endorsed with a consensus rate of at least 91% regarding diagnosis, monitoring and management of ASC in children. A summary flowchart is presented based on daily scoring of the Paediatric Ulcerative Colitis Activity Index (PUCAI). Several topics have been altered since the previous 2011 guidelines and from those published in adults.

Discussion: These guidelines standardize the management of ASC in children in an attempt to optimize outcomes of this intensive clinical scenario.

Keywords: Ulcerative Colitis; acute severe colitis; steroids; pediatric ulcerative colitis activity index (PUCAI), anti-TNF, anti-coagulants; antibiotics; mesalamine; colectomy; prediction

What is known

- The previously published ESPGHAN-ECCO guidelines on acute severe colitis (ASC) were published in 2011 and are updated herein

What is new

- In addition to providing an update of new literature, several major topics have changed from the previous guidelines. A PUCAI-based algorithm dictates a day-by-day therapeutic and monitoring management; the use of thrombotic prophylaxis has been revisited based on predicting variables; sequential therapy has been newly presented; recommendations for therapeutic drug monitoring have been provided; and other sections updated.

INTRODUCTION

Acute severe ulcerative colitis (ASC), a medical emergency in children, is defined by a paediatric UC activity index (PUCAI) score of at least 65 points (1-3) (Table 1). Paediatric onset UC is often more extensive than in adults and more dynamic in progression (4, 5). Since disease severity has been consistently associated with disease extent, children are especially susceptible to refractory severe attacks. The Hungarian paediatric IBD registry (HUPIR), reported that 11% children had severe disease at some stage during the disease course of UC (6). In an Italian cohort of 109 children, 9% presented with ASC and 23% had at least one episode by the end of the follow-up of 48 months (7). Comparable rates were found in a multicenter paediatric UC inception cohort, in which 15% of children developed ASC within 3 months of diagnosis (8). In an older population-based retrospective cohort, 28% of children required hospitalization within the first 3 years of disease (9). The difference between the older and newer cohorts possibly reflects the advent of biologics which allow outpatient treatment of some children with UC.

With few exceptions, children with ASC should be admitted to hospital for immediate evaluation and intensive medical treatment with intravenous corticosteroids (IVCS). A PUCAI≥65 is associated with a more refractory disease course in paediatric UC, both at disease onset and thereafter (8-10). In a systematic review, the pooled steroid-refractory rate in ASC across all paediatric studies was 34% (11), slightly higher than the pooled 29% rate found in adult studies (12). In two paediatric inception cohorts, the occurrence of ASC was associated with an increased risk of colectomy (7, 8). The advent of calcineurin inhibitors and infliximab has reduced the short term colectomy rate from 40-70% (9, 11-13) to approximately 10-20% in children (10, 14, 15) and the 1-year colectomy rate from ~60% (9, 16) to 18-22% (10, 14, 16). Among those who fail IVCS treatment, roughly 50-60% of responders to salvage medical therapy will require colectomy within 1-2 years (10, 14). To add to the complexity, enteric infections and adverse events to medications (primarily mesalamine and thiopurines intolerance) can mimic ASC. Consequently, a child who ever developed an episode of ASC is at a particular risk for a more refractory disease course and colectomy and is labeled by the Paris classification as S1 (17).

Mortality in ASC has decreased in adults from over 70% in 1933 to 20-25% in the 1950's when the importance of timely urgent colectomy was first recognized (18, 19). Later, the mortality rate was further reduced to 7% with the introduction of IVCS as the mainstay of treatment, and eventually to less than 1% nowadays (12, 20-22). Rare cases of mortality have been reported also in children (23), emphasizing the importance of a structured approach to management and monitoring during the admission.

Since the publication of the previous ECCO-ESPGHAN guidelines on paediatric ASC in 2011 (1), new data have accumulated regarding management, diagnosis, and outcomes. We thus aimed to update the guidelines for managing ASC in children based on a systematic review of the literature and a robust consensus process from ECCO and the Paediatric IBD Porto group of ESPGHAN. The methods can be found in the beginning of Part 1 of these guidelines. Surgical considerations are also presented in Part 1.

INITIAL MANAGEMENT

Infectious screening

<u>Recommendations</u>

1. Bacterial causes for ASC should be excluded by a stool culture including *Clostridium difficile (C. difficile)* toxins A and B [EL4, adult EL3] **(100% agreement)**

2. Oral vancomycin should be considered as first line therapy for *C. difficile* infection in severe UC [EL4, adults EL1] **(100% agreement)**
3. Cytomegalovirus (CMV) colitis should be excluded in children not responding to 3 days of IVCS [EL4, adults EL3] **(98% agreement)**
4. Other infections should be considered when relevant, including viral and parasitic (e.g. Cryptosporidium and amoebiasis), such as in the presence of fever, other affected household members or non-bloody diarrhea; stool testing for *Entamoeba histolytica* should be performed in endemic areas or recent travel to these areas [EL4, adults EL4] **(100% agreement)**

<u>Practice points</u>

1. It is important to test for both *C. difficile* toxin A and B; repeated sampling is required unless a PCR-based test is available- then one stool sample is sufficient **(100% agreement)**.
2. Oral vancomycin for *C. difficile* should be prescribed for 10-14 days in doses of 10mg/kg per dose 4 times daily up to an adult dose of 125-250mg increased if needed to maximum of 500mg 4 times daily, although national recommendations vary. Oral metronidazole may be used in the absence of oral vancomycin at a dose of 7.5-10mg/kg per dose 3 times daily (to a maximum of 2g/24hrs) for 10-14 days **(100% agreement)**.
3. CMV infection is best identified by obtaining mucosal biopsies via a flexible sigmoidoscopy. Biopsies should be stained using both hematoxylin eosin and immunohistochemistry for CMV. Positive PCR in the absence of inclusion bodies or positive staining is insufficient for diagnosing CMV since PCR lacks specificity **(100% agreement)**.

4. For CMV infection, ganciclovir should be used at a dose of 5 mg/kg twice daily for 21 days. Response is anticipated within a few days and management should be re-considered with an infectious-diseases specialist if this has not been achieved. Switching to oral valganciclovir may be considered after several days of successful intravenous treatment **(100% agreement)**.

Many gastrointestinal infections have been associated with paediatric ASC. In one retrospective study, 24% (22/92) of flares in children requiring hospital admission for IBD were associated with some enteric infection (24). Stool bacterial culture was positive in 2% of children admitted for UC exacerbation, as reported in two paediatric cohorts (15) (25).

C. difficile is the most commonly identified organism, ranging in paediatric IBD from 3%-47% of flares (24-32), compared with 7.5% per year of follow-up in outpatient paediatric IBD, which may include some asymptomatic carriers (33). A *C. difficile* rate of 25% was reported in a retrospective study of 81 children admitted with active colonic IBD (compared with 8.9 % in non-IBD controls) (26). An administrative database study among adults and children showed that the rate of *C. difficile* was more than 12 times greater in IBD compared with non-IBD hospitalizations with increasing incidence over time (29). In hospitalized paediatric and adult IBD patients *C. difficile* is associated with increased morbidity including extended hospital stays, colectomy rate, and even mortality (27, 34-43).

Toxigenic culture, the gold standard for detecting C. *difficile*, is both time intensive and expensive (44). Rapid enzyme immunoassays (EIA) detect a common product of *C. difficile,* glutamate dehydrogenase (GDH), or the toxin products (toxin A & B). The sensitivity and specificity of both tests vary and recent guidance advises testing initially for GDH EIA and if positive, confirming the results by EIA for toxins A and B (45, 46) (47). Nucleic acid amplification tests (NAAT), targeting genes for toxin A and B by mainly PCR, can be used instead of EIA and due to their high sensitivity and specificity only one stool sample is required (48).

In hospitalized IBD children with C. *difficile*, 75% responded to metronidazole and the others responded to vancomycin (24). Similarly, a recent RCT of metronidazole vs. rifaximin for treating C. *difficile* in children with IBD (not with ASC) showed eradication rate of 71% versus 79%, respectively (49). A retrospective paediatric case series showed no difference in response rates between metronidazole (n=15 (41%)) and vancomycin (n=16 (43%)) but results were not stratified according to disease severity (28). Furthermore, an increasing number of adult studies show a poor *C. difficile* eradication rate with metronidazole and only a moderate success rate (66-76%) for severe *C. difficile* infection compared with vancomycin (79%-97%) (44, 50-52). Although a Cochrane systematic review showed no difference in efficacy between vancomycin and metronidazole, it was not specific to IBD and most studies excluded severe disease (53). A diminished colectomy rate (from 46 to 25%) was reported using vancomycin as primary therapy for *C. difficile* in hospitalized IBD patients (39). Moreover, hospitalized UC patients with *C. difficile* had fewer reported readmissions and a shorter length of hospital stay when treated with oral vancomycin compared with metronidazole (54). Adult ECCO opportunistic infection guidelines therefore advise oral vancomycin in severe disease as first line (55). Fidoxamicin has not been studied in IBD specifically, but in adult *C. difficile* infection it has been shown to be non-inferior to vancomycin with significantly lower recurrence rates (56-58) (59). Its use is limited by its high cost compared to vancomycin. There is currently no evidence to support the use of faecal microbial transplantation (FMT) in ASC associated with *C. difficile* in children or adults. However, FMT is highly effective for eradication of recurrent *C. difficile (60)* (albeit perhaps slightly less in IBD (61)) and could be considered in refractory *C. difficile* in UC. A systematic review of FMT including 22 IBD patients with *C. difficile* showed a response in 20/22 (91%) (62). A review of 80 immunocompromised adults and children with *C. difficile* reported a cure rate of 89% with FMT (63).

Systematic reviews in adults have proposed that anti-CMV treatment may be clinically effective in ASC but there is inconsistency regarding the method of defining CMV infection (64-67). Recent ECCO adult guidelines report that intestinal CMV disease requires the presence of multiple inclusion bodies on histology and/or positive staining on immunohistochemistry rather than merely positive PCR (68-71). A recent meta-analysis reported benefit of antiviral treatment in steroid refractory IBD patients (OR=0.20 (95%CI 0.08-0.49)). The risk of colectomy after receiving anti-viral therapy was lower in patients in whom CMV was diagnosed based on histology and/or immunohistochemistry (3 studies; OR=0.06 (95%CI 0.01–0.34) rather than tissue PCR (64). One report described a child who underwent colectomy with subsequent identification of CMV, highlighting the importance of treating true infections in a timely manner (72). A case report of 6 children with CMV during an IBD flare suggested that ganciclovir treatment may be beneficial in some (73). In a recent case-control study from the Porto group of ESPGHAN including children admitted with ASC (15 CMV positive and 41 CMV negative), steroid failure was higher in the 15 CM- positive (93%) than the 41 negative matched controls (56%; p=0.009) (74). Of the CMV group, 93% were treated with ganciclovir (5/14 (36%) with 5mg/kg and 9/14 (64%) with 10mg/kg). Colectomy rates were higher in the CMV group on univariate analysis (33%) vs. the CMV negative controls (13%; p=0.049).

Although enteric viruses have been associated with IBD flares (24, 75), limited data exist regarding their role in ASC. In one report, enteric viruses were identified in 1% of hospitalized children with IBD (24). In another small study of 9 IBD children, norovirus was suggested as a cause for disease exacerbations (75). The sensitivity of ova and parasites testing in one stool specimen usually exceeds 80% (76, 77) and up to three samples, as well as immunofluorescence or EIA for specific parasites, (e.g. *Giardia lamblia*) increase the sensitivity (77, 78). In a retrospective case control study, cryptosporidium was identified in 4.5% of all paediatric IBD relapses, including hospitalized UC. In that small report, treatment with nitazoxanide led to a better outcome (79).

Pain management

<u>Recommendation</u>

1. Non-steroidal anti-inflammatory drugs (NSAID) should be avoided in ASC [EL5, adults EL3**] (98% agreement)**
2. Opiates should be used exceptionally with caution and close monitoring, in doses equivalent to 0.1 mg/kg morphine, given the remote risk of facilitating megacolon [EL5, adults EL5**] (98% agreement)**

<u>Practice points</u>

1. Bowel perforation or megacolon should be considered in case of severe or escalating abdominal pain **(100% agreement)**.
2. Hot packs and paracetamol could be attempted for pain management **(95% agreement)**.

Despite limited data, withdrawal of opiates has been suggested in adults given the potential of opiates and anticholinergics to trigger toxic megacolon, possibly due to decreased intestinal peristalsis (80-84). In a paediatric case-control study, 20% of patients with toxic megacolon received opiates (85) but it is unclear whether opiates are a marker of disease severity or a true predisposing factor for toxic megacolon. There are reports (but not in UC) that combined prolonged-release oxycodone and naloxone may manage pain without gastrointestinal complications (86).

In adults with IBD, NSAIDs have been associated with exacerbation or new onset disease (82, 87-92) and thus their use is discouraged in adult guidelines (80, 83). The data are conflicting regarding selective COX-2 inhibitors, but low doses and short treatment duration appear to be safe in UC (93-95). Several case reports describe ketamine use for pain management of IBD (96, 97) including one in paediatric ASC suggesting that ketamine may be effective at reducing opiate and NSAID use (97). Cannabinoids modulate visceral sensation and pain in animal models (98-100), however there is no relevant evidence in ASC and it may be potentially hazardous given its inhibitory effect on bowel peristalsis. There is very limited or no evidence for use of clonidine or naloxone (with opioids) in ASC.

Nutritional support

Recommendations

1. Regular diet should be continued in most ASC cases. Enteral (or parenteral in those not tolerating enteral) nutrition may be used if oral feeding is not tolerated or in malnutrition [EL4, adults EL1] **(98% agreement)**
2. Oral or enteral feeding is contraindicated in cases of megacolon, or when surgery is imminent [EL5, adults EL5] **(100% agreement)**

Practice points

1. Body weight, caloric intake and hydration status should be monitored daily, including review by a dietician as needed **(100% agreement)**.
2. In non-septic patients, standard caloric, protein and micronutrient intake should be provided according to age. In malnourished patients or those at risk for malnutrition, additional calories may be needed, while monitoring closely for re-feeding syndrome **(100% agreement)**.
3. There are no data showing a benefit of specific diets in ASC and thus they should be avoided **(98% agreement)**.
4. Electrolyte imbalance (especially hypokalaemia and hypomagnesaemia) can promote colonic dilatation. Thus, electrolytes should be monitored, at least every 1-3 days, according to the degree of the baseline values and clinical status **(98% agreement)**.

RCTs in adults have shown no benefit of bowel rest in ASC (101, 102). In one adult trial in ASC, enteral polymeric nutrition had a similar remission rate and need for colectomy as compared with TPN, but a higher increase of serum albumin (17% vs 4.6%, P=0.019), fewer adverse events (9% vs. 35%, P=0.046) and fewer postoperative infections (P=0.028) (103). In a retrospective case series of 15 children with ASC who had bowel rest and TPN, 5 (33%) required colectomy which is identical to the colectomy rate reported otherwise (13). In the prospective OSCI study of 128 children admitted for ASC (10), 74 (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 (personal communication from DT).

Thromboprophylaxis

<u>Recommendation</u>

1. The use of anticoagulation for preventing venous thromboembolic events (VTE) is recommended when one or more risk factors are present)according to age- see practice points) since the relative risk of VTE is higher during ASC, although the absolute rate is much lower than in adults [EL5, adults EL4] **(98% agreement)**

Practice points

1. Subcutaneous low molecular weight heparin (LMWH) should be considered in adolescents with ASC when one or more risk factors are present: smoking, oral contraceptives, complete immobilisation, central venous catheters (including PICC line), obesity, concurrent significant infection (e.g. respiratory, urinary, skin, and intra-abdominal), known prothrombotic disorder, previous VTE, and family history of VTE. Treatment duration should be individualized in consultation with the haematologists **(91% agreement).**
2. In prepubertal children, further evaluation of the safety and efficacy of thromboprophylaxis is required prior to widespread use. Thus, thromboprophylaxis may be considered in those with at least two risk factors **(95% agreement)**.
3. The most common LMWH is subcutaneous enoxaparin 1mg/kg/day (100IU/kg/day) in one daily dose. Monitoring with anti-Xa activity level is not usually required, except in children with significant renal impairment **(100% agreement)**.
4. Mobilization, adequate hydration, and prompt removal of un-needed central venous and arterial catheters, should be encouraged **(100% agreement)**.

Adult guidelines (104-106) recommend that LMWH should be commenced in ASC to prevent VTE which are much more common than in quiescent IBD (107) (108) (109) (110-114).

Heparin, however, is not effective for treating the colitis itself, as found in two meta-analyses (115, 116).

Studies suggest that the risk for VTE complications is increased also in children with ASC (117-119). While the absolute risk of VTE is much lower in children as compared with adults (9 events per 10,000 patient/years in children vs. 24 in those 40-60 years of age), the odds-ratio compared with controls is higher (OR~5 in children vs. ~2 in the 40-60 years old), given the very low background risk (112). The risk for VTE occurs mostly during active disease, and more frequently in UC compared to Crohn's disease (120). In a systematic review of paediatric studies, 50% of IBD children who developed VTE had at least one risk factor; 24% of whom had at least two (120). The site of VTE was cerebral in 54%, limbs in 26%, and abdominal vessels in 26%. Taken together, it could be concluded that while ASC increases the risk for VTE also in children, the absolute risk is lower than in adults, especially in the youngest age groups. Therefore, the presence of risk factors may identify those who are at particular risk (120).

Enoxaparin is the most frequently used drug for prophylaxis of VTE in children and adolescents (121) (122) (123). LMWH at prophylactic doses is effective, well tolerated and safe in children and adolescents while significant bleeding complications are very rare (124, 125). Minor bleeding episodes during prophylactic use of enoxaparin were reported at ~5-6% (126) (127).

5-ASA preparations

<u>Recommendation</u>

1. All mesalamine preparations (oral and rectal) should be discontinued upon admission to exclude mesalamine-intolerance, especially when mesalamine has been commenced

during the preceding few weeks; (re-) introduction should be considered after significant improvement in the clinical condition [EL5, adult EL5] **(100% agreement)**

The potential minimal effectiveness of oral or rectal mesalamine preparations is diluted by the severity of the disease in ASC and thus they are best stopped during the acute phase. There have been case reports of exacerbation of colitis symptoms in patients with mesalamine intolerance (128, 129), reported in 2-10% of patients (130).

Antibiotics

Recommendation

1. Antibiotics are not routinely recommended in children with ASC at admission. However, empiric antibiotic treatment may be considered when *C. difficile* or other bacterial infection is suspected until stool analysis is available [EL5, adults EL5] **(100% agreement)**

Two meta-analyses of antibiotic therapy in adult patients with ASC found nine RCTs, involving more than 600 patients, showing a statistically significant benefit for antibiotics in inducing remission (131, 132). Interestingly, all trials on intravenous antibiotics (133) (134) (135) showed no beneficial effects, whereas most of the trials on oral antibiotics (136) (137) (138) (139) (140) (141) (142) (143) showed some beneficial effects, as observed by Turner and colleagues (144). Nevertheless, a funnel plot suggested publication bias, and antibiotic regimens differed substantially. Current adult guidelines (105, 106, 145) recommend the use of antibiotics only if infection is considered, or immediately prior to surgery.

A small retrospective multicentre study (144) stated that the use of an oral wide-spectrum antibiotic cocktail (including metronidazole, amoxicillin, doxycycline and – in hospitalized patients – also vancomycin) in children with moderate to severe UC, refractory to multiple immunosuppressants, was effective in 47% of patients. This cocktail has been further explored in a pilot RCT, the PRASCO trial, in which the oral antibiotic cocktail was prescribed as an add-on therapy to IVCS in 28 children admitted with ASC (146). Day 5 PUCAI was significantly lower in the antibiotics+IVCS arm vs IVCS alone (25±16.7 vs 40.4±20.4, p=0.037), meeting the primary outcome of that trial. However the trial was not powered to detect differences in need for 2nd line therapy because there were only 2-3 IVCS failures in each group. Some of the authors of these guidelines have used the cocktail in treating steroid-refractory children with ASC as a last resort, at times awaiting colectomy, and a response has been clearly documented in some. Taken together, a short course of the oral antibiotic cocktail could be considered in selected severe refractory cases, while preparing for colectomy. Antibiotics should be discontinued if no significant response has been observed in 4-7 days. In any case, salvage therapy should not be delayed for the sake of this attempt.

Corticosteroids

Recommendation

1. Intravenous methylprednisolone 1 mg/kg/day (up to 40 mg/day) once daily in the morning is recommended as the initial treatment at admission [EL2, adults EL1]; a higher dose of 1.5 mg/kg/day (up to 60 mg/day) in one or two divided daily doses should be reserved to the more severe end of the spectrum and for children who have failed oral steroids prior to admission [EL4, adults EL4] **(100% agreement)**

Practice points:

1. As there is no firm evidence that the higher dose is superior to the lower dose, a rapid decline of methylprednisolone to 1mg/kg/d (40 mg/d) should be employed once response has been observed **(98% agreement)**.
2. Methylprednisolone has less mineralocorticoid effect and thus is preferred over hydrocortisone **(98% agreement)**.
3. Continuous IVCS infusion has no advantage over bolus administration **(100% agreement)**.

IVCS leads to clinical improvement in ~70% of paediatric ASC patients and its advent in the landmark trial of Truelove and Witts was the most important factor in the reduced mortality rate in ASC during the last century (9-11, 21, 147-151). Of those not responding to oral prednisone/prednisolone, approximately 2/3 will respond to IVCS. However, the initial response to corticosteroids is not influenced by the pharmacokinetics of steroids and the reason for the improved effectiveness with intravenous formulation is not entirely understood (11, 152, 153). Trials in adults with ASC have shown similar efficacy of adrenocorticotropic hormone (ACTH) to hydrocortisone (147, 154-158).

In a RCT in ambulatory adult patients, remission rate was higher in patients given oral prednisone 60mg or 40mg daily vs 20mg daily. Side effects were higher among patients given 60mg daily (159). In a meta-regression of cohorts studies in ASC, mainly in adults, colectomy rate did not correlate with methylprednisolone dose at or above 60mg/day as reported in the individual manuscripts (12).

A prospective multicenter cohort study in children with ASC (the OSCI study) showed that more than 70% of patients responded to daily methylprednisolone dose of 1-1.5 mg/kg (up to 40-60 mg) with no statistical difference in dose between responders and non-responders (10). Higher doses were also not justified according to a recent propensity score analysis in a large paediatric cohort of ASC (including among others the children from the OSCI study) (160) and, in a retrospective study among children with ASC, the dose of corticosteroids within the standard range was not different between those who responded and those who failed IVCS (9). Nonetheless, some case series suggested a benefit to higher and even pulse doses (161-163) while others did not (164, 165). It could be concluded that the vast majority of evidence suggests that 40 mg is not less effective than higher doses in ASC but, given the few anecdotal reports and the severity of ASC, it is not unreasonable to dose higher in selected patients for several days until response has been achieved.

Powell-Tuck et al. reported comparable efficacy and safety of once daily oral 40mg prednisolone to four divided doses in ambulatory UC and this has been traditionally extrapolated to the acute severe setting (166). This has been supported by another study in adults with ASC, in which continuous steroid infusion had neither better efficacy nor safety than bolus administration (149).

Radiography and toxic megacolon

Recommendations

1. Abdominal x-ray (AXR) should be performed upon admission with a low threshold especially in children with abdominal tenderness or distension, significant pain and those with systemic toxicity [EL4, adults EL4] **(100% agreement)**

2. Children with toxic megacolon, defined in Table 3, should be evaluated promptly by surgeons and conservative management should only be considered in stable clinical conditions and in highly specialized centres under close monitoring; urgent colectomy is recommended if no improvement is apparent within 24-72 hours [EL4, adults EL4] **(98% agreement)**

Practical points

1. An abdominal CT-scan or MRI may be indicated in patients without megacolon on AXR but who have signs of peritonitis or unexplained deterioration, to exclude a perforation **(98% agreement)**.
2. Evidence of transverse colon diameter >55 mm (or > 40 mm in children younger than 10 years) with signs of systemic toxicity are diagnostic of toxic megacolon in children. Features of systemic toxicity for diagnosing toxic megacolon in children include fever, tachycardia, dehydration, electrolyte disturbance, altered level of consciousness, and hypotension; steroids may mask peritoneal signs **(100% agreement)**.
3. The initial management of toxic megacolon includes, in addition to IVCS, intravenous fluid resuscitation, intravenous antibiotics (covering Gram-negative and anaerobic bacteria e.g. ampicillin, gentamycin and metronidazole), bowel rest and preparation for surgery. Insertion of a nasogastric tube, and rectal decompression tube as well as positional changes have been used in adults but supportive evidence is absent in children. Oral vancomycin may be considered until *C. difficile* status is known **(100% agreement)**.

4. Cyclosporine, tacrolimus and anti-TNFs are not recommended in the routine management of toxic megacolon although several successful case reports have been published **(100% agreement)**.

Toxic megacolon is a rare complication of ASC, occurring in 1-2% of paediatric ASC (15) and is associated with a high rate of mortality if left untreated. Megacolon is easily diagnosed by a simple AXR film, which may also play a predictive role in paediatric ASC (see section on prediction below) (167). Risk factors for toxic megacolon include CMV or *C. difficile* infection, hypokalaemia, hypomagnesemia, and the use of anticholinergics, antidepressants, loperamide, and opioids. Paediatric diagnostic criteria for toxic megacolon differ from those of adults, since altered level of consciousness and hypotension are less frequent in children (85) (168). In adults, long rectal tube insertion combined with intermittent rolling manoeuvres (169) and the knee-elbow position (170) have been used to promote decompression. Case reports indicate potential effectiveness of infliximab (171-173), leukocytapheresis (174), tacrolimus (175, 176), or hyperbaric oxygen (177) for treating toxic megacolon, but the evidence is anecdotal. Although CMV infection is more commonly associated with toxic megacolon, there is not enough evidence to support empiric treatment with ganciclovir without confirmation of CMV infection (178).

Ultrasonography (US) by an experienced radiologist directed at the colonic wall may have a role in providing valuable information regarding the extent of disease and severity of inflammation. Civitelli et al's study of 50 children with UC reported that bowel wall thickness, increased vascularity, loss of haustra and loss of stratification of the bowel wall independently predicted endoscopic severity (179). Each of these four variables was assigned a value of 1 (present) or 0 (absent); a score >2 had a sensitivity of 100% and a specificity of 93% (area under ROC curve of 0.98) for predicting severe disease at endoscopy. The US score strongly correlated with clinical (PUCAI, r=0.90) and endoscopic disease activity (Mayo endoscopy sub-score, r=0.94).

Monitoring disease and when to start 2nd line therapy (Figure 1)

Recommendations

1. A PUCAI >45 points on the third day of IVCS treatment should dictate planning for second-line therapy between days 3-5 [EL2, adults EL2] **(100% agreement)**
2. Second line therapy should be initiated on the fifth day of IVCS treatment in children with a PUCAI >65 points [EL2, adults EL2] **(100% agreement)**
3. IVCS should be continued for an additional 2-5 days in children with a PUCAI of 35-65 on day 5; daily monitoring for confirming gradual response is recommended before a decision on second line therapy is made in most cases within a total of 7-10 days of treatment [EL2, adults EL2] **(100% agreement)**

Practice points

1. Management of ASC may be initiated in local paediatric centres. Transfer to referral paediatric IBD centres should take place as needed but certainly by day 3 of IVCS in patients with a PUCAI >45 **(95% agreement)**.
2. Recommended planning for second line therapy between days 3-5 in non-responders (see section of 2nd line therapy) includes sigmoidoscopy (to detect infectious colitis (most notably CMV), granulomas and degree of inflammation), surgical consult, discussion

with a stoma specialist, exclusion of latent tuberculosis, serology for HBV and HCV, and/or blood tests required prior to treatment with calcineurin inhibitors (creatinine, lipids and magnesium) **(95% agreement)**.

3. Frequent monitoring of laboratory tests (including complete blood count, CRP, ESR, albumin and electrolytes) is advisable as needed but at least at diagnosis and on days 3 and 5 thereafter. CRP, albumin, and ESR have some value to predict IVCS failure and should be monitored also for that purpose **(100% agreement)**.
4. Faecal inflammatory markers have no role in the diagnosis or management of ASC **(95% agreement)**.

Clinical guidelines for adults recommend that second-line therapy should be initiated if no response to IVCS is achieved within 3-10 days after initiation as further steroid treatment in non-responding patients is associated with complications (106). The most commonly employed adult prediction rule, the Oxford index, focuses on stool frequency and CRP at day 3 (180). Other adult rules for predicting steroid refractoriness included also ESR, hemoglobin, albumin, transverse colon diameter on AXR and an Ulcerative Colitis Endoscopy Index of Severity (UCEIS) score $\geq$ 7 on admission (181-185).

PUCAI score at day 3 and 5 is the best validated predictive and decision making tool in children (9, 10, 186). In a retrospective study of 99 children with ASC, the PUCAI performed better than the adult indices to differentiate responders from non-responders at days 3 and 5 of IVCS treatment (9). These findings were then validated in the OSCI study of 128 children with ASC (10). A PUCAI>45 points on day 3 predicted non-response to IVCS with a sensitivity of 92%, specificity of 50%, NPV of 94% and a PPV of 43%, indicating that complete response is anticipated in those with PUCAI ≤45. A PUCAI>70 points on day 5 was associated with IVCS failure with a specificity of 100%, PPV of 100%, sensitivity of 35% and NPV of 79%, indicating that response is highly unlikely in the presence of PUCAI>70. Using a cut-off of >65 points had a specificity of 96%, PPV 82%, sensitivity 49% and NPV 82% (10). Likewise, in a retrospective multicenter study of 153 adults, a PUCAI>45 points on day 3 had a NPV of 88% and PPV of 54% for salvage therapy (anti-TNF, cyclosporine or colectomy), whereas a PUCAI >65 on day 5 had a PPV of 85% and NPV of 72% (187). Although a small minority of children with a day 5 PUCAI>65 may respond eventually, delaying second-line therapy has the potential of increasing morbidity in ASC as shown both in children (188) and adults (189).

The PUCAI performed better than four faecal markers (calprotectin, lactoferrin, M2-pyruvate kinase (M2-PK) and S100A12), in predicting IVCS failure in paediatric ASC (186). Ancillary studies from the OSCI cohort showed that both IL-6 (190) and the microbiome pattern at day 3 (191) have a role in predicting the need for second-line therapy in children with ASC, but this remains investigational. Livshits et al (167) reported that findings on AXR performed on 56 children with ASC during the first three days of admission were different between IVCS responders and non-responders (mucosal ulcerations: 3% vs 30%, p=0.006; mucosal tags: 9% vs 30%, p=0.073; and megacolon: 0% vs 13%, p=0.064).

Anemia is of particular concern in ASC and blood transfusion should be considered when haemoglobin level is below 8mg/dL. Iron replacement without the need for transfusion should be considered in children whose rectal bleeding has ceased (192). Intravenous iron infusion has not been widely reported in ASC so should be used with caution or deferred until after the acute phase has resolved (193). Generally, there is no need to correct hypoalbuminemia by albumin infusion unless the reduced oncotic pressure is associated with clinically significant complications (e.g. pulmonary edema, pleural infusions, or dyspnoea). Although hypoalbuminemia is associated with a decrease effectiveness of infliximab treatment, there are no published data that infusing albumin prior to infliximab administration improves outcome.

WHEN STEROIDS FAIL

Medical second-line therapies

Recommendations

1. Infliximab is recommended as the second-line medical therapy for anti-TNF naive children failing IVCS [EL3, adults EL1] **(100% agreement)**
2. Calcineurin inhibitors (tacrolimus and cyclosporine) can be considered as an alternative second-line medical therapy [EL4, adults EL1] **(100% agreement)**
3. When introducing second-line therapy, the possibility of non-response and therefore need for colectomy must always be discussed [EL4, adults EL4] **(100% agreement)**

Practice points:

1. The role of cyclosporine or tacrolimus as a rescue therapy is only as a bridge to long-term maintenance therapy. Hence, among steroid-refractory patients who have failed prior thiopurine maintenance therapy, infliximab is the preferred second-line medical therapy, unless bridging to vedolizumab is being considered **(100% agreement)**.
2. Dosing and target levels for infliximab, cyclosporine, and tacrolimus are given in Table 2. Other biologics (e.g. other anti-TNF regimens and vedolizumab) have not been studied in hospitalized steroid-refractory patients and thus should be generally avoided as induction treatments in this setting **(100% agreement)**.

3. Due to rapid clearance of infliximab in ASC, intensification of induction regimen is often needed to provide drug exposure equivalent to that attained with standard dosing outside the ASC setting. Doses of infliximab up to 10 mg/kg/dose may be considered and may be given more frequently than usual (e.g. weeks 0, 1, and 4-5). Drug levels obtained during induction may guide maximization of efficacy **(95% agreement)**.
4. Response to infliximab or calcineurin inhibitors should be judged daily by PUCAI and with attention to serum CRP and albumin. Significant response (PUCAI drop of at least 20 points) is anticipated within 4-7 days with either therapy **(100% agreement)**.
5. To reduce unnecessary immunosuppression, corticosteroids (which have been ineffective) should be weaned following introduction to second-line therapy or decision to proceed to colectomy. The taper strategy should be individualized based on the prior steroid exposure and the clinical status **(100% agreement)**.
6. Among responders to intensified induction, subsequent doses of infliximab during maintenance phase can often be gradually lowered and adjusted to standard dosing, ideally guided by therapeutic drug monitoring **(100% agreement)**.
7. Children who develop steroid-refractory ASC are at particular risk for colectomy within one year. Therefore, the addition of an immunomodulator is recommended in responders to infliximab for at least six months. Thiopurine therapy is preferred over methotrexate in UC given its superior effect on treating the colitis itself. The latter, however, is associated with reduced risk for lymphoma and thus the risk-benefit ratio should be individually balanced **(100% agreement)**.

It is essential that ineffective steroid therapy is not prolonged unduly and that therapeutic alternatives are considered early, utilizing a PUCAI-based algorithm on days 3 and 5. Both infliximab and calcineurin inhibitors are equally effective in inducing clinical remission in ASC in both children (11) and adults (194, 195). However, use of infliximab is currently more common in paediatric practice, due to greater familiarity with this agent, the ability to continue as maintenance therapy, and the overall better risk-benefit profile (10).

Infliximab

Jarnerot et al. first reported that 71% of 45 adults receiving one dose of 5mg/kg infliximab avoided colectomy vs. 34% receiving placebo (183). Observational studies among adult patients have reported short-term colectomy rates after rescue therapy with infliximab ranging from 20% to 75% (196). In the only prospective multicentre cohort study of ASC in children, the OSCI study, 33 of those failing IVCS received infliximab as rescue therapy, of whom 76% were able to be discharged without colectomy and the cumulative 1-year sustained response rate was 55% (18/33) (10, 197). Anecdotally, all 8 infliximab non-responders had new-onset disease vs. 10 (40%) of the responders (P=0.03); fecal biomarkers were not useful in predicting outcome, but higher disease activity, judged clinically, at admission and day 3 and 5 was associated with reduced response to infliximab (186, 198). Other case series have reported the use of infliximab in children with ASC, with pooled short-term response rate of 75% (95%CI 67-83); (n = 126, six studies) and a pooled 1-year response of 64% (95%CI 56–72) (11). In another prospective paediatric study, of 52 subjects who received infliximab (~half with acute severe colitis) the steroid free remission rate at 1 and 2 years was 38% and 21% and the likelihood of avoiding colectomy by 2 years was 61% (199).

Conventional weight-based regimens of infliximab (5 mg/kg at weeks 0, 2, 6) used in ambulatory patients might be insufficient for ASC. Infliximab pharmacokinetics can be influenced by multiple factors such as body mass index (BMI), serum albumin level, burden of inflammation, and concomitant use of immunosuppressive medications. The influence of these factors on infliximab clearance has been reviewed specifically in the setting of acute severe colitis (196) (200). High concentrations of circulating and tissue TNF may act as a 'sponge' that rapidly absorbs or neutralises anti-TNF (201). Excessive fecal losses of infliximab may occur as a result of protein leakage or blood loss via the inflamed colon (202).

In support of the need for intensive dosing, Ungar et al. found infliximab trough levels at day 14 to be significantly lower in adult patients with ASC compared with moderately severe UC patients (200). Limited data exist concerning optimal target infliximab levels during induction in any UC patients, and particularly in the setting of ASC. Among 101 adult patients with UC (but including only 15 with ASC) treated with standard 5 mg/kg dosing at weeks 0, 2 and 6, a trough level of $\geq$15 ug/ml at week 6 best predicted likelihood of short-term mucosal healing (area under the ROC of 0.69) (203). The rate of early colectomy was 6.7% in patients treated prospectively with an "accelerated" induction regimen, compared with 40% in a group of similar historical controls treated with the standard induction regimen, but long-term colectomy rates were similar between the two groups (204). In retrospective analysis of a paediatric cohort of hospitalized patients with steroid-refractory UC, higher clinical remission rates and a lower colectomy rate at one year were observed with intensified versus standard dosing (205).

Cyclosporine

In the first RCT on cyclosporine in ASC, Lichtiger et al reported that 9/11 patients improved on 4 mg/kg/day intravenous cyclosporine, whilst all 9 receiving placebo failed to improve. In a further trial among adults with acute severe UC, 73 patients (but not all failing IVCS) were randomised to either 2 mg/kg or 4 mg/kg of intravenous cyclosporine (206). Response rates at day 8 were similar in both groups (83% and 82% respectively), with 9% coming to colectomy in the 2 mg/kg group and 13% in the 4mg/kg group, with the former, therefore, being the preferred dose. Pooled results from controlled and uncontrolled trials in adults suggest that 76%-85% of patients respond to intravenous cyclosporine and avoid colectomy in the short term, with a median time to response of 4 days (207). In a systematic review of paediatric non-randomized studies, the pooled short-term success rate with cyclosporine was 81% [95%CI 76–86]; *n* = 94 from eight studies) (11).

Tacrolimus

Tacrolimus has been studied in two double-blind RCT's. In the first, 60 corticosteroid-refractory UC patients were randomly assigned to receive oral tacrolimus at high (10−15 ng/mL; n=19) or low (5−10 ng/mL; n=21) serum trough levels, or placebo (n=20) (208). Clinical response rates were 68% and 38% in the high and low trough groups, respectively, and 10% in the placebo. Another RCT treated 62 patients with corticosteroid-refractory, moderate-to-severe UC with tacrolimus to trough levels of 10−15 ng/mL (209). Clinical response rate of 50% was noted in the tacrolimus group and 13% in the placebo group at week 2 (p=0.003). A systematic review has combined the data of these two trials and other observational studies, and demonstrated that clinical response at 2 weeks was significantly higher with tacrolimus compared with placebo

(RR=4.61, 95%CI 2.09-10.2) especially in those treated with thiopurines in paralel. Colectomy-free rates at 1, 3, 6, and 12 months were 0.86, 0.84, 0.78, and 0.69 respectively (210).

Paediatric studies of tacrolimus as rescue therapy in ASC have been limited to retrospectively reported single-centre case series and one small multi-centre prospective study. In the latter, of 14 children with ASC, 69% responded to tacrolimus, but 44% of responders underwent colectomy by 1 year (211). Short-term response rates, meaning hospital discharge without colectomy ranged between 60% and 90% in the retrospective case series, with at least 40-50% requiring surgery by one to two years (212-215).

Infliximab vs. calcineurin inhibitors

Tacrolimus has never been included in a comparative trial with biologic therapy, but comparable efficacy of infliximab (with standard dosing) and cyclosporine has been demonstrated in two randomized comparative trials in adults (194, 195) and in meta-analysis of retrospective studies (216). The open label CYSIF trial showed that treatment failure at day 98 was reported in 60% patients with cyclosporine vs. 54% with infliximab (p=0.49). Colectomy rate by day 98 was 18% versus 21%, respectively (p=0.66) (194). Similarly, the randomised controlled Comparison Of iNfliximab and cyclosporine in STeroid Resistant Ulcerative Colitis (CONSTRUCT) trial found no significant difference regarding colectomy, mortality rates or the occurence of serious infections in 270 patients with steroid-resistant ASC treated with cyclosporine or infliximab (195).

Close monitoring of cyclosporine and tacrolimus levels is required, given the narrow margin between therapeutic and toxic levels. The individual circumstances of each patient should be considered when deciding between options for salvage therapy. Calcineurin inhibitors should be avoided in patients with low cholesterol or magnesium in view of the increased risk for neurological side effects, in the presence of diabetes, and in those with azotemia given the potential for renal-toxicity. On the other hand, infliximab is more costly and if an exit strategy is available (thiopurines in those previously naïve to thiopurines, or vedolizumab) then calcineurin inhibitors may be equally considered.

Third line and sequential medical therapy

Recommendations

1. In general, prompt referral for urgent colectomy is recommended following failure of one second-line medical therapy [EL3, adult EL2] **(95% agreement)**.

Practice points

1. n highly specialized centres and in selected non-fulminant cases, sequential therapy of calcineurin inhibitors after infliximab or vice versa might be considered after weaning off steroids since concomitant steroid therapy is the main contributor for infections. Steroid substitution therapy may be prescribed at physiological doses to avoid adrenal insufficiency when needed **(95% agreement)**.
2. Sequential therapy should not be considered unless an undetectable level of the previous drug has been documented **(93% agreement)**.
3. If sequential therapy is used, *Pneumocystis jiroveci pneumonia* (PJP) prophylaxis should be considered especially if triple immunosuppressive treatment is used **(98% agreement)**.

Third line medical therapy in ASC occurs when sequential medical therapy is used for salvage of the steroid-refractory patient – infliximab follows or is followed by a calcineurin inhibitor (cyclosporine or tacrolimus). This is a separate scenario from sequential therapy in the chronic active UC patient who is steroid-dependent or refractory. There have been no reports of 3rd line therapy in paediatric ASC to date in the literature. A systematic review of sequential therapy in adult ASC include 10 case series or cohort studies (314 participants), of which only one was prospective (but no RCT) [217]. It should be noted that many of the source studies contained a mixture of chronically active UC as well as ASC cases. A short-term response was seen in 62% of patients (95%CI 57-68) and remission in 39% (95%CI 34-44); colectomy rates were 28% (95%CI 22-35) and 42% (95%CI 36-49) at 3 and 12 months, respectively. Adverse events occurred in 23% (95%CI 18-28), including serious infection in 7% and mortality in 1%. The review concluded that the risk of sequential therapy seems lower than initially reported.

Given the potential for serious adverse events in these adult series and lack of paediatric studies, extrapolation from adults should follow the precautionary principal on this matter. It thus would be prudent to ensure that the levels of the 2nd line medication have cleared or nearly cleared before starting the 3rd line therapy in paediatric ASC. Further, multiple studies of IBD therapies have demonstrated that infectious complications are highest with concomitant corticosteroid therapy, and thus steroids must be weaned before 3rd line therapy is started. Until paediatric data are available, children with fulminant colitis who cannot safely wait until weaning must be referred without delay to colectomy.

SYNTHESIS AND SUMMARY

Discharge Recommendations

Recommendations

1. Children should not be discharged from hospital unless the disease is at most mild (i.e. PUCAI <35 points) but preferably closer to remission (i.e. PUCAI <10 points) [EL3, adult EL3] **(98% agreement)**
2. Thiopurine maintenance is generally recommended after ASC responsive to IVCS; exclusive mesalamine maintenance therapy could be considered if a response to steroids has been rapid and the patient was mesalamine naïve prior to admission [EL4, adult EL3] **(100% agreement)**
3. Patients responding to infliximab commenced during ASC should continue this drug as a maintenance treatment post discharge [EL2, adult EL2] **(100% agreement)**

Practice points

1. Before discharge, the following should be ensured: stable vital signs, adequate oral nutrition, stable haemoglobin, improving trend in inflammatory markers and albumin, toleration of oral medication, and discontinuation of pain-control medications at least 24 hours prior to discharge **(100% agreement)**.
2. Methylprednisolone should be converted prior to discharge to the biologically equivalent dose of prednisone. 1mg of methylprednisolone is equivalent to 1.25mg of prednisone (i.e. 40mg is equivalent to 50mg, respectively) **(98% agreement)**.
3. Thiopurines may take 10-14 weeks to have full therapeutic effect and should be introduced at full dose once the patient is responding to corticosteroids (details in Part 1 of these guidelines) **(98% agreement)**.

4. If cyclosporine or tacrolimus is commenced during ASC treatment this should be weaned within several months as a bridge to thiopurine or other maintenance medication, such as vedolizumab, to minimize adverse drug events **(98% agreement)**.
5. *Pneumocystis jiroveci pneumonia* (PJP) prophylaxis with trimethoprim-sulfamethoxazole should be considered for triple immunosuppression which includes anti-TNF or a calcineurin inhibitor plus 2 other immunosuppressants, mainly steroids. Trimethoprim-sulfamethoxazole dosing: 450mg/m^2 twice daily for 3 days each week, (maximum daily dose 1.92g) either consecutive or alternate day dosing (note 480mg of trimethoprim-sulfamethoxazole consists of trimethoprim 80mg and sulfamethoxazole 400mg) **(100% agreement)**.
6. Oral iron supplements should be commenced after discharge in cases of anemia with haemoglobin ≥10g/dL and quiescent disease. Intravenous iron should be considered in severe anemia (i.e. <10g/dL), active disease or if oral supplements are not tolerated **(98% agreement)**.
7. Mesalamine may be introduced or re-introduced at discharge, as appropriate **(100% agreement)**.
8. Children should be reviewed clinically within 2-3 weeks of discharge post ASC and then as needed **(98% agreement)**.

The timing of discharge and tight monitoring of the management during the immediate post-discharge period are crucial for avoiding early recurrence. In a post hoc analysis of 37 children with UC commenced on infliximab (90% moderate-severe activity) a week 8 PUCAI <10 points best predicted those in steroid-free remission after 1 year (218). Fifty-three percent of children with a PUCAI<10 at week 8 compared with 20% otherwise were in remission (p=0.036). Similarly, in the recent prospective PROTECT study, 148 children with UC were admitted at diagnosis for ASC. Failure to be in clinical remission (PUCAI<10) by week 4 was highly associated with need for additional medical therapy by Week 12 (week 4 remission was achieved in 80% of those with steroid-free remission at week 12 vs. 49% of those with active disease at week 12 and only 6% of those who required additional therapy; p<0.0001) (219). It is therefore important to optimize treatment in those who do not attain complete clinical remission post discharge.

In the prospective OSCI study in paediatric ASC, the mean PUCAI decreased from 72+/-12 points on admission to 18+/-13 points at discharge in those who responded to either steroids or second line therapy (p<0.0001) (10). Of the infliximab responders, 28% (7/25) were discharged in clinical remission (PUCAI <10 points) and 72% (18/25) had mild disease at most (PUCAI <35 points) at discharge. This is in keeping with a study which highlighted a median discharge PUCAI score of 25 points (IQR 15-30) following an admission for ASC (15). In the adult literature there is evidence that achieving complete clinical remission (≤3 stools/day with no visible blood) during the index hospital admission improves long term outcome and delays the need for colectomy (220).

Post paediatric ASC discharge, 49% of initial IVCS responders lost clinical response despite maintenance mesalamine or thiopurine therapy during the subsequent 1 year and 14% became steroid dependent (10). In order to limit steroid exposure to the minimum necessary, expert consensus steroid tapering algorithm has been proposed (see Table in Part 1 of these recommendations).

Azathioprine has been shown to be superior to mesalamine in maintaining remission post IVCS in one small paediatric study (221). Two adult RCTs also showed superiority of thiopurines over mesalamine (222) (223). A combination of azathioprine with mesalamine leads to higher 6-TGN levels and improves the likelihood of avoiding rescue therapy at 2 years, as found in a prospective multicenter study (224, 225). Given the severity of ASC, the higher likelihood of colectomy in the subsequent year (7, 10), and the excellent safety profile of mesalamine, combination therapy of mesalamine with thiopurines should be favoured. If exclusive mesalamine treatment is to be used, there should be a low threshold for treatment optimization and escalation.

Calcineurin inhibitors should be used only as a bridge to thiopurines or other maintenance treatment such as vedolizumab after several months to avoid toxicity (213, 226). Success rate is higher in children who are treated with cyclosporine combined with immunomodulatory therapy prior to discharge with a pooled long term colectomy free rate of 71% (55-83%) (11, 227, 228). Being thiopurine-naïve is associated with lower colectomy risk in adult ASC (229-233) consequently, maintenance with vedolizumab post discharge could be considered in those who failed thiopurines prior to salvage with calcineurin inhibitors.

IBD patients are at an increased relative risk of *Pneumocystic jiroveci* (PJP) (HR, 2.96; 95% CI 1.75-4.29) but low absolute risk (234). PJP has been described in IBD patients on corticosteroids, calcineurin inhibitors, thiopurines and anti-TNF agents (235-240), while a recent administrative study showed low risk even on triple therapy (albeit the vast majority were not during an ASC episode) (241). There is only one paediatric IBD case report of PJP (associated with infliximab monotherapy)(242). Corticosteroids are a major contributor to PJP in the non-HIV population and the use of multiple immunosuppressive agents increases the risk further (243-246). To date, 162 cases of PJP are reported in the IBD and rheumatology literature associated with anti-TNF therapy with a 20-27% mortality rate (234, 239, 240, 242, 247-256) (239). A meta-analysis of prophylactic treatment with co-trimoxazole in patients with hematological cancers and transplant recipients reported a 91% reduction in PJP incidence (257). As there are no robust studies in children, benefits of treatment must be balanced against medication side effects. The ECCO opportunistic infection guidelines recommend PJP prophylaxis in IBD patients on triple immunosuppression with one of these being either a calcineurin inhibitor or anti-TNF therapy (55).

CONCLUSION

Based on systematic review of the literature and a consensus process, we yielded 24 recommendations and 43 practice points. We have attempted to provide some practical guidance even when data were insufficient. In these cases we emphasized that the guidance is based on common knowledge and experts' opinion. Recognizing the unique considerations in children, some of the recommendations are different than those published for adults.

We have summarized the recommendations in a treatment algorithm; this must be used in conjunction with the supporting text (Figure 1). 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 STATEMENT

ESPGHAN and ECCO are not responsible for the practices of physicians and provides guidelines and position papers as indicators of best practice only. 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.

DISCLAIMER

ESPGHAN is not responsible for the practices of physicians and provides guidelines and position papers as indicators of best practice only. Diagnosis and treatment is at the discretion of physicians.

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Figure and Table Legends

Figure 1: Algorithm for management of acute severe pediatric UC

Footnote:

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 guidelines.

1. Complete blood count, electrolytes, liver enzymes, albumin, C-reactive protein, erythrocyte sedimentation rate, blood culture (if febrile)
2. Stool culture, viruses and C. *difficile* toxin
3. Continue normal diet if possible. If 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
4. Dilatation on plain abdominal X-ray is suggested by colonic width of >56mm in children older than 10 years of age and >40mm in younger children. Defined as toxic megacolon if associated with toxicity (table 3 in the text).

NPO, nothing per-os

*Revised with permission from: Turner D, Travis SP, Griffiths AM et al. 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. American Journal of Gastroenterology 2011;**106**(4):574-88.*

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Table 1: Paediatric Ulcerative Colitis Activity Index (PUCAI)

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

Table 2: Second-line rescue therapies in paediatric steroid-refractory acute severe UC

	Infliximab	Cyclosporine	Tacrolimus
Tests before treatment	Excluding tuberculosis; varicella, hepatitis B, and hepatitis C (and HIV when appropriate) serology	Serum creatinine, glucose, electrolytes (including magnesium), serum cholesterol	As per cyclosporine
Initial dosing	5-10 mg/kg for dose 1 and consider repeat at week 1 and week 4. Emerging data in ASC indicate that intensified induction is more successful than standard 5 mg/kg given at weeks 0, 2, 6.	2 mg/kg/day continuous intravenous infusion	0.1 mg/kg/dose orally twice daily
Main toxicity	Infusion reactions, immune suppression and rare opportunistic infections	Hypertension, hyperglycemia, hypomagnesemia, immune suppression, azotemia, seizures (dose and hypercholesterolemia dependent), hirsutism	As per cyclosporine, but without hirsutism. Additionally self-remitting tremor.
Ongoing treatment following response	Continue regularly scheduled maintenance infusions (q 4-8 weeks), ideally guided by therapeutic drug monitoring	Initiate thiopurines (or other agent to maintain remission) so that cyclosporine can be discontinued within several months	Initiate thiopurines (or other agent to maintain remission) so that tacrolimus can be discontinued within several months
Target drug levels during induction	Limited data on target levels during induction	Aim initially for 150-300 ng/ml	Aim initially for 10-15 ng/ml
Target levels once response achieved	Minimum 5-10 ug/ml at trough during maintenance	100-200 ng/ml once remission achieved	5-7 ng/ml once remission achieved; longer duration treatment using lower levels of 2-5 have been reported
Monitoring/ prevention of toxicity	PJP prophylaxis to be strongly considered with calcineurin inhibitors, IMM and steroids	PJP prophylaxis to be strongly considered with calcineurin inhibitors, IMM and steroids Monitor drug levels,	PJP prophylaxis to be strongly considered with calcineurin inhibitors, IMM and steroids Monitor drug levels,

		creatinine, glucose, electrolytes (including magnesium), lipid levels, blood pressure	creatinine, glucose, electrolytes (including magnesium), lipid levels, blood pressure

Table 3: Previously established adult and the currently suggested Paediatric criteria for diagnosis of toxic megacolon

Adult criteria (168)	**Suggested Paediatric criteria (85)**
A) Radiographic evidence of colonic distention B) At least three of the following: 1. Fever >38 degrees Celsius 2. Heart rate >120/min 3. Neutrophilic leukocytosis >10.5 x 108 /L 4. Anemia C) In addition to the above, at least one of the following: 1. Dehydration 2. Altered level of consciousness 3. Electrolyte disturbances 4. Hypotension	A) Radiographic evidence of transverse colon diameter ≥56 mm (or >40mm in those <10 years) PLUS B) Evidence of systemic toxicity, such as: 1. Fever >38 degrees Celsius 2. Tachycardia (heart rate >2 SD above mean for age) 3. Dehydration 4. Electrolyte disturbance (sodium, potassium or chloride) 5. Altered level of consciousness or coma 6. Hypotension or shock

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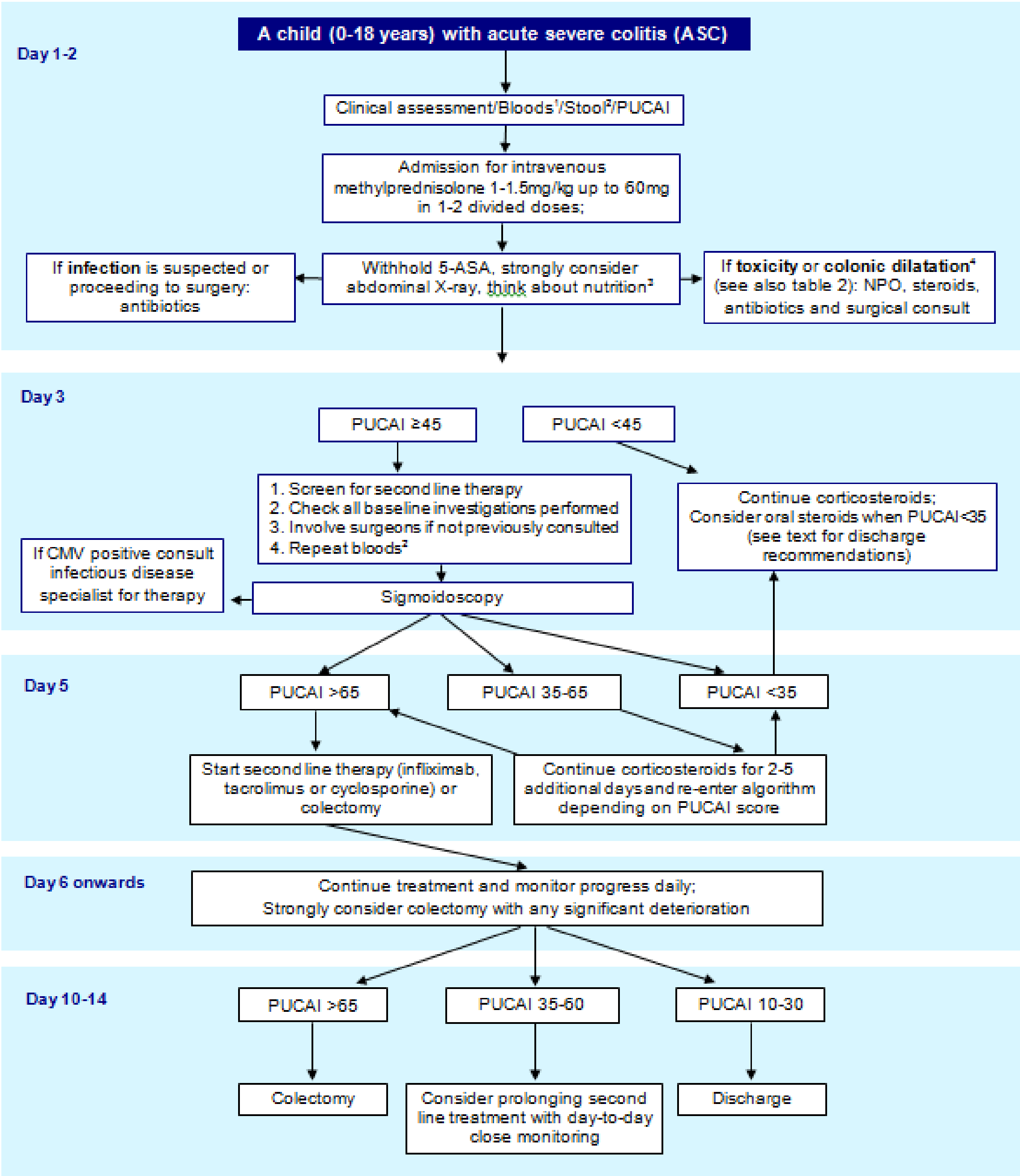
Figure 1: Algorithm for management of acute severe pediatric UC



Footnote:

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 guidelines.

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1. Complete blood count, electrolytes, liver enzymes, albumin, C-reactive protein, erythrocyte sedimentation rate, blood culture (if febrile). Blood transfusion should be considered when haemoglobin level s below 8mg/dL. Intravenous iron infusion has not been widely reported in ASC so should be used with caution or deferred until after the acute phase has resolved. Generally, there is no need to correct hypoalbuminemia by albumin infusion unless the reduced oncotic pressure is associated with clinically significant complications (see text).
2. Stool culture, viruses and C. *difficile* toxin.
3. Continue normal diet if possible. If 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
4. Dilatation on plain abdominal X-ray is suggested by colonic width of >56mm in children older than 10 years of age and >40mm in younger children. Defined as toxic megacolon if associated with toxicity (table 3 in the text).

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