

Management of Paediatric Ulcerative Colitis, Part 2: Acute Severe Colitis—An Evidence-based Consensus Guideline From the European Crohn's and Colitis Organization and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition

*Dan Turner, †Frank M. Ruemmele, *Esther Orlanski-Meyer, ‡Anne M. Griffiths, §Javier Martin de Carpi, ||Jiri Bronsky, ¶Gabor Veres, #Marina Aloï, **Caterina Strisciuglio, ††Christian P. Braegger, ††Amit Assa, §§Claudio Romano, ||||Séamus Hussey, ¶¶Michael Stanton, ###Mikko Pakarinen, ***Lissy de Ridder, †††Konstantinos H. Katsanos, †††Nick Croft, §§§Victor Manuel Navas-López, |||||David C. Wilson, ¶¶¶Sally Lawrence, and ####Richard K. Russell

ABSTRACT

Background and aim: Acute severe colitis (ASC) is one of the few emergencies in pediatric 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 2 face-to-face meetings, was followed by voting of 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. 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.

Key Words: acute severe colitis, antibiotics, anti-coagulants, anti-TNF, colectomy, mesalamine, Pediatric Ulcerative Colitis Activity Index, prediction, steroids, ulcerative colitis

(*JPGN* 2018;67: 292–310)

Received December 16, 2017; accepted April 16, 2018.

From the *Shaare Zedek Medical Center, The Hebrew University of Jerusalem, Jerusalem, Israel, the †Université Paris Descartes, Sorbonne Paris Cité, AHPH, Hôpital Necker Enfants Malades, Paris, France, the ‡The Hospital for Sick Children, University of Toronto, Toronto, Canada, the §Hospital Sant Joan de Déu, Barcelona, Spain, the ||Department of Paediatrics, University Hospital Motol, Prague, Czech Republic, the ¶1st Department of Pediatrics, Semmelweis University, Budapest, Hungary, the #Pediatric Gastroenterology and Liver Unit, Sapienza University of Rome, Rome, the **Department of Woman, Child and General and Specialistic Surgery, University of Campania “Luigi Vanvitelli,” Napoli, Italy, the ††University Children's Hospital, Zurich, Switzerland, the ††Schneider Children's Hospital, Petach Tikva (affiliated to the Sackler Faculty of Medicine), Tel Aviv University, Tel Aviv, Israel, the §§Pediatric Department, University of Messina, Messina, Italy, the

What Is Known

- The previously published European Society of Paediatric Gastroenterology, Hepatology and Nutrition and European Crohn's and Colitis Organization guidelines on acute severe colitis 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 Paediatric Ulcerative Colitis Activity Index-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.

||||National Children's Research Centre, Royal College of Surgeons of Ireland and University College Dublin, Ireland; and University College Dublin, Dublin, Ireland, the ¶||Southampton Children's Hospital, Southampton, UK, the ##Helsinki University Children's Hospital, Department of Pediatric Surgery, Helsinki, Finland, the ***Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands, the †††Medical School and University Hospital of Ioannina, Ioannina, Greece, the †††Barts and the London School of Medicine, Queen Mary University of London, London, UK, the §§§Pediatric Gastroenterology and Nutrition Unit, Hospital Materno, IBIMA, Málaga, Spain, the |||||Child Life and Health, University of Edinburgh, Edinburgh, UK, the ¶¶BC Children's Hospital, University of British Columbia, Vancouver BC, Canada, and the ####The Royal Hospital for Children, Glasgow, UK.

INTRODUCTION

Acute severe ulcerative colitis (ASC), a medical emergency in children, is defined by a Paediatric Ulcerative Colitis Activity Index (PUCAI) score of at least 65 points (1–3) (Table 1). Pediatric-onset ulcerative colitis (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 Inflammatory Bowel Disease 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 1 episode by the end of the follow-up of 48 months (7). Comparable rates were found in a multicenter pediatric 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 \geq 65 is associated with a more refractory disease course in pediatric UC, both at disease onset and thereafter (8–10). In a systematic review, the pooled steroid-refractory rate in ASC across all pediatric studies was 34% (11), slightly higher than the pooled 29% rate found in adult studies (12). In 2 pediatric 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 between 40% to 70% (9,11–13) to approximately 10% to 20% in children (10,14,15) and the 1-year colectomy rate from \sim 60% (9,16) to between 18% to 22% (10,14,16). Among those who fail IVCS treatment, roughly 50% to 60% of responders to salvage medical therapy will require colectomy within 1 to 2 years (10,14). To add to the complexity, enteric infections, and adverse events to medications (primarily mesalamine and thiopurines) 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).

TABLE 1. Paediatric Ulcerative Colitis Activity Index

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 hours	
0–2	0
3–5	5
6–8	10
>8	15
(5) Nocturnal stools (any episode causing waking)	
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 (2).

PUCAI = Paediatric Ulcerative Colitis Activity Index.

Mortality in ASC has decreased in adults from over 70% in 1933 to 20% to 25% in the 1950s 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 <1% nowadays (12,20–22).

Address correspondence and reprint requests to Dan Turner, Shaare Zedek Medical Center, Jerusalem, Israel (e-mail: turnerd@szmc.org.il).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jpgn.org).

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.

The study was supported by ECCO and ESPGHAN.

D.T. for last 3 years received consultation fee, research grant, royalties, or honorarium from Janssen, Pfizer, Hospital for Sick Children (UC activity index royalties from industry trials), Ferring, AstraZeneca, Abbvie, Takeda, Ferring, Boehringer Ingelheim, Biogen, Atlantic Health, Shire, and Celgene; J.M.d.C., last 3 years received consultation fee, research grant, travel grant, or honorarium from Abbvie, Abbot, Nestle, MSD, Otsuka, Faes, Nutricia, and Fresenius; J.B. received honoraria, speaker's fees and/or congress fees from Abbvie, MSD, Nestle, Nutricia, and Biocodex. G.V., received consultation fee from Nestle, Danone, and Abbvie. M.A., last 3 years received honorarium from Abbvie; F.M.R. received speaker fees from Schering-Plough, Nestlé, Mead Johnson, Ferring, MSD, Johnson & Johnson, Centocor, Abbvie; serves as a board member for: SAC:DEVELOP (Johnson & Johnson), CAPE (ABBVIE), LEA (ABBVIE) and has been invited to

MSD France, Nestlé Nutrition Institute, Nestlé Health Science, Danone, TAKEDA, CELGENE, BIOGEN, SHIRE, PFIZER, and THERAKOS. A.A. received research grant from Abbvie; S.H. received a travel bursary from Abbvie; L.d.R., last 3 years received consultation fee, research grant, or honorarium from ZonMw (National Health Institute), Janssen, Pfizer, Mundipharma, Shire, and Abbvie; K.K., honoraria for consulting services (educational services, scientific articles, participation in Advisory Boards, clinical trials, others) from the companies as follows Abbvie, ENORASIS, Ferring, JANNSEN, MSD, and Takeda; V.N.L., last 3 years received consultation fee or honorarium from Abbvie, Otsuka, and Nestlé Health Science; S.L., last 2 years received honorarium from Janssen; R.K.R. has received speaker's fees, travel support, or has performed consultancy work with Nestlé Health Science, Abbvie, Napp, Celltrion, Shire, and Janssen. E.O. has received honoraria from Abbvie; N.C., research funding for trials, speaker fees, and travel for conferences from Takeda, Shire, Celgene, Roche; M.P. lectures and congress fees sponsored by Astellas, Baxter, and Shire; A.M.G. consultancy, speakers fees, or research support for Abbvie, Celgene, Ferring, Gilead, Janssen, Pfizer, and Takeda. D.C.W. has received speaker's fees, travel support, or has performed consultancy work with Abbvie, Takeda, and Falk. M.S., C.S., C.B., and C.R. report no conflicts of interests to declare.

Copyright © 2018 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
DOI: 10.1097/MPG.0000000000002036

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 European Crohn's and Colitis Organization–European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ECCO-ESPGHAN) guidelines on pediatric 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. (Supplemental Digital Content include ASC Tables of evidence December 14, 2017, <http://links.lww.com/MPG/B395>).

INITIAL MANAGEMENT

Infectious Screening

Recommendations

1. Bacterial causes for ASC should be excluded by a stool culture including *Clostridium 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 (eg, 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**).

Practice Points

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 1 stool sample is sufficient (**100% agreement**).
2. Oral vancomycin for *C difficile* should be prescribed for 10 to 14 days in doses of 10 mg/kg per dose 4 times daily up to an adult dose of 125 to 250 mg increased if needed to maximum of 500 mg 4 times daily, although national recommendations vary. Oral metronidazole may be used in the absence of oral vancomycin at a dose of 7.5 to 10 mg/kg per dose 3 times daily (to a maximum of 2 g/24 h) for 10 to 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-disease 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 pediatric ASC. In 1 retrospective study, 24% (22/92) of flares in children requiring hospital admission for inflammatory bowel disease (IBD) were associated with some enteric infection (24). Stool bacterial culture was positive in 2% of children admitted for UC exacerbation, as reported in 2 pediatric cohorts (15,25).

C difficile is the most commonly identified organism, ranging in pediatric IBD from 3% to 47% of flares (24–32), compared with 7.5% per year of follow-up in outpatient pediatric IBD, which may also 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 >12 times greater in IBD compared with non-IBD hospitalizations with increasing incidence over time (29). In hospitalized pediatric 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 criterion 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, or the toxin products (toxin A and B). The sensitivity and specificity of both tests vary and recent guidance advises testing initially for glutamate dehydrogenase EIA and if positive, confirming the results by EIA for toxins A and B (45–47). Nucleic acid amplification tests, 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 1 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 randomized controlled trial (RCT) of metronidazole versus rifaximin for treating *C difficile* in children with IBD (not with ASC) showed eradication rate of 71% versus 79%, respectively (49). A retrospective pediatric 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 poorer *C difficile* eradication rate with metronidazole (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). Fidaxomicin 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 (56–59). Its use is limited by its high cost compared to vancomycin. There is currently no evidence to support the use of fecal microbial transplantation (FMT) in ASC associated with *C difficile* in children or adults. FMT is, however, highly effective for eradication of recurrent *C difficile* (60) albeit perhaps slightly less in IBD (61) and could be considered

also 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 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% confidence interval [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 CMV-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 5 mg/kg and 9/14 (64%) with 10 mg/kg). Colectomy rates were higher in the CMV group on univariate analysis (33%) versus 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 1 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 1 stool specimen usually slightly exceeds 80% (76,77) and up to 3 samples, as well as immunofluorescence or EIA for specific parasites, (eg, *Giardia lamblia*) increase the sensitivity (77,78). In a retrospective case control study, cryptosporidium was identified in 4.5% of all pediatric IBD relapses, including hospitalized UC. In that small report, treatment with nitazoxanide led to a better outcome (79).

Pain Management

Recommendations

1. Non-steroidal anti-inflammatory drugs (NSAIDs) 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)**.

Practice Points

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 pediatric 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 1 in pediatric 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 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 to 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 1 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

Recommendation

1. The use of anticoagulation for preventing venous thromboembolic event (VTE) is recommended when 1 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 1 or more risk factors are present: smoking, oral contraceptives, complete immobilization, central venous catheters (including PICC line), obesity, concurrent significant infection (eg, 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 hematologists (**91% agreement**).
2. In prepubertal children, further evaluation of the safety and efficacy of thromboprophylaxis is required before widespread use. Thus, thromboprophylaxis may be considered in those with at least 2 risk factors (**95% agreement**).
3. The most common LMWH is subcutaneous enoxaparin 1 mg/kg/day (100 IU/kg/day) in 1 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 VT which are much more common than in quiescent IBD (107–114). Heparin, however, is not effective for treating the colitis itself, as found in 2 meta-analyses (115,116).

Studies suggest that the risk for VTE complications is increased also in children with ASC (117–119). Although the absolute risk of VTE is much lower in children as compared with adults (9 events per 10,000 patient per 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 low background risk (112). The risk for VTE occurs mostly during active disease, and more frequently in UC compared to Crohn

disease (120). In a systematic review of pediatric studies, 50% of IBD children who developed VTE had at least 1 risk factor; 24% of whom had at least 2 (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 one or more risk factors may identify those who are at particular risk and who would therefore benefit from thromboprophylaxis (120).

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

5-ASA Preparations

Recommendation

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% to 10% of patients (130).

Antibiotics

Recommendation

1. Antibiotics are not routinely recommended in children with ASC at admission. Empiric antibiotic treatment may, however, 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 9 RCTs, involving >600 patients, showing a statistically significant benefit for antibiotics in inducing remission (131,132). Interestingly, all trials on intravenous antibiotics (133–135) showed no beneficial effects, whereas most of the trials on oral antibiotics (136–143) showed some beneficial effects, as observed by Turner et al (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 before surgery.

A small retrospective multicenter 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 the pilot PRASCO trial, in which 28 children admitted with ASC were randomized to receiving the oral antibiotic cocktail as an add-on therapy to IVCS (146). Day 5 PUCAI was significantly lower in the antibiotics+IVCS arm versus IVCS alone (25 ± 16.7 vs 40.4 ± 20.4 , $P=0.037$), meeting the primary outcome of that trial. The trial was, however, not powered to detect differences in need for second-line therapy because there were only 2 to 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 to 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 1 or 2 divided daily doses should be reserved to the more severe end of the spectrum and for children who have failed oral steroids before 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 1 mg/kg/day (40 mg/day) should be employed once response has been observed **(98% agreement)**.
2. Methylprednisolone as before 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 pediatric 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 two-third will respond to IVCS. The initial response to corticosteroids is, however, 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 to hydrocortisone (147,154–158).

In an RCT in ambulatory adult patients, remission rate was higher in patients given oral prednisone 60 or 40 mg daily versus 20 mg daily. Adverse effects were higher among patients given 60 mg daily (159). In a meta-regression of cohort studies in ASC, mainly in

adults, colectomy rate did not correlate with methylprednisolone dose at or above 60 mg/day as reported in the individual manuscripts (12).

A prospective multicenter cohort study in children with ASC (the OSCI study) showed that >70% of patients responded to daily methylprednisolone dose of 1 to 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 pediatric 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 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 40 mg prednisolone to 4 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 2, should be evaluated promptly by surgeons and conservative management should only be considered in stable clinical conditions and in highly specialized centers under close monitoring; urgent colectomy is recommended if no improvement is apparent within 24 to 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 >56 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, eg, ampicillin, gentamycin, and metronidazole), bowel rest, and preparation for

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

Adult criteria (168)	Suggested Paediatric criteria (85)
(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 3 of the following: (1) Fever $>38^{\circ}\text{C}$ (2) Heart rate $>120/\text{min}$ (3) Neutrophilic leukocytosis $>10.5 \times 10^8/\text{L}$ (4) Anemia	PLUS
(C) In addition to the above, at least 1 of the following: (1) Dehydration (2) Altered level of consciousness (3) Electrolyte disturbances (4) Hypotension	(B) Evidence of systemic toxicity, such as: (1) Fever $>38^{\circ}\text{C}$ (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

Reproduced with permission from (1).

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**).

- 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% to 2% of pediatric 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 pediatric ASC (see section Monitoring Disease and When to Start Second line Therapy) (167). Risk factors for toxic megacolon include CMV or *C difficile* infection, hypokalaemia, hypomagnesemia, and the use of anticholinergics, antidepressants, loperamide, and opioids. Pediatric 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 maneuvers (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 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 4 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 receiver operator characteristic [ROC] curve of 0.98) for predicting severe disease at endoscopy. The ultrasonography score strongly correlated with clinical (PUCAL, $r=0.90$) and endoscopic disease activity (Mayo endoscopy subscore, $r=0.94$).

Monitoring Disease and When to Start Second-line Therapy

Recommendations

- A PUCAL >45 points on the third day of IVCS treatment should dictate planning for second-line therapy between days 3 to 5 [EL2, adults EL2] (**100% agreement**).
- Second-line therapy should be initiated on the fifth day of IVCS treatment in children with a PUCAL >65 points [EL2, adults EL2] (**100% agreement**).
- IVCS should be continued for an additional 2 to 5 days in children with a PUCAL of 35 to 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 to 10 days of treatment [EL2, adults EL2] (**100% agreement**) (Fig. 1).

Practice Points

- Management of ASC may be initiated in local pediatric centers. Transfer to referral pediatric IBD centers should take place as needed but certainly by day 3 of IVCS in patients with a PUCAL >45 (**95% agreement**).
- Recommended planning for second-line therapy between days 3 and 5 in non-responders (see section of second-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 before treatment with calcineurin inhibitors (creatinine, lipids, and magnesium) (**95% agreement**).
- Frequent monitoring of laboratory tests (including complete blood count, c-reactive protein (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

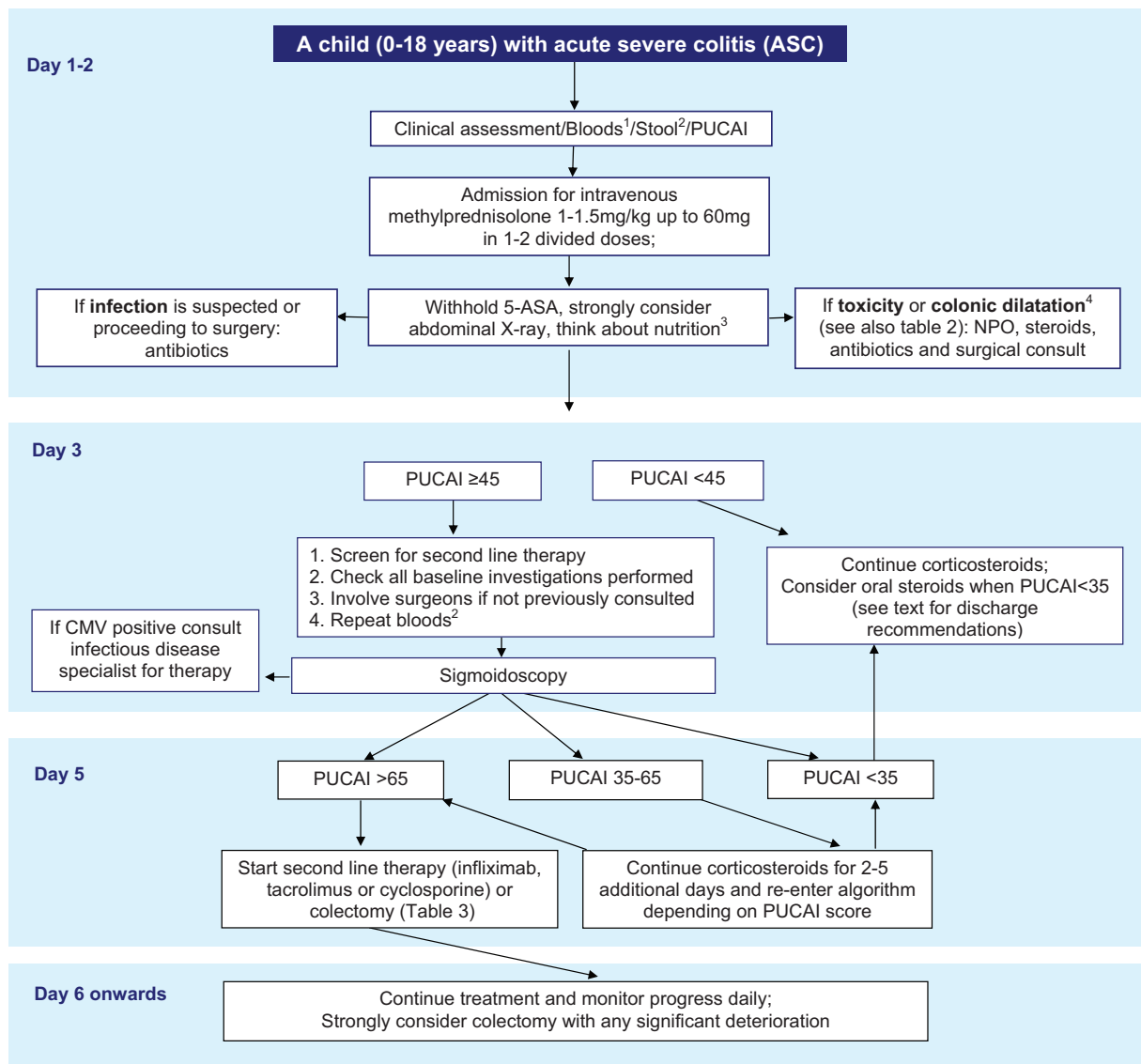


FIGURE 1. Algorithm for management of acute severe pediatric ulcerative colitis (UC). This is a guide to aid the clinician in the management of a pediatric patient with ASC for timely decision making. It acts as a guide only and does not replace clinical assessment for individual patients. It should be interpreted in conjunction with the text of the supporting guidelines. (1) Complete blood count, electrolytes, liver enzymes, albumin, C-reactive protein, erythrocyte sedimentation rate, blood culture (if febrile). (2) Stool culture, viruses and *Clostridium 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 >56 mm in children older than 10 years of age and >40 mm in younger children. Defined as toxic megacolon if associated with toxicity (Table 2 in the text). NPO = nothing per-os. Reproduced with permission from (1).

IVCS failure and should be monitored also for that purpose (**100% agreement**).

4. Fecal 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 to 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 score ≥ 7 on admission (181–185).

PUCAI score at days 3 and 5 is the best validated predictive and decision-making tool in children with ASC (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%, negative predictive value (NPV) of 94% and a positive predictive value (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 cutoff 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 an NPV of 88% and PPV of 54% for salvage therapy (anti-tumor necrosis factor [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 4 fecal markers (calprotectin, lactoferrin, M2-pyruvate kinase [M2-PK] and S100A12), in predicting IVCS failure in pediatric ASC (186). Ancillary studies from the OSCI cohort showed that both interleukin-6 (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 3 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 hemoglobin level is below 8 mg/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 (eg, pulmonary edema, pleural effusions, or dyspnea). Although hypoalbuminemia is associated with a decrease effectiveness of infliximab treatment, there are no published data that infusing albumin before 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 3. Other biologics (eg, 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 per dose may be considered and may be given more frequently than usual (eg, 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 to 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 1 year. Therefore, the addition of an immunomodulator is recommended in responders to infliximab for at least 6 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). Use of infliximab is, however, currently more common in pediatric practice, due to greater familiarity with this agent, the ability to continue as maintenance and the overall better risk-benefit profile (10).

Infliximab

Jamerot et al first reported that 71% of 45 adults receiving 1 dose of 5 mg/kg infliximab avoided colectomy versus 34% receiving placebo (183). Observational studies among adult patients have reported short-term colectomy rates after rescue therapy with

TABLE 3. Second-line rescue therapies in pediatric steroid-refractory acute severe ulcerative colitis

	Infliximab	Cyclosporine	Tacrolimus
Tests before treatment	Excluding tuberculosis; serology for varicella, hepatitis B, and hepatitis C (and HIV when appropriate)	Serum creatinine, glucose, electrolytes (including magnesium), serum cholesterol	
Initial dosing	5–10 mg/kg for dose 1. 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 per 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, gingival hyperplasia	As per cyclosporine, but less hirsutism and gingival hyperplasia. Additionally self-remitting tremor
Ongoing treatment following response	Continue regularly scheduled maintenance infusions (4–8 weeks), ideally guided by therapeutic drug monitoring	Initiate thiopurines (or other agent to maintain remission such as vedolizumab) so that cyclosporine can be discontinued within several months	As per cyclosporine
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	5–10 µg/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 considered with IMM and steroids	PJP prophylaxis to be strongly considered with IMM and steroids. Monitor drug levels, creatinine, glucose, electrolytes (including magnesium), lipid levels, blood pressure	PJP prophylaxis to be strongly considered with IMM and steroids. Monitor drug levels, creatinine, glucose, electrolytes (including magnesium), lipid levels, blood pressure

ASC = acute severe colitis; IMM = immunomodulators; PJP = *Pneumocystis jiroveci pneumonia*

infliximab ranging from 20% to 75% (196). In the prospective multicenter OSCI study of ASC in children, 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 versus 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 days 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) ($n = 126$, 6 studies), and a pooled 1-year response of 64% (95% CI 56–72) (11). In another prospective pediatric study, of 52 subjects who received infliximab (~half with acute severe colitis [ASC]) 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 may 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 ASC (196,200). High concentrations of circulating and tissue TNF may act as a “sponge” that rapidly absorbs or neutralizes

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 ≥ 15 µg/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 2 groups (204). In retrospective analysis of a pediatric cohort of hospitalized patients with steroid-refractory UC, higher clinical remission rates and a lower colectomy rate at 1 year were observed with intensified versus standard dosing (205).

Cyclosporine

In the first RCT on cyclosporine in ASC, Lichtiger et al (206) 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 randomized to either 2 or 4 mg/kg of intravenous cyclosporine (207). 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 4 mg/kg group. Pooled results from controlled and uncontrolled trials in adults suggest that 76% to 85% of patients respond to intravenous cyclosporine and avoid colectomy in the short term, with a median time to response of 4 days (208). In a systematic review of pediatric non-randomized studies, the pooled short-term success rate with cyclosporine was 81% [95% CI 76–86]; n = 94 from 8 studies) (11).

Tacrolimus

Tacrolimus has been studied in 2 double-blind RCTs. 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) (209). 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 to 15 ng/mL (210). A 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 2 trials and other observational studies, and demonstrated that clinical response at 2 weeks was significantly higher with tacrolimus compared with placebo (relative risk = 4.61, 95% CI 2.09–10.2) especially in those treated with thiopurines in parallel. Colectomy-free rates at 1, 3, 6, and 12 months were 0.86, 0.84, 0.78, and 0.69, respectively (211).

Pediatric studies of tacrolimus as rescue therapy in ASC have been limited to retrospectively reported single-center case series and 1 small multi-center prospective study. In the latter, of 14 children with ASC, 69% responded to tacrolimus, but 44% of responders underwent colectomy by 1 year (212). Short-term response rates, meaning hospital discharge without colectomy ranged between 60% and 90% in the retrospective case series, with at least 40% to 50% requiring surgery by 1 to 2 years (213–216).

Infliximab Versus 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 2 randomized comparative trials in adults (194,195) and in meta-analysis of retrospective studies (217). The open-label CYSIF trial showed that treatment failure at day 98 was reported in 60% patients with cyclosporine versus 54% with infliximab ($P = 0.49$). Colectomy rate by day 98 was 18% versus 21%, respectively ($P = 0.66$) (194). Similarly, the randomized controlled Comparison Of iNfliximab and cyclosporine in STeroid Resistant Ulcerative Colitis (CONSTRUCT) trial found no significant difference regarding colectomy, mortality rates or the occurrence 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

Recommendation

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

Practice Points

1. Despite the above recommendation, in highly specialized centers and in selected non-fulminant cases, sequential therapy of calcineurin inhibitors after infliximab or vice versa may 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 jirovecii 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 third-line therapy in pediatric 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 1 was prospective (but no RCT's) (218). It should be noted that many of the source studies contained a mixture of chronically active UC and 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 pediatric studies, extrapolation from adults should follow the precautionary principal on this matter. It thus would be prudent to ensure that the levels of the second-line medication have cleared or nearly cleared before starting the third-line therapy in pediatric ASC. Furthermore, multiple studies of IBD therapies have demonstrated that infectious complications are highest with concomitant corticosteroid therapy, and thus steroids must be weaned before third-line therapy is started. Until pediatric 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 (ie, PUCAI <35 points) but preferably closer to remission (ie, 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 before 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 hemoglobin, improving trend in inflammatory markers and albumin, toleration of oral medication, and discontinuation of pain-control medications at least 24 hours before discharge **(100% agreement)**.
2. Methylprednisolone should be converted before discharge to the biologically equivalent dose of prednisone. One milligram of methylprednisolone is equivalent to 1.25 mg of prednisone (ie, 40 mg is equivalent to 50 mg, respectively) **(98% agreement)**.
3. Thiopurines may take 10 to 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. 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: 450 mg/m² twice daily for 3 days each week, (maximum daily dose 1.92 g) either consecutive or alternate day dosing (note 480 mg of trimethoprim-sulfamethoxazole consists of trimethoprim 80 mg and sulfamethoxazole 400 mg) **(100% agreement)**.
6. Oral iron supplements should be commenced after discharge in cases of anemia with hemoglobin ≥ 10 g/dL and quiescent disease. Intravenous iron should be considered in severe anemia (ie, <10 g/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 to 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 (219). 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 apparent in 80% of those with steroid-free remission at week 12 versus 49% of those with active disease at week 12 and only 6% of those who required additional therapy; $P < 0.0001$) (220). It is therefore important to optimize treatment in those who do not attain complete clinical remission post discharge.

In the prospective OSCI study in pediatric 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 (interquartile range 15–30) following an admission for ASC (15). Similarly, 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 (221).

Post pediatric 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 1 small pediatric study (222). Two adult RCTs also showed superiority of thiopurines over mesalamine (223,224). A combination of azathioprine with mesalamine leads to higher 6-thioguanine (6-TGN) levels and improves the likelihood of avoiding rescue therapy at 2 years, as found in a prospective multicenter study (225,226). 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 favored. 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 (214,227). Success rate is higher in children who are treated with cyclosporine combined with immunomodulatory therapy before discharge with a pooled long-term colectomy-free rate of 71% (55%–83%) (11,228,229). Being thiopurine-naïve is associated with lower colectomy risk in adult ASC (230–234). Maintenance with vedolizumab post induction with calcineurin inhibitors could be considered in those who failed thiopurines before the admission.

IBD patients are at an increased relative risk of PJP (HR, 2.96; 95% CI 1.75–4.29) but low absolute risk (235). PJP has been described in IBD patients on corticosteroids, calcineurin inhibitors,

thiopurines, and anti-TNF agents (236–241), while a recent administrative study showed low risk even on triple therapy (albeit the vast majority were not during an ASC episode) (242). There is only 1 pediatric IBD case report of PJP (associated with infliximab monotherapy) (243). Corticosteroids are a major contributor to PJP in the non-HIV population and the use of multiple immunosuppressive agents increases the risk further (244–247). To date, 162 cases of PJP are reported in the IBD and rheumatology literature associated with anti-TNF therapy with a 20% to 27% mortality rate (235,240,241,243,248–257). A meta-analysis of prophylactic treatment with co-trimoxazole in patients with hematological cancers and transplant recipients reported a 91% reduction in PJP incidence (258). 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).

CONCLUSIONS

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 (Fig. 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 provide 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.

Acknowledgments: The authors wish to thank the following individuals for their valuable assistance in preparing these guidelines: the national representatives of ECCO; the members of the IBD Interest and Porto group of ESPGHAN, Henkjan Verkade, Tamar Altaraz, and Shoshana Vilk.

REFERENCES

1. Turner D, Travis SP, Griffiths AM, et al. European Crohn's and Colitis Organization; Porto IBD Working Group, European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. 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. *Am J Gastroenterol* 2011;106:574–88.
2. Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology* 2007;133:423–32.
3. Turner D, Hyams J, Markowitz J, et al. Appraisal of the Pediatric Ulcerative Colitis Activity Index (PUCAI). *Inflamm Bowel Dis* 2009;15:1218–23.
4. Griffiths AM. Specificities of inflammatory bowel disease in childhood. *Best Pract Res Clin Gastroenterol* 2004;18:509–23.
5. Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology* 2008;135:1114–22.
6. Muller KE, Lakatos PL, Arato A, et al. Hungarian IBD Registry Group (HUPIR). Incidence, Paris Classification, and follow-up in a nationwide incident cohort of pediatric patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2013;57:576–82.
7. Aloï M, D'Arcangelo G, Pofi F, et al. Presenting features and disease course of pediatric ulcerative colitis. *J Crohns Colitis* 2013;7:e509–15.
8. Schechter A, Griffiths C, Gana JC, et al. Early endoscopic, laboratory and clinical predictors of poor disease course in paediatric ulcerative colitis. *Gut* 2015;64:580–8.
9. Turner D, Walsh CM, Benchimol EI, et al. Severe paediatric ulcerative colitis: incidence, outcomes and optimal timing for second-line therapy. *Gut* 2008;57:331–8.
10. Turner D, Mack D, Leleiko N, et al. Severe pediatric ulcerative colitis: a prospective multicenter study of outcomes and predictors of response. *Gastroenterology* 2010;138:2282–91.
11. Turner D, Griffiths AM. Acute severe ulcerative colitis in children: a systematic review. *Inflamm Bowel Dis* 2011;17:440–9.
12. Turner D, Walsh CM, Steinhart AH, et al. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol* 2007;5:103–10.
13. Barabino A, Tegaldo L, Castellano E, et al. Severe attack of ulcerative colitis in children: retrospective clinical survey. *Dig Liver Dis* 2002;34:44–9.
14. Aloï M, D'Arcangelo G, Capponi M, et al. Managing paediatric acute severe ulcerative colitis according to the 2011 ECCO-ESPGHAN guidelines: efficacy of infliximab as a rescue therapy. *Dig Liver Dis* 2015;47:455–9.
15. Russell RK, Protheroe A, Roughton M, et al. Contemporary outcomes for ulcerative colitis inpatients admitted to pediatric hospitals in the United Kingdom. *Inflamm Bowel Dis* 2013;19:1434–40.
16. Choshen S, Finnermore H, Auth M, et al. The availability of calcineurin inhibitors and infliximab in acute severe colitis have reduced colectomy rates in 283 children admitted during 1990–2012. *J Pediatr Gastroenterol Nutr* 2016;62(suppl 1):13.
17. Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis* 2011;17:1314–21.
18. Hardy TL, Bulmer E. Ulcerative colitis: a survey of ninety-five cases. *Br Med J* 1933;2:812–5.
19. Rice-Oxley JM, Truelove S. Complications of ulcerative colitis. *Lancet* 1950;255:607–11.
20. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J* 1955; 2:1041–8.
21. Truelove SC, Jewell DP. Intensive intravenous regimen for severe attacks of ulcerative colitis. *Lancet* 1974;1:1067–70.
22. Lynch RW, Lowe D, Protheroe A, et al. Outcomes of rescue therapy in acute severe ulcerative colitis: data from the United Kingdom inflammatory bowel disease audit. *Aliment Pharmacol Ther* 2013;38:935–45.
23. de Ridder L, Turner D, Wilson DC, et al. Porto IBD Working Group of ESPGHAN. Malignancy and mortality in pediatric patients with inflammatory bowel disease: a multinational study from the Porto Pediatric IBD group. *Inflamm Bowel Dis* 2014;20:291–300.
24. Vadlamudi NB, Hitch MC, Thame KA, et al. Enteric infections in hospitalized pediatric inflammatory bowel disease patients with relapse. *Internet J Paediatr Neonatol* 2013;16:1–7.
25. Ihekweazu FD, Ajjarapu A, Kellermayer R. Diagnostic yield of routine enteropathogenic stool tests in pediatric ulcerative colitis. *Ann Clin Lab Sci* 2015;45:639–42.
26. Pascarella F, Martinelli M, Miele E, et al. Impact of *Clostridium difficile* infection on pediatric inflammatory bowel disease. *J Pediatr* 2009;154:854–8.

27. Pant C, Anderson MP, Deshpande A, et al. Health care burden of *Clostridium difficile* infection in hospitalized children with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;19:1080–5.
28. Mezzoff E, Mann EA, Hart KW, et al. *Clostridium difficile* infection and treatment in the pediatric inflammatory bowel disease population. *J Pediatr Gastroenterol Nutr* 2011;52:437–41.
29. Hourigan SK, Oliva-Hemker M, Hutflless S. The prevalence of *Clostridium difficile* infection in pediatric and adult patients with inflammatory bowel disease. *Dig Dis Sci* 2014;59:2222–7.
30. Hojsak I, Ferenc T, Bojanic K, et al. Incidence of *Clostridium difficile* infection in children with inflammatory bowel disease compared to oncology and immunocompetent patients. *Digestion* 2012;86:6–11.
31. Banaszkiwicz A, Kowalska-Duplaga K, Pytrus T, et al. *Clostridium difficile* infection in newly diagnosed pediatric patients with inflammatory bowel disease: prevalence and risk factors. *Inflamm Bowel Dis* 2012;18:844–8.
32. Hourigan SK, Chirumamilla SR, Ross T, et al. *Clostridium difficile* carriage and serum antitoxin responses in children with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;19:2744–52.
33. Martinelli M, Strisciuglio C, Veres G, et al. Porto IBD Working Group of European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). *Clostridium difficile* and pediatric inflammatory bowel disease: a prospective, comparative, multicenter, ESPGHAN study. *Inflamm Bowel Dis* 2014;20:2219–25.
34. Fu N, Wong T. *Clostridium difficile* infection in patients with inflammatory bowel disease. *Curr Infect Dis Rep* 2016;18:19.
35. Ricciardi R, Ogilvie JW Jr, Roberts PL, et al. Epidemiology of *Clostridium difficile* colitis in hospitalized patients with inflammatory bowel diseases. *Dis Colon Rectum* 2009;52:40–5.
36. Nguyen GC, Kaplan GG, Harris ML, et al. A national survey of the prevalence and impact of *Clostridium difficile* infection among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol* 2008;103:1443–50.
37. Ananthakrishnan AN, McGinley EL, Saecian K, et al. Temporal trends in disease outcomes related to *Clostridium difficile* infection in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2011;17:976–83.
38. Rodemann JF, Dubberke ER, Reske KA, et al. Incidence of *Clostridium difficile* infection in inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2007;5:339–44.
39. Issa M, Vijayapal A, Graham MB, et al. Impact of *Clostridium difficile* on inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2007;5:345–51.
40. Jen MH, Saxena S, Bottle A, et al. Increased health burden associated with *Clostridium difficile* diarrhoea in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2011;33:1322–31.
41. Murthy SK, Steinhart AH, Tinmouth J, et al. Impact of *Clostridium difficile* colitis on 5-year health outcomes in patients with ulcerative colitis. *Aliment Pharmacol Ther* 2012;36:1032–9.
42. Berg AM, Kelly CP, Farraye FA. *Clostridium difficile* infection in the inflammatory bowel disease patient. *Inflamm Bowel Dis* 2013;19:194–204.
43. Issa M, Ananthakrishnan AN, Binion DG. *Clostridium difficile* and inflammatory bowel disease. *Inflamm Bowel Dis* 2008;14:1432–42.
44. Bagdasarian N, Rao K, Malani PN. Diagnosis and treatment of *Clostridium difficile* in adults: a systematic review. *JAMA* 2015;313:398–408.
45. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol* 2013;108:478–98quiz 99.
46. Health UDo. Updated guidance on the diagnosis and reporting of *Clostridium difficile*. 2012. Available at <https://www.gov.uk/government/publications/updated-guidance-on-the-diagnosis-and-reporting-of-clostridium-difficile>.
47. Markowitz JE, Brown KA, Mamula P, et al. Failure of single-toxin assays to detect *Clostridium difficile* infection in pediatric inflammatory bowel disease. *Am J Gastroenterol* 2001;96:2688–90.
48. Planche TD, Davies KA, Coen PG, et al. Differences in outcome according to *Clostridium difficile* testing method: a prospective multicentre diagnostic validation study of *C difficile* infection. *Lancet Infect Dis* 2013;13:936–45.
49. Gawronska A, Banasiuk M, Lachowicz D, et al. Metronidazole or rifaximin for treatment of *Clostridium difficile* in pediatric patients with inflammatory bowel disease: a randomized clinical trial. *Inflamm Bowel Dis* 2017;23:2209–14.
50. Zar FA, Bakkanagari SR, Moorthi KM, et al. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis* 2007;45:302–7.
51. Musher DM, Aslam S, Logan N, et al. Relatively poor outcome after treatment of *Clostridium difficile* colitis with metronidazole. *Clin Infect Dis* 2005;40:1586–90.
52. Johnson S, Louie TJ, Gerding DN, et al. Vancomycin, metronidazole, or tolevamer for *Clostridium difficile* infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis* 2014;59:345–54.
53. Nelson RL, Kelsey P, Leeman H, et al. Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults. *Cochrane Database of Systematic Reviews* (3):2011:CD004610.
54. Horton HA, Dezfoli S, Berel D, et al. Antibiotics for treatment of *Clostridium difficile* infection in hospitalized patients with inflammatory bowel disease. *Antimicrob Agents Chemother* 2014;58:5054–9.
55. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2014;8:443–68.
56. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med* 2011;364:422–31.
57. Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. *Lancet Infect Dis* 2012;12:281–9.
58. Lee C, Louie TJ, Weiss K, et al. Fidaxomicin versus vancomycin in the treatment of *Clostridium difficile* infection: Canadian outcomes. *Can J Infect Dis Med Microbiol* 2016;2016:8048757.
59. Clutter DS, Dubrovskaya Y, Merl MY, et al. Fidaxomicin versus conventional antimicrobial therapy in 59 recipients of solid organ and hematopoietic stem cell transplantation with *Clostridium difficile*-associated diarrhea. *Antimicrob Agents Chemother* 2013;57:4501–5.
60. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. *Clin Infect Dis* 2011;53:994–1002.
61. Khoruts A, Rank KM, Newman KM, et al. Inflammatory bowel disease affects the outcome of fecal microbiota transplantation for recurrent *Clostridium difficile* infection. *Clin Gastroenterol Hepatol* 2016;14:1433–8.
62. Sha S, Liang J, Chen M, et al. Systematic review: faecal microbiota transplantation therapy for digestive and nondigestive disorders in adults and children. *Aliment Pharmacol Ther* 2014;39:1003–32.
63. Kelly CR, Ihunnah C, Fischer M, et al. Fecal microbiota transplant for treatment of *Clostridium difficile* infection in immunocompromised patients. *Am J Gastroenterol* 2014;109:1065–71.
64. Shukla T, Singh S, Loftus EV Jr et al. Antiviral therapy in steroid-refractory ulcerative colitis with cytomegalovirus: systematic review and meta-analysis. *Inflamm Bowel Dis* 2015;21:2718–25.
65. Wu XW, Wu L, Ji HZ, et al. Relationship between cytomegalovirus infection and steroid resistance in inflammatory bowel disease: a meta-analysis. *Dig Dis Sci* 2015;60:3203–8.
66. Kopylov U, Sasson G, Geysish B, et al. Cytomegalovirus positive ulcerative colitis: a single center experience and literature review. *World J Gastrointest Pathophysiol* 2013;4:18–23.
67. Romkens TE, Bulte GJ, Nissen LH, et al. Cytomegalovirus in inflammatory bowel disease: a systematic review. *World J Gastroenterol* 2016;22:1321–30.
68. Langner C, Magro F, Driessen A, et al. The histopathological approach to inflammatory bowel disease: a practice guide. *Virchows Arch* 2014;464:511–27.
69. Hommes DW, Sterringa G, van Deventer SJ, et al. The pathogenicity of cytomegalovirus in inflammatory bowel disease: a systematic review and evidence-based recommendations for future research. *Inflamm Bowel Dis* 2004;10:245–50.

70. Kojima T, Watanabe T, Hata K, et al. Cytomegalovirus infection in ulcerative colitis. *Scand J Gastroenterol* 2006;41:706–11.
71. Zidar N, Ferkolj I, Tepes K, et al. Diagnosing cytomegalovirus in patients with inflammatory bowel disease—by immunohistochemistry or polymerase chain reaction? *Virchows Arch* 2015;466:533–9.
72. Sebastian-Planas M, Barrio-Merino A, Avilla-Hernandez J, et al. Cytomegalovirus infection of the colon in ulcerative colitis: a pediatric case. *J Pediatr Gastroenterol Nutr* 1996;23:186–90.
73. Ghidini B, Bellaiche M, Berrebi D, et al. Cytomegalovirus colitis in children with inflammatory bowel disease. *Gut* 2006;55:582–3.
74. Cohen S, Martinez-Vinson C, Aloï M, et al., Pediatric IBD Porto Group of ESPGHAN. CMV infection in pediatric severe ulcerative colitis—a multicenter study from the Pediatric IBD Porto Group of ESPGHAN. *Pediatr Infect Dis J* 2017;3:197–201.
75. Khan RR, Lawson AD, Minnich LL, et al. Gastrointestinal norovirus infection associated with exacerbation of inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2009;48:328–33.
76. Senay H, MacPherson D. Parasitology: diagnostic yield of stool examination. *CMAJ* 1989;140:1329–31.
77. Thielman NM, Guerrant RL. Persistent diarrhea in the returned traveler. *Infect Dis Clin North Am* 1998;12:489–501.
78. Okhuysen PC. Traveler's diarrhea due to intestinal protozoa. *Clin Infect Dis* 2001;33:110–4.
79. Vadlamudi N, Maclin J, Dimmitt RA, et al. Cryptosporidial infection in children with inflammatory bowel disease. *J Crohns Colitis* 2013;7:e337–43.
80. Dignass A, Lindsay JO, Sturm A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis* 2012;6:991–1030.
81. Gan SI, Beck PL. A new look at toxic megacolon: an update and review of incidence, etiology, pathogenesis, and management. *Am J Gastroenterol* 2003;98:2363–71.
82. Long MD, Barnes EL, Herfarth HH, et al. Narcotic use for inflammatory bowel disease and risk factors during hospitalization. *Inflamm Bowel Dis* 2012;18:869–76.
83. Mowat C, Cole A, Windsor A, et al., IBD Section of the British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2011;60:571–607.
84. Whorwell PJ, Isaacson P. Toxic dilatation of colon in Crohn's disease. *Lancet* 1981;2:1334–7.
85. Benchimol EI, Turner D, Mann EH, et al. Toxic megacolon in children with inflammatory bowel disease: clinical and radiographic characteristics. *Am J Gastroenterol* 2008;103:1524–31.
86. Lowenstein O, Leyendecker P, Hopp M, et al. Combined prolonged-release oxycodone and naloxone improves bowel function in patients receiving opioids for moderate-to-severe non-malignant chronic pain: a randomised controlled trial. *Expert Opin Pharmacother* 2009;10:531–43.
87. Felder JB, Korelitz BI, Rajapakse R, et al. Effects of nonsteroidal anti-inflammatory drugs on inflammatory bowel disease: a case-control study. *Am J Gastroenterol* 2000;95:1949–54.
88. Kaufmann HJ, Taubin HL. Nonsteroidal anti-inflammatory drugs activate quiescent inflammatory bowel disease. *Ann Intern Med* 1987;107:513–6.
89. Kefalakes H, Stylianides TJ, Amanakis G, et al. Exacerbation of inflammatory bowel diseases associated with the use of nonsteroidal anti-inflammatory drugs: myth or reality? *Eur J Clin Pharmacol* 2009;65:963–70.
90. Kvasnovsky CL, Aujla U, Bjarnason I. Nonsteroidal anti-inflammatory drugs and exacerbations of inflammatory bowel disease. *Scand J Gastroenterol* 2015;50:255–63.
91. Long MD, Kappelman MD, Martin CF, et al. Role of nonsteroidal anti-inflammatory drugs in exacerbations of inflammatory bowel disease. *J Clin Gastroenterol* 2016;50:152–6.
92. Takeuchi K, Smale S, Premchand P, et al. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2006;4:196–202.
93. Mahadevan U, Loftus EV Jr, Tremaine WJ, et al. Safety of selective cyclooxygenase-2 inhibitors in inflammatory bowel disease. *Am J Gastroenterol* 2002;97:910–4.
94. Matuk R, Crawford J, Abreu MT, et al. The spectrum of gastrointestinal toxicity and effect on disease activity of selective cyclooxygenase-2 inhibitors in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2004;10:352–6.
95. Reinisch W, Miehsler W, Dejaco C, et al. An open-label trial of the selective cyclo-oxygenase-2 inhibitor, rofecoxib, in inflammatory bowel disease-associated peripheral arthritis and arthralgia. *Aliment Pharmacol Ther* 2003;17:1371–80.
96. Duncan MA, Spiller JA. Analgesia with ketamine in a patient with perioperative opioid tolerance. *J Pain Symptom Manage* 2002;24:8–11.
97. White M, Shah N, Lindley K, et al. Pain management in fulminating ulcerative colitis. *Paediatr Anaesth* 2006;16:1148–52.
98. Fioramonti J, Bueno L. Role of cannabinoid receptors in the control of gastrointestinal motility and perception. *Expert Rev Gastroenterol Hepatol* 2008;2:385–97.
99. Sanson M, Bueno L, Fioramonti J. Involvement of cannabinoid receptors in inflammatory hypersensitivity to colonic distension in rats. *Neurogastroenterol Motil* 2006;18:949–56.
100. Storr MA, Yuce B, Andrews CN, et al. The role of the endocannabinoid system in the pathophysiology and treatment of irritable bowel syndrome. *Neurogastroenterol Motil* 2008;20:857–68.
101. Dickinson RJ, Ashton MG, Axon AT, et al. Controlled trial of intravenous hyperalimentation and total bowel rest as an adjunct to the routine therapy of acute colitis. *Gastroenterology* 1980;79:1199–204.
102. McIntyre PB, Powell-Tuck J, Wood SR, et al. Controlled trial of bowel rest in the treatment of severe acute colitis. *Gut* 1986;27:481–5.
103. Gonzalez-Huix F, Fernandez-Banares F, Esteve-Comas M, et al. Enteral versus parenteral nutrition as adjunct therapy in acute ulcerative colitis. *Am J Gastroenterol* 1993;88:227–32.
104. Brown SR, Haboubi N, Hampton J, et al. The management of acute severe colitis: ACPGBI position statement. *Colorectal Dis* 2008;10(suppl 3):8–29.
105. Travis SP, Stange EF, Lemann M, et al. European evidence-based Consensus on the management of ulcerative colitis: current management. *J Crohns Colitis* 2008;2:24–62.
106. Harbord M, Eliakim R, Bettenworth D, et al., European Crohn's and Colitis Organisation [ECCO]. Third European Evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J Crohns Colitis* 2017;11:769–84.
107. Nguyen GC, Sam J. Rising prevalence of venous thromboembolism and its impact on mortality among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol* 2008;103:2272–80.
108. Novacek G, Weltermann A, Sobala A, et al. Inflammatory bowel disease is a risk factor for recurrent venous thromboembolism. *Gastroenterology* 2010;139:779–878 e1.
109. Danese S, Papa A, Saibeni S, et al. Inflammation and coagulation in inflammatory bowel disease: the clot thickens. *Am J Gastroenterol* 2007;102:174–86.
110. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. *Lancet* 2010;375:657–63.
111. Harbord M, Annesse V, Vavricka SR, et al. The First European Evidence-based Consensus on extra-intestinal manifestations in inflammatory bowel disease. *J Crohns Colitis* 2016;10:239–54.
112. Kappelman MD, Horvath-Puho E, Sandler RS, et al. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. *Gut* 2011;60:937–43.
113. Nguyen GC, Bernstein CN, Bitton A, et al. Consensus statements on the risk, prevention, and treatment of venous thromboembolism in inflammatory bowel disease: Canadian Association of Gastroenterology. *Gastroenterology* 2014;146:835.e6–48.e6.
114. Nguyen GC, Yeo EL. Prophylaxis of venous thromboembolism in IBD. *Lancet* 2010;375:616–7.
115. Chande N, McDonald JW, Macdonald JK, et al. Unfractionated or low-molecular weight heparin for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* (10):2010:CD006774.
116. Shen J, Ran ZH, Tong JL, et al. Meta-analysis: the utility and safety of heparin in the treatment of active ulcerative colitis. *Aliment Pharmacol Ther* 2007;26:653–63.

117. Barclay AR, Keightley JM, Horrocks I, et al. Cerebral thromboembolic events in pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2010;16:677–83.
118. Keene DL, Matzinger MA, Jacob PJ, et al. Cerebral vascular events associated with ulcerative colitis in children. *Pediatr Neurol* 2001;24:238–43.
119. Nguyen LT, Laberge JM, Guttman FM, et al. Spontaneous deep vein thrombosis in childhood and adolescence. *J Pediatr Surg* 1986;21:640–3.
120. Lazzerini M, Bramuzzo M, Maschio M, et al. Thromboembolism in pediatric inflammatory bowel disease: systematic review. *Inflamm Bowel Dis* 2011;17:2174–83.
121. Molinari AC, Banov L, Bertamino M, et al. A practical approach to the use of low molecular weight heparins in VTE treatment and prophylaxis in children and newborns. *Pediatr Hematol Oncol* 2015;32:1–10.
122. Ko RH, Young G. Pharmacokinetic- and pharmacodynamic-based antithrombotic dosing recommendations in children. *Expert Rev Clin Pharmacol* 2012;5:389–96.
123. Albisetti M, Andrew M. Low molecular weight heparin in children. *Eur J Pediatr* 2002;161:71–7.
124. Trame MN, Mitchell L, Krumpel A, et al. Population pharmacokinetics of enoxaparin in infants, children and adolescents during secondary thromboembolic prophylaxis: a cohort study. *J Thromb Haemost* 2010;8:1950–8.
125. Nowak-Gottl U, Bidlingmaier C, Krumpel A, et al. Pharmacokinetics, efficacy, and safety of LMWHs in venous thrombosis and stroke in neonates, infants and children. *Br J Pharmacol* 2008;153:1120–7.
126. Dix D, Andrew M, Marzintotto V, et al. The use of low molecular weight heparin in pediatric patients: a prospective cohort study. *J Pediatr* 2000;136:439–45.
127. Schobess R, During C, Bidlingmaier C, et al. Long-term safety and efficacy data on childhood venous thrombosis treated with a low molecular weight heparin: an open-label pilot study of once-daily versus twice-daily enoxaparin administration. *Haematologica* 2006;91:1701–4.
128. Hojsak I, Pavic AM, Kolacek S. Mesalamine treatment mimicking relapse in a child with ulcerative colitis. *World J Pediatr* 2014;10:371–3.
129. Iofel E, Chawla A, Daum F, et al. Mesalamine intolerance mimics symptoms of active inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2002;34:73–6.
130. Loftus EV Jr, Kane SV, Bjorkman D. Systematic review: short-term adverse effects of 5-aminosalicylic acid agents in the treatment of ulcerative colitis. *Aliment Pharmacol Ther* 2004;19:179–89.
131. Khan KJ, Ullman TA, Ford AC, et al. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2011;106:661–73.
132. Wang SL, Wang ZR, Yang CQ. Meta-analysis of broad-spectrum antibiotic therapy in patients with active inflammatory bowel disease. *Exp Ther Med* 2012;4:1051–6.
133. Chapman RW, Selby WS, Jewell DP. Controlled trial of intravenous metronidazole as an adjunct to corticosteroids in severe ulcerative colitis. *Gut* 1986;27:1210–2.
134. Mantzaris GJ, Petraki K, Archavlis E, et al. A prospective randomized controlled trial of intravenous ciprofloxacin as an adjunct to corticosteroids in acute, severe ulcerative colitis. *Scand J Gastroenterol* 2001;36:971–4.
135. Mantzaris GJ, Hatzis A, Kontogiannis P, et al. Intravenous tobramycin and metronidazole as an adjunct to corticosteroids in acute, severe ulcerative colitis. *Am J Gastroenterol* 1994;89:43–6.
136. Ohkusa T, Kato K, Terao S, et al. Newly developed antibiotic combination therapy for ulcerative colitis: a double-blind placebo-controlled multicenter trial. *Am J Gastroenterol* 2010;105:1820–9.
137. Ohkusa T, Nomura T, Terai T, et al. Effectiveness of antibiotic combination therapy in patients with active ulcerative colitis: a randomized, controlled pilot trial with long-term follow-up. *Scand J Gastroenterol* 2005;40:1334–42.
138. Terao S, Yamashiro K, Tamura I, et al. Antibiotic combination therapy for steroid withdrawal in steroid-dependent ulcerative colitis. *Digestion* 2011;83:198–203.
139. Dickinson RJ, O'Connor HJ, Pinder I, et al. Double blind controlled trial of oral vancomycin as adjunctive treatment in acute exacerbations of idiopathic colitis. *Gut* 1985;26:1380–4.
140. Burke DA, Axon AT, Clayden SA, et al. The efficacy of tobramycin in the treatment of ulcerative colitis. *Aliment Pharmacol Ther* 1990;4:123–9.
141. Turunen UM, Farkkila MA, Hakala K, et al. Long-term treatment of ulcerative colitis with ciprofloxacin: a prospective, double-blind, placebo-controlled study. *Gastroenterology* 1998;115:1072–8.
142. Gionchetti P, Rizzello F, Ferrieri A, et al. Rifaximin in patients with moderate or severe ulcerative colitis refractory to steroid-treatment: a double-blind, placebo-controlled trial. *Dig Dis Sci* 1999;44:1220–1.
143. Mantzaris GJ, Archavlis E, Christoforidis P, et al. A prospective randomized controlled trial of oral ciprofloxacin in acute ulcerative colitis. *Am J Gastroenterol* 1997;92:454–6.
144. Turner D, Levine A, Kolho KL, et al. Combination of oral antibiotics may be effective in severe pediatric ulcerative colitis: a preliminary report. *J Crohns Colitis* 2014;8:1464–70.
145. Carter MJ, Lobo AJ, Travis SP. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004;53(suppl 5):V1–6.
146. Turner D, Vlamakis H, Marcus D, et al. Manipulating the microbiome in pediatric Acute Severe Colitis with antibiotics cocktail: a pilot randomized controlled trial. ESPGHAN 51st Annual meeting 9-12 May, 2018 2018.
147. Truelove SC, Witts LJ. Cortisone and corticotrophin in ulcerative colitis. *Br Med J* 1959;1:387–94.
148. Truelove SC, Willoughby CP, Lee EG, et al. Further experience in the treatment of severe attacks of ulcerative colitis. *Lancet* 1978;2:1086–8.
149. Bossa F, Fiorella S, Caruso N, et al. Continuous infusion versus bolus administration of steroids in severe attacks of ulcerative colitis: a randomized, double-blind trial. *Am J Gastroenterol* 2007;102:601–8.
150. Kjeldsen J. Treatment of ulcerative colitis with high doses of oral prednisolone. The rate of remission, the need for surgery, and the effect of prolonging the treatment. *Scand J Gastroenterol* 1993;28:821–6.
151. Cakir M, Ozgenc F, Yusekkaya HA, et al. Steroid response in moderate to severe pediatric ulcerative colitis: a single center's experience. *World J Pediatr* 2011;7:50–3.
152. Berghouse LM, Elliott PR, Lennard-Jones JE, et al. Plasma prednisolone levels during intravenous therapy in acute colitis. *Gut* 1982;23:980–3.
153. Faure C, Andre J, Pelatan C, et al. Pharmacokinetics of intravenous methylprednisolone and oral prednisone in paediatric patients with inflammatory bowel disease during the acute phase and in remission. *Eur J Clin Pharmacol* 1998;54:555–60.
154. Meyers S, Lerer PK, Feuer EJ, et al. Predicting the outcome of corticoid therapy for acute ulcerative colitis. Results of a prospective, randomized, double-blind clinical trial. *J Clin Gastroenterol* 1987;9:50–4.
155. Meyers S, Sachar DB, Goldberg JD, et al. Corticotropin versus hydrocortisone in the intravenous treatment of ulcerative colitis. A prospective, randomized, double-blind clinical trial. *Gastroenterology* 1983;85:351–7.
156. Kaplan HP, Portnoy B, Binder HJ, et al. A controlled evaluation of intravenous adrenocorticotropic hormone and hydrocortisone in the treatment of acute colitis. *Gastroenterology* 1975;69:91–5.
157. Powell-Tuck J, Buckell NA, Lennard-Jones JE. A controlled comparison of corticotropin and hydrocortisone in the treatment of severe proctocolitis. *Scand J Gastroenterol* 1977;12:971–5.
158. Kugathasan S, Dubinsky MC, Keljo D, et al. Severe colitis in children. *J Pediatr Gastroenterol Nutr* 2005;41:375–85.
159. Baron JH, Connell AM, Kanaghinis TG, et al. Out-patient treatment of ulcerative colitis. Comparison between three doses of oral prednisone. *Br Med J* 1962;2:441–3.
160. Choshen S, Finamore H, Auth MK, et al. Corticosteroid dosing in pediatric acute severe ulcerative colitis: a propensity score analysis. *J Pediatr Gastroenterol Nutr* 2016;63:58–64.
161. Kudo T, Nagata S, Ohtani K, et al. Pulse steroids as induction therapy for children with ulcerative colitis. *Pediatr Int* 2011;53:974–9.
162. Nagata S, Shimizu T, Kudo T, et al. Efficacy and safety of pulse steroid therapy in Japanese pediatric patients with ulcerative colitis: a survey of the Japanese Society for Pediatric Inflammatory Bowel Disease. *Digestion* 2010;81:188–92.

163. Vora R, Fimmamore HE, Crook K, et al. Clinical experience of use of high-dose intravenous methylprednisolone in children with acute moderate to severe colitis. *J Pediatr Gastroenterol Nutr* 2016;63:51–7.
164. Rosenberg W, Ireland A, Jewell DP. High-dose methylprednisolone in the treatment of active ulcerative colitis. *J Clin Gastroenterol* 1990;12:40–1.
165. Oshitani N, Kamata N, Oiso R, et al. Outpatient treatment of moderately severe active ulcerative colitis with pulsed steroid therapy and conventional steroid therapy. *Dig Dis Sci* 2003;48:1002–5.
166. Powell-Tuck J, Bown RL, Lennard-Jones JE. A comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis. *Scand J Gastroenterol* 1978;13:833–7.
167. Livshits A, Fisher D, Hadas I, et al. Abdominal x-ray in pediatric acute severe colitis and radiographic predictors of response to intravenous steroids. *J Pediatr Gastroenterol Nutr* 2016;62:259–63.
168. Jalan KN, Sircus W, Card WI, et al. An experience of ulcerative colitis. I. Toxic dilation in 55 cases. *Gastroenterology* 1969;57:68–82.
169. Present DH, Wolfson D, Gelernt IM, et al. Medical decompression of toxic megacolon by “rolling”. A new technique of decompression with favorable long-term follow-up. *J Clin Gastroenterol* 1988;10:485–90.
170. Panos MZ, Wood MJ, Asquith P. Toxic megacolon: the knee-elbow position relieves bowel distension. *Gut* 1993;34:1726–7.
171. Castro Fernandez M, Garcia Romero D, Sanchez Munoz D, et al. Severe ulcerative colitis, with toxic megacolon, resolved with infliximab therapy. *Rev Esp Enferm Dig* 2007;99:426–7.
172. Sriram PV, Reddy KS, Rao GV, et al. Infliximab in the treatment of ulcerative colitis with toxic megacolon. *Indian J Gastroenterol* 2004;23:22–3.
173. Sinagra E, Orlando A, Renna S, et al. Is really megacolon a contraindication to infliximab in Crohn's disease? *Acta Gastroenterol Belg* 2013;76:442–4.
174. Sawada K, Egashira A, Ohnishi K, et al. Leukocytapheresis (LCAP) for management of fulminant ulcerative colitis with toxic megacolon. *Dig Dis Sci* 2005;50:767–73.
175. Narabayashi K, Inoue T, Sakanaka T, et al. Oral tacrolimus for megacolon in patients with severe ulcerative colitis. *Intern Med* 2014;53:1755–8.
176. Pascu M, Müller AR, Wiedenmann B, et al. Rescue therapy with tacrolimus in a patient with toxic megacolon. *Int J Colorectal Dis* 2003;18:271–5.
177. Kuroki K, Masuda A, Uehara H, et al. A new treatment for toxic megacolon. *Lancet* 1998;352:782.
178. Criscuolo V, Rizzuto MR, Gallo E, et al. Toxic megacolon and human Cytomegalovirus in a series of severe ulcerative colitis patients. *J Clin Virol* 2015;66:103–6.
179. Civitelli F, Di Nardo G, Oliva S, et al. Ultrasonography of the colon in pediatric ulcerative colitis: a prospective, blind, comparative study with colonoscopy. *J Pediatr* 2014;165:78–84.
180. Travis SP, Farrant JM, Ricketts C, et al. Predicting outcome in severe ulcerative colitis. *Gut* 1996;38:905–10.
181. Corte C, Fernandopulle N, Catuneanu A, et al. Association between the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and outcomes in acute severe ulcerative colitis. *J Crohns Colitis* 2015;9:376–81.
182. Ho GT, Mowat C, Goddard CJR, et al. Predicting the outcome of severe ulcerative colitis: development of a novel risk score to aid early selection of patients for second-line medical therapy or surgery. *Aliment Pharmacol Ther* 2004;19:1079–87.
183. Jarnerot G, Hertvig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology* 2005;128:1805–11.
184. Lindgren SC, Flood LM, Kilander AF, et al. Early predictors of glucocorticosteroid treatment failure in severe and moderately severe attacks of ulcerative colitis. *Eur J Gastroenterol Hepatol* 1998;10:831–5.
185. Seo M, Okada M, Yao T, et al. Evaluation of the clinical course of acute attacks in patients with ulcerative colitis through the use of an activity index. *J Gastroenterol* 2002;37:29–34.
186. Turner D, Leach ST, Mack D, et al. Faecal calprotectin, lactoferrin, M2-pyruvate kinase and S100A12 in severe ulcerative colitis: a prospective multicentre comparison of predicting outcomes and monitoring response. *Gut* 2010;59:1207–12.
187. Koslowsky B, Gupta A, Livovsky DM, et al. The use of the Pediatric Ulcerative Colitis Activity Index (PUCAI) in adults with acute severe ulcerative colitis (ASC). *J Crohn Colitis* 2014;8:S108.
188. Soon IS, Wrobel I, deBruyn JC, et al. Postoperative complications following colectomy for ulcerative colitis in children. *J Pediatr Gastroenterol Nutr* 2012;54:763–8.
189. Randall J, Singh B, Warren BF, et al. Delayed surgery for acute severe colitis is associated with increased risk of postoperative complications. *Br J Surg* 2010;97:404–9.
190. Wine E, Mack DR, Hyams J, et al. Interleukin-6 is associated with steroid resistance and reflects disease activity in severe pediatric ulcerative colitis. *J Crohns Colitis* 2013;7:916–22.
191. Michail S, Durbin M, Turner D, et al. Alterations in the gut microbiome of children with severe ulcerative colitis. *Inflamm Bowel Dis* 2012;18:1799–808.
192. Fell JM, Muhammed R, Spray C, et al. Management of ulcerative colitis. *Arch Dis Child* 2016;101:469–74.
193. Aksan A, Isik H, Radeke HH, et al. Systematic review with network meta-analysis: comparative efficacy and tolerability of different intravenous iron formulations for the treatment of iron deficiency anaemia in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2017;45:1303–18.
194. Laharie D, Bourreille A, Branche J, et al. Cyclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. *Lancet* 2012;380:1909–15.
195. Williams JG, Alam MF, Alrubaiy L, et al. Comparison of infliximab and cyclosporin in STeroid Resistant Ulcerative Colitis: pragmatic randomised Trial and economic evaluation (CONSTRUCT). *Health Technol Assess* 2016;20:1–320.
196. Rosen MJ, Minar P, Vinks AA. Review article: applying pharmacokinetics to optimise dosing of anti-TNF biologics in acute severe ulcerative colitis. *Aliment Pharmacol Ther* 2015;41:1094–103.
197. Turner D, Mack DR, Wine E, et al. A prospective multicenter study: outcomes and predictors of response to infliximab given as a rescue therapy in severe pediatric ulcerative colitis. *Gastroenterology* 2010;138(suppl 1):S-29.(Abst 149).
198. Sylvester FA, Turner D, Draghi A 2nd et al. Fecal osteoprotegerin may guide the introduction of second-line therapy in hospitalized children with ulcerative colitis. *Inflamm Bowel Dis* 2011;17:1726–30.
199. Hyams JS, Lerer T, Griffiths A, et al. Outcome following infliximab therapy in children with ulcerative colitis. *Am J Gastroenterol* 2010;105:1430–6.
200. Ungar B, Mazor Y, Weissshof R, et al. Induction infliximab levels among patients with acute severe ulcerative colitis compared with patients with moderately severe ulcerative colitis. *Aliment Pharmacol Ther* 2016;43:1293–9.
201. Yarur AJ, Jain A, Sussman DA, et al. The association of tissue anti-TNF drug levels with serological and endoscopic disease activity in inflammatory bowel disease: the ATLAS study. *Gut* 2016;65:249–55.
202. Brandse JF, van den Brink GR, Wildenberg ME, et al. Loss of infliximab into Feces Is Associated With Lack of Response to Therapy in Patients With Severe Ulcerative Colitis. *Gastroenterology* 2015;149:350.e2–5.e2.
203. Papamichael K, Van Stappen T, Vande Castele N, et al. Infliximab concentration thresholds during induction therapy are associated with short-term mucosal healing in patients with ulcerative colitis. *Clin Gastroenterol Hepatol* 2016;14:543–9.
204. Gibson DJ, Heetun ZS, Redmond CE, et al. An accelerated infliximab induction regimen reduces the need for early colectomy in patients with acute severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2015;13:330.e1–5.e1.
205. Ho S, Church P, Sharma A, et al. Intensification of infliximab induction regimen improves response rate in steroid-refractory pediatric ulcerative colitis. *Gastroenterology* 2016;150(4 suppl 1):S131–2.
206. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994;330:1841–5.
207. Van Assche G, D'Haens G, Noman M, et al. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. *Gastroenterology* 2003;125:1025–31.

208. Hindryckx P, Jairath V, D'Haens G. Acute severe ulcerative colitis: from pathophysiology to clinical management. *Nat Rev Gastroenterol Hepatol* 2016;13:654–64.
209. Ogata H, Matsui T, Nakamura M, et al. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut* 2006;55:1255–62.
210. Ogata H, Kato J, Hirai F, et al. Double-blind, placebo-controlled trial of oral tacrolimus (FK506) in the management of hospitalized patients with steroid-refractory ulcerative colitis. *Inflamm Bowel Dis* 2012;18:803–8.
211. Komaki Y, Komaki F, Ido A, et al. Efficacy and safety of tacrolimus therapy for active ulcerative colitis: a systematic review and meta-analysis. *J Crohns Colitis* 2016;10:484–94.
212. Bousvaros A, Kirschner BS, Werlin SL, et al. Oral tacrolimus treatment of severe colitis in children. *J Pediatr* 2000;137:794–9.
213. Navas-Lopez VM, Blasco Alonso J, Serrano Nieto MJ, et al. Oral tacrolimus for pediatric steroid-resistant ulcerative colitis. *J Crohns Colitis* 2014;8:64–9.
214. Ziring DA, Wu SS, Mow WS, et al. Oral tacrolimus for steroid-dependent and steroid-resistant ulcerative colitis in children. *J Pediatr Gastroenterol Nutr* 2007;45:306–11.
215. Watson S, Pensabene L, Mitchell P, et al. Outcomes and adverse events in children and young adults undergoing tacrolimus therapy for steroid-refractory colitis. *Inflamm Bowel Dis* 2011;17:22–9.
216. Romano C, Comito D, Famiani A, et al. Oral tacrolimus (FK 506) in refractory paediatric ulcerative colitis. *Aliment Pharmacol Ther* 2010;31:676–7.
217. Narula N, Marshall JK, Colomel JF, et al. Systematic review and meta-analysis: infliximab or cyclosporine as rescue therapy in patients with severe ulcerative colitis refractory to steroids. *Am J Gastroenterol* 2016;111:477–91.
218. Narula N, Fine M, Colomel JF, et al. Systematic review: sequential rescue therapy in severe ulcerative colitis: do the benefits outweigh the risks? *Inflamm Bowel Dis* 2015;21:1683–94.
219. Turner D, Griffiths AM, Veerman G, et al. Endoscopic and clinical variables that predict sustained remission in children with ulcerative colitis treated with infliximab. *Clin Gastroenterol Hepatol* 2013;11:1460–5.
220. Hyams JS, Davis S, Mack DR, et al. Factors associated with early outcomes following standardised therapy in children with ulcerative colitis (PROTECT): a multicentre inception cohort study. *Lancet Gastroenterol Hepatol* 2017;2:855–68.
221. Bojic D, Radojicic Z, Nedeljkovic-Protic M, et al. Long-term outcome after admission for acute severe ulcerative colitis in Oxford: the 1992-1993 cohort. *Inflamm Bowel Dis* 2009;15:823–8.
222. Hernandez DS, Hernandez CR, Muncunil GP, et al. Mesalamine versus azathioprine for maintenance treatment after steroid induced remission in pediatric ulcerative colitis. *J Crohns Colitis* 2015;9:S397.
223. Ardizzone S, Maconi G, Russo A, et al. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut* 2006;55:47–53.
224. Mate-Jimenez J, Hermida C, Cantero-Perona J, et al. 6-mercaptopurine or methotrexate added to prednisone induces and maintains remission in steroid-dependent inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2000;12:1227–33.
225. Hyams JS, Lerer T, Mack D, et al. Outcome following thiopurine use in children with ulcerative colitis: a prospective multicenter registry study. *Am J Gastroenterol* 2011;106:981–7.
226. Hande S, Wilson-Rich N, Bousvaros A, et al. 5-Aminosalicylate therapy is associated with higher 6-thioguanine levels in adults and children with inflammatory bowel disease in remission on 6-mercaptopurine or azathioprine. *Inflamm Bowel Dis* 2006;12:251–7.
227. Sternthal MB, Murphy SJ, George J, et al. Adverse events associated with the use of cyclosporin in patients with inflammatory bowel disease. *Am J Gastroenterol* 2008;103:937–43.
228. Castro M, Papadatou B, Ceriati E, et al. Role of cyclosporin in preventing or delaying colectomy in children with severe ulcerative colitis. *Langenbecks Arch Surg* 2007;392:161–4.
229. Ramakrishna J, Langhans N, Calenda K, et al. Combined use of cyclosporine and azathioprine or 6-mercaptopurine in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 1996;22:296–302.
230. Moskovitz DN, Van AG, Maenhout B, et al. Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2006;4:760–5.
231. Cheifetz AS, Stern J, Garud S, et al. Cyclosporine is safe and effective in patients with severe ulcerative colitis. *J Clin Gastroenterol* 2011;45:107–12.
232. Bamba S, Tsujikawa T, Inatomi O, et al. Factors affecting the efficacy of cyclosporin A therapy for refractory ulcerative colitis. *J Gastroenterol Hepatol* 2010;25:494–8.
233. Walch A, Meshkat M, Vogelsang H, et al. Long-term outcome in patients with ulcerative colitis treated with intravenous cyclosporine A is determined by previous exposure to thiopurines. *J Crohns Colitis* 2010;4:398–404.
234. Cohen RD, Stein R, Hanauer SB. Intravenous cyclosporin in ulcerative colitis: a five-year experience. *Am J Gastroenterol* 1999;94:1587–92.
235. Long MD, Farraye FA, Okafor PN, et al. Increased risk of *Pneumocystis jirovecii* pneumonia among patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;19:1018–24.
236. Bernstein CN, Kolodny M, Block E, et al. *Pneumocystis carinii* pneumonia in patients with ulcerative colitis treated with corticosteroids. *Am J Gastroenterol* 1993;88:574–7.
237. Khatchaturian M, Seaton TL. An unusual complication of immunosuppressive therapy in inflammatory bowel disease. *Am J Gastroenterol* 1997;92:1558–60.
238. Scott AM, Myers GA, Harms BA. *Pneumocystis carinii* pneumonia postrestorative proctocolectomy for ulcerative colitis: a role for perioperative prophylaxis in the cyclosporine era? Report of a case and review of the literature. *Dis Colon Rectum* 1997;40:973–6.
239. Escher M, Stange EF, Herrlinger KR. Two cases of fatal *Pneumocystis jirovecii* pneumonia as a complication of tacrolimus therapy in ulcerative colitis—a need for prophylaxis. *J Crohns Colitis* 2010;4:606–9.
240. Kaur N, Mahl TC. *Pneumocystis jirovecii* (carinii) pneumonia after infliximab therapy: a review of 84 cases. *Dig Dis Sci* 2007;52:1481–4.
241. Desales AL, Mendez-Navarro J, Mendez-Tovar LJ, et al. Pneumocystosis in a patient with Crohn's disease treated with combination therapy with adalimumab. *J Crohns Colitis* 2012;6:483–7.
242. Cotter TG, Gathaiya N, Catania J, et al. Low risk of pneumonia from *Pneumocystis jirovecii* infection in patients with inflammatory bowel disease receiving immune suppression. *Clin Gastroenterol Hepatol* 2017;15:850–6.
243. Tschudy J, Michail S. Disseminated histoplasmosis and pneumocystis pneumonia in a child with Crohn disease receiving infliximab. *J Pediatr Gastroenterol Nutr* 2010;51:221–2.
244. Okafor PN, Nunes DP, Farraye FA. *Pneumocystis jirovecii* pneumonia in inflammatory bowel disease: when should prophylaxis be considered? *Inflamm Bowel Dis* 2013;19:1764–71.
245. Yale SH, Limper AH. *Pneumocystis carinii* pneumonia in patients without acquired immunodeficiency syndrome: associated illness and prior corticosteroid therapy. *Mayo Clin Proc* 1996;71:5–13.
246. Grubbs JA, Baddley JW. *Pneumocystis jirovecii* pneumonia in patients receiving tumor-necrosis-factor-inhibitor therapy: implications for chemoprophylaxis. *Curr Rheumatol Rep* 2014;16:445.
247. Toruner M, Loftus EV Jr, Harmsen WS, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 2008;134:929–36.
248. Takeuchi T, Tatsuki Y, Nogami Y, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. *Ann Rheum Dis* 2008;67:189–94.
249. Kaur N. *Pneumocystis carinii* pneumonia associated with oral candidiasis after infliximab therapy for Crohn's disease. *Dig Dis Sci* 2004;49:1458–60.
250. Sharma K, Rao P. *Pneumocystis carinii* pneumonia following infliximab infusion for Crohn disease. *South Med J* 2007;100:331–3.
251. Tai TL. *Pneumocystis carinii* pneumonia following a second infusion of infliximab. *Rheumatology (Oxford)* 2002;41:951–2.
252. Velayos FS, Sandborn WJ. *Pneumocystis carinii* pneumonia during maintenance anti-tumor necrosis factor-alpha therapy with infliximab for Crohn's disease. *Inflamm Bowel Dis* 2004;10:657–60.
253. Seddik M, Melliez H, Seguy D, et al. *Pneumocystis jirovecii* (carinii) pneumonia after initiation of infliximab and azathioprine therapy in a patient with Crohn's disease. *Inflamm Bowel Dis* 2005;11:618–20.

254. Komano Y, Harigai M, Koike R, et al. *Pneumocystis jiroveci* pneumonia in patients with rheumatoid arthritis treated with infliximab: a retrospective review and case-control study of 21 patients. *Arthritis Rheum* 2009;61:305–12.
255. Lawrance IC, Radford-Smith GL, Bampton PA, et al. Serious infections in patients with inflammatory bowel disease receiving anti-tumor-necrosis-factor-alpha therapy: an Australian and New Zealand experience. *J Gastroenterol Hepatol* 2010;25:1732–8.
256. Iwama T, Sakatani A, Fujiya M, et al. Increased dosage of infliximab is a potential cause of *Pneumocystis carinii* pneumonia. *Gut Pathog* 2016;8:2.
257. Estrada S, Garcia-Campos F, Calderon R, et al. *Pneumocystis jiroveci* (carinii) pneumonia following a second infusion of infliximab in a patient with ulcerative colitis. *Inflamm Bowel Dis* 2009;15:315–6.
258. Green H, Paul M, Vidal L, et al. Prophylaxis of pneumocystis pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. *Mayo Clin Proc* 2007;82:1052–9.