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PRACTICE GUIDELINE

Management of paediatric ulcerative colitis, part 2: Acute severe colitis—An updated evidence-based consensus guideline from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition and the European Crohn's and Colitis Organization

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Abstract

Acute severe colitis (ASC) is a relatively frequent manifestation in children with ulcerative colitis and one of the few emergencies in paediatric gastroenterology. A standardized proactive approach based on tight monitoring and timely medical and surgical interventions may improve patients' outcomes. We aimed to update the previous ASC guidelines using detailed recommendations and practice points, based on a systematic review of the literature and consensus of experts. These guidelines update is a joint effort of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition and the European Crohn's and Colitis Organization. A systematic search was performed in Pubmed Ovid Medline, Embase and Cochrane databases using 13 predefined PICO (patient, intervention, comparison, outcomes) based questions and 30 non-PICO based questions. Grading methodology was based on the Oxford Centre for Evidence-Based Medicine—Levels of evidence. The questions were addressed by working subgroups following an iterative consensus voting process, including three

For affiliations refer to page 840.

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online voting meetings and one face-to-face meeting. A total of 36 recommendations and 72 practice points were endorsed with a consensus rate of at least 88% for all statements, regarding initial evaluation, monitoring, medical and surgical treatment of ASC in children. Several topics have been revised since the previous 2018 guidelines and differ from corresponding published adult guidelines. These guidelines present a comprehensive overview of the management of ASC in children, offering practical recommendations and practice points aiming to standardize clinical and surgical treatment and improve outcomes of this severe scenario.

KEYWORDS

children, colectomy, guidelines, inflammatory bowel disease, monitoring, treatment

1 | INTRODUCTION

Compared with adult-onset disease, paediatric ulcerative colitis (UC) is more extensive with approximately 70% presenting with either extensive or pancolonic disease,[1] nearly twice the adult rate.[2,3] As such, UC in children is more likely to be associated with acute severe exacerbations and failure of therapeutic regimens.[4] Medical and surgical management of severe UC in children is often complicated by age-related concerns such as toxicity of medications, body image, psychological impact and other outcomes following potential colectomy. Despite a major leap in biologic agent and small molecule development for the treatment of severe or refractory UC in adults, only two biologic agents are currently approved for children (infliximab and adalimumab). This everlasting problem significantly delays data on pharmacokinetics and safety of new drugs in paediatric patients and severely restricts the use of third and fourth-line new therapies for acute severe exacerbations in this vulnerable population.

Since the publication of the previous European Society of Paediatric Gastroenterology, Hepatology and Nutrition and the European Crohn's and Colitis Organization–(ESPGHAN-ECCO) guidelines on paediatric acute severe colitis (ASC) in 2018,[5] new data have accumulated, particularly concerning management and outcomes. Therefore, we aimed to update the guidelines for managing ASC in children based on an updated systematic review of the literature with an emphasis on practical recommendations and practice points. In contrast to the previous guidelines, we have focused on all surgical aspects of the disease (peri-operative management, surgical considerations and pouchitis) in the ASC chapter, thus also including recommendations and practice points relevant for elective surgery. Furthermore, as venous thromboembolism (VTE) is predominantly a complication of ASC rather than of ambulatory patients, the VTE section is included in the ASC chapter.

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 2018 and are updated herein.

What is New

- We provide an update of guidelines based on new literature, leading to several major changes from the previous guidelines.
- The new guidelines advocate for a wider use of thromboprophylaxis, based on new data, and present an updated approach to second- and third-line therapy for acute severe colitis cases refractory to intravenous corticosteroids, enabling a fourth-line option in selected cases.
- Furthermore, new recommendations for therapeutic drug monitoring have been provided and other sections updated.

2 | METHODS

A detailed elaboration on the methods used can be found in the beginning of Part 1 of these guidelines.

Briefly, 25 international experts in paediatric inflammatory bowel disease (IBD) were selected by the steering committee (E.W., A.A., R.K.R. and D.T.), including two early career members, an adult gastroenterologist, and an adult surgeon. A systematic review of the literature was performed centrally by a librarian, guided by search terms developed by the study leads (E.W. and A.A.). For the ASC manuscript, electronic systematic searches were performed on 15 June 2023,

using Pubmed, Ovid Medline, Embase and Cochrane databases using 13 predefined PICO (patient, intervention, comparison, outcomes)-based questions and 30 non-PICO-based questions (Table S1). Given the paucity of evidence for some topics, key papers published after the initial search and up to the final submission of the guidelines were also included. As many reports on patients with ASC were published as part of larger cohorts of patients with UC, any study retrieved by the general search that included patients with ASC and had separate relevant analysis of its ASC subcohort was included. Topics selected for the ASC chapters were assigned to 10 working groups and involved diagnostic evaluation, therapeutic support including VTE prophylaxis, medical treatments, monitoring of treatment response, surgical treatments and discharge recommendations (Tables of evidence provided in Table S2). A total of 36 recommendations and 72 practice points were endorsed, and the consensus rate was at least 88% for approved statements. There were no statements or practice points that received less than 80% agreement rate during the voting process.

3 | DEFINING THE PROBLEM

ASC is an emergency in children with IBD and is defined by a Paediatric Ulcerative Colitis Activity Index (PUCAI) ≥ 65, either at diagnosis or during disease flare.[6] As a general rule, children with ASC should be admitted to hospital for immediate evaluation and intensive medical management. ASC was the first presentation at diagnosis in 13% of children (median of 11 years old, interquartile range [IQR]: 7–13) in an Italian cohort,[7] in 23% in a European and Israeli cohort,[8] in 28% in a cohort from Canada[9] and 32% in the United States.[10]

During follow-up of children diagnosed with UC, the development of ASC has been reported in another 24% and 27% of children during 12 months and 24 months of follow-up from diagnosis, respectively.[8] Another study with a follow-up of 5-years revealed an additional 13% rate of ASC development in Italian children since diagnosis.[7] Diagnosis of ASC was apparent mainly in children with extensive colitis or pancolitis (E3–E4); 87% and 71% in Canadian and European cohorts, respectively.[9,11]

A large retrospective cohort[11] demonstrated that initial therapeutic management included intravenous corticosteroids (IVCS) in virtually all patients, while consequent treatment escalation (infliximab or cyclosporin) was started in 23% or 52% (mostly infliximab) in Europe[11] and Canada,[9] respectively.

Colectomy rates for children experiencing ASC were reported as 8% in the Canadian cohort within the first year of follow-up,[9] while this was as high as 29%, 34% and 36% at 1, 3 and 5 years, respectively, in a multicentre European cohort of children admitted with ASC between 2009 and 2011.[11] A more recent study reported a much lower rate of approximately 6% during a median follow-up of 3 years,[12] implying that the overall colectomy rate in ASC continues to decline. Those colectomy rates represent an improvement when compared to those published before the era of biologics of 42%, 58% and 61% at discharge, 1 year, and 6 years after admission, respectively.[13] As already outlined in the previous guidelines, the mortality rate after ASC has decreased to <1% (comparable to the adult population) after IVCS introduction.[5] This is confirmed by later cohorts, which did not report any death among children with ASC.[9,11]

The European and Canadian cohorts[9,11] reported poor prognostic value for corticosteroids refractoriness on colectomy rates, for both short and long follow-up. Corticosteroid-free remission rate at 52 weeks after experiencing ASC was reported in 61% of children,[9] most of whom (71%) while receiving biologics.

4 | INITIAL WORKUP

4.1 | Prediction of outcomes and diagnostic evaluation

Recommendations:

1. Initial workup should include complete blood count, urea and serum electrolytes, liver enzymes, albumin, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). If not assessed previously, adequate infectious work-up including chest X-ray and tuberculosis screening should be performed early during admission in preparation for potential biologic therapy [EL4, adults EL3] (*100% agreement).
2. Microbial causes for ASC should be excluded by a stool pathogen detection panel or stool culture and by a multistep algorithm testing for *Clostridioides difficile* [EL4, adults EL3] (*100% agreement).
3. Oral vancomycin should be recommended as first-line therapy for *C. difficile* infection (CDI) in severe UC [EL4, adults EL1] (*100% agreement).
4. Sigmoidoscopy with multiple biopsies should be performed in children not responding to 3 days of IVCS to exclude cytomegalovirus (CMV) colitis [EL4, adults EL3] (*100% agreement).

Practice points:

1. Multistep algorithm testing for *C. difficile* includes detection of glutamate dehydrogenase (GDH) plus toxin A and B and, if discordant, an additional nucleic acid amplification test (NAAT) or alternatively, NAAT plus toxin (*100% agreement).
2. Oral vancomycin for *C. difficile* should be prescribed for 10–14 days at doses of 10 mg/kg per dose four times daily up to an adult dose of 250 mg per dose

and increased to maximum of 500 mg four times daily in more severe cases; national recommendations vary. Oral metronidazole may be used in the absence of oral vancomycin at a dose of 7.5–10 mg/kg per dose, three times daily (to a maximum of 2 g/24 h) for 10–14 days (*100% agreement).
3. Fidaxomicin is another option for treating *C. difficile* in children, either as first-line or after failing oral vancomycin. Weight-based dosing is 16 mg/kg per dose (max 200 mg per dose) twice daily for 10 days, available as tablet and liquid formulations for children ≥6 months of age and ≥4 kg (*96% agreement).
4. Faecal microbial transplantation (FMT) is not recommended in ASC associated with *C. difficile* [EL4, adults EL3] (*96% agreement).
5. Other infections, including viral and parasitic (e.g., *Cryptosporidium* and amoebiasis), should be considered within clinically relevant settings, such as in the presence of fever, with other affected household members, or with nonbloody diarrhoea; stool testing for *Entamoeba histolytica* should be performed in endemic areas or with recent travel to these areas [EL4, adults EL4] (*100% agreement).
6. CMV infection is best identified by obtaining mucosal biopsies via a flexible sigmoidoscopy. Biopsies should be stained using both haematoxylin and 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 for a clinically meaningful infection (*100% agreement).
7. For CMV infection, IV ganciclovir should be used at a dose of 5 mg/kg twice daily for 14–21 days. Response is anticipated within a few days and management should be re-considered with an infectious-disease specialist if response has not been achieved. Switching to oral valganciclovir may be considered after several days of successful intravenous treatment (*100% agreement).

All children admitted with ASC should undergo baseline blood tests including complete blood count, urea and serum electrolytes, liver enzymes, albumin, CRP and ESR, stool culture and *C. difficile* assay with close monitoring after admission. In addition, tests required before possible biologic treatment should be performed, including screening for latent tuberculosis, if not assessed previously.[14,15]

A systematic review of the literature, with selected meta-analysis, shows that haemoglobin, haematocrit and albumin levels may predict need for colectomy, while CRP on Days 3 and 5 of hospital admission has been shown to predict failure of IVCS.[16] Electrolytes do not have a predictive role, but form part of the definition of toxic megacolon (TM) and help guide supportive fluid therapy.[17]

Paediatric IBD is associated with a high relative risk of any gastrointestinal infections.[18] Stool bacterial culture has been reported positive in 2% of children admitted for UC exacerbation, as demonstrated in two paediatric cohorts.[19,20] CDI remains the most frequently identified infectious complication, ranging in from 3% to 47% of paediatric IBD flares.[21–26] Patients with IBD presented with more CDI-related hospital admissions than those without IBD.[27,28] CDI in children with IBD is an established risk factor for severe exacerbations and related hospitalizations.[29] Another paediatric population-based study showed an incidence rate of hospitalization for CDI in children with IBD of 49.1 (95% confidence interval [CI]: 39.4–61.1) per 10,000 person-years, nearly 70-fold higher than in age- and sex-matched children without IBD.[30] In hospitalized IBD patients, CDI is associated with increased morbidity, including extended hospital stays, higher colectomy rate and mortality.[22,31–39] Symptoms of CDI cannot be distinguished from those of a relapse of IBD, therefore, CDI should be ruled out before modifying IBD treatment.[40] Current paediatric recommendations suggest multistep test algorithms that include detection of GDH, which is present in both toxigenic and nontoxigenic strains, plus toxin and if discordant, an additional NAAT or alternatively NAAT plus toxin.[41] Immunoassays for GDH detect a metabolic enzyme highly expressed in all *C. difficile* isolates.[42–44]

There are no specific published guidelines for the treatment of CDI in children with IBD to date. A randomized controlled trial (RCT) of metronidazole versus rifaximin for treating CDI in children with IBD (not with ASC) showed eradication rate of 71% versus 79%, respectively.[45] While a retrospective paediatric case series showed no difference in response rates between metronidazole (41%) and vancomycin (43%),[23] studies in adults have shown increasing rate of metronidazole failures. Two large multicentre phase three studies showed that clinical success was 73% in the metronidazole arm compared with 81% in the vancomycin arm ($p = 0.02$), while in severe CDI success rates were 66% and 79% ($p = 0.059$), respectively.[46] Another therapeutic option is fidaxomicin, which has been recently approved for the treatment of CDI in children. In the recent Sunshine study, 142 children with CDI were age-stratified and randomized to receive either oral fidaxomicin or vancomycin for 10 days. No difference in clinical response at the end of therapy was shown, however, at 30 days after therapy, the rate of sustained response was higher with fidaxomicin (68%) compared with vancomycin (50%), with an adjusted treatment difference of 19% (95% CI: 1.5%–35%).[47] Nevertheless, the use of fidaxomicin is limited by its high cost compared to vancomycin.

FMT is recommended for CDI in children with severe disease unresponsive to antibiotics, or recurrence after treatment of ≥3 infections including antibiotic taper.[41] However, there is currently no evidence to support the use of FMT in ASC associated with CDI.[48] Furthermore, the US Food and Drug Administration (FDA) published safety alerts regarding the transmission of pathogenic organisms and potential severe outcomes, including death.[49]

The significance of CMV colitis in patients with ASC is still controversial, and it is yet to be clarified whether CMV is a pathogen that aggravates ASC or whether its presence simply reflects disease severity.[50] Studies on CMV infection complicating ASC in children are scarce. A case-control study[51] demonstrated an increased prevalence of CMV in severe refractory colitis, previously CMV negative (7/48 [15%]). A multicentre retrospective case-controlled study compared the outcomes of CMV-positive to CMV-negative children with ASC.[52] Of the CMV-positive group, 93% were treated with ganciclovir. The study reported that more CMV-positive children were resistant to corticosteroids. By 12 months, five (33%) CMV-positive and five (13%) CMV-negative patients ($p = 0.049$) required colectomy, but the difference did not reach a level of significance on multivariate analysis. Refractoriness to corticosteroids as a risk factor for CMV colitis was observed in other studies.[53] It was consistently demonstrated that only detection of CMV in the intestinal mucosa by immunohistochemistry (i.e., CMV disease) and not in the blood (i.e., CMV infection) is clinically relevant in IBD.[54,55] Intravenous ganciclovir for 2–3 weeks represents the first line therapy, although patients can be switched to oral valganciclovir after 3–5 days depending on their clinical response.[5] In a meta-analysis of adult studies, antiviral therapy was associated with a 80% reduction in colectomy risk in patients with corticosteroid refractory disease (odds ratio [OR] = 0.20, 95% CI: 0.08–0.49).[56]

Although enteric viruses have been associated with IBD flares, limited data exist regarding their role in ASC. In one report, enteric viruses were identified in 1% of hospitalized children with IBD.[57] In another small study of nine children with IBD, norovirus was suggested as a cause for disease exacerbations.[58] In a retrospective case control study, *Cryptosporidium* was identified in 5% of all paediatric IBD relapses, including hospitalized UC and treatment with nitazoxanide led to a better outcome.[59]

4.2 | Radiologic evaluation and toxic mega-colon

Recommendations:

1. Abdominal X-ray (AXR) should be performed upon admission in children with abdominal tenderness or distension, significant pain or systemic toxicity, to exclude intra-abdominal complications including TM [EL4, adults EL4] (*100% agreement).
2. Children with TM, defined by paediatric criteria (Table 1), should be evaluated promptly by surgeons. Conservative management should only be considered in stable clinical conditions and in highly specialized centres under close monitoring. Urgent colectomy is recommended in unstable cases and if no improvement is apparent within 24–72 h [EL4, adults EL4] (*100% agreement).

TABLE 1 Toxic megacolon: Paediatric criteria.

A.	Radiographic evidence of transverse colon diameter ≥56 mm *(or > 40 mm in those <10 years)*
Plus any of the following:	
B.	Evidence of systemic toxicity, such as:
1.	*Fever > 38.8°C*
2.	*Tachycardia (heart rate > 2 Standard deviation above mean for age)*
3.	*Dehydration*
4.	*Electrolyte disturbance (sodium, potassium, or chloride)*
5.	*Altered level of consciousness or coma*
6.	*Hypotension or shock*

Note: Adapted from Desai et al.[60]

Practice points:

1. Urgent abdominal computed tomography (CT)-scan may be indicated in patients without megacolon on AXR but who have signs of peritonitis or unexplained deterioration, to exclude perforation (*100% 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 TM in children (Table 1). Features of systemic toxicity for diagnosing TM in children include fever, tachycardia, dehydration, electrolyte disturbance, altered level of consciousness, and hypotension; corticosteroids may mask peritoneal signs. PUCAI may not reflect the clinical status in TM due to reduced stool output (*100% agreement).
3. Initial management of TM includes, in addition to IVCS, intravenous fluid resuscitation, intravenous antibiotics (covering gram-negative and anaerobic bacteria), bowel rest, and preparation for surgery. There is no evidence to prefer any specific antibiotic regimen but the combination of a 3rd generation cephalosporin with metronidazole, or a quinolone with metronidazole, can be effective. 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. Empiric oral vancomycin may be considered until *C. difficile* status is known (*100% agreement).
4. Infliximab and calcineurin inhibitors (CNIs) (cyclosporine, tacrolimus) are not routinely recommended in TM, but can be considered in nonseptic patients who are hemodynamically stable, as successful case reports have been published (*100% agreement).

TM and subsequent perforation is one of the most severe, life-threatening complication in ASC episodes. Risk factors for TM in patients with UC include CMV or CDI, hypokalaemia, hypomagnesemia, and the use of anticholinergics, antidepressants, loperamide and opioids.[60] Pathophysiologically, megacolon involves a severe inflammation that ultimately causes dystonia of the bowel smooth muscle layer.[60] The occurrence of TM must be actively ruled out, especially in patients with abdominal distension and tenderness, significant pain, systemic toxicity (including fever, tachycardia, dehydration, electrolyte disturbance, altered level of consciousness and hypotension), and sudden cessation of bowel movements due to colonic atony. Although incidence of TM in ASC is rare, occurring in 1%–2% of UC cases,[19] TM is associated with a high mortality rate if left untreated. As symptoms and signs in children differ from those of adults (altered level of consciousness and hypotension being less frequent), specific diagnostic criteria for TM in children were proposed in the previous ESPGHAN-ECCO ASC guidelines published in 2018, and since then commonly used among the paediatric IBD community (Table 1).[5] AXR remains the first-line test to be performed in clinically suspected TM. Radiographic evidence of transverse colon diameter ≥56 mm (or 40 mm under 10 years of age)[61] is the main criterion (together with systemic toxicity) to confirm TM and its finding should warrant prompt surgical evaluation. In cases where radiographic evidence of significant dilation is absent but there are signs suggestive of bowel perforation, additional urgent radiological imaging (CT-scan) should be performed. Initial management should include IVCS treatment initiation and adequate support measures: fluid resuscitation, parenteral nutrition, antithrombotic prophylaxis and broad-spectrum antibiotic therapy. Antibiotics should cover Gram negative bacteria and anaerobes. A combination of fluoroquinolones or cephalosporins with metronidazole is considered appropriate.[62] Nasogastric tube aspiration is also recommended. In adults, additional measures to promote decompression have been proposed, such as rectal tube insertion combined with intermittent rolling manoeuvres[63] or the knee-elbow position,[64] without evidence in paediatric patients. Although CMV infection is more commonly associated with TM, there is not enough evidence to support empiric treatment with ganciclovir without confirmation of CMV infection. Apart from patients in a stable clinical condition, in highly specialized centres and under close monitoring, all other cases should be considered for urgent colectomy. Anecdotal potential effectiveness of cyclosporine,[65] tacrolimus,[66,67] leukocytapheresis[68] or hyperbaric oxygen,[69] and growing evidence of infliximab efficacy[70] in the era of biologics, have been reported, although a personalized balance between risks and benefits in this severe condition must be considered. If these different conservative measures show no effect within 24–72 h, urgent colectomy should be performed.

5 | THERAPEUTIC SUPPORT

5.1 | Antibiotics

Recommendations:

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

Practice points:

1. Intravenous antibiotic treatment (covering both gram negative and anaerobic pathogens) is indicated when the ASC is suspected to be worsened by bacterial bowel infection, if the patient is septic or if there is suspicion of TM (*100% agreement).
2. In an unstable patient, treatment with antibiotics for disease complications should never delay surgical salvage treatment. Second-line medication rescue therapy may be delayed until the patient is nonseptic and hemodynamically stable (*96% agreement).
3. In treatment refractory cases, a combination of oral antibiotics (amoxicillin, vancomycin, metronidazole and doxycycline/ciprofloxacin) may be considered as an adjunct to induction therapies. Recommended doses: amoxicillin—50 mg/kg/day divided by 3 up to 500 mg × 3/day; vancomycin—250 mg × 4/day (or 125 mg × 4/day if <8 years); metronidazole—5 mg/kg × 3/day up to 250 mg × 3/day; doxycycline—2 mg/kg × 2/day up to 100 mg × 2/day (or alternatively, ciprofloxacin—10 mg/kg × 2/day up to 250 mg × 2/day in children <7 years) (*100% agreement).

In the most recent systematic review and meta-analysis on antibiotics for induction and maintenance of remission in UC,[71] 13 trials were included, of which five evaluated antibiotics as treatment for ASC,[72–76] including one in a paediatric population.[76] Four of the five trials on antibiotic use in ASC used intravenous antibiotics (adults, $n = 183$ in total), and one used a combination of several oral antibiotics (children,

$n = 28$). The pooled OR of achieving clinical response with antibiotic use was 1.74 (95% CI: 1.17–2.58, $I^2 = 29\%$, i.e., moderate heterogeneity) when analysing all 13 trials (12 adult studies and 8 in active non-severe colitis). While the use of (mostly oral) antibiotics was associated with clinical response in active non-severe UC (OR: 2.31, 95% CI: 1.45–3.69, $I^2 = 30\%$), the use of (mostly intravenous) antibiotics in ASC was not effective (OR: 0.94, 95% CI: 0.51–1.74, $I^2 = 0\%$). Current adult guidelines recommend strongly against the routine use of broad-spectrum antibiotics in the management of ASC and suggest use of antibiotics only if infection is considered, or immediately before urgent surgery.[77,78]

A case series of 15 children with refractory ASC were treated with a quadruple combination of oral antibiotics (the 'Jerusalem cocktail') that includes metronidazole, amoxicillin, doxycycline and vancomycin, with half of them responding.[79] The same cocktail was evaluated in the only paediatric study[76] of antibiotics in ASC, which randomized 28 children to IVCS with or without oral antibiotics (amoxicillin, vancomycin, metronidazole and doxycycline/ciprofloxacin) for 3 weeks. There was a significant mean 5-day PUCAI reduction but no difference in faecal calprotectin at discharge or colectomy rates at 1 year (although the study was underpowered for that analysis). Taken together, a short course of the oral antibiotic cocktail could be considered in selected severe refractory cases, while preparing for colectomy or awaiting effect from other management strategies. Antibiotics should be discontinued if no significant response has been observed in 4–7 days and attention should be given to the risk of adverse events and challenges with adherence. In any case, salvage therapy should not be delayed for the sake of this attempt.

5.2 | Pain management

Recommendations:

1. Nonsteroidal anti-inflammatory drugs (NSAIDs) for pain management should be avoided in ASC, due to the possible risk of exacerbating disease or other gastrointestinal symptoms [EL5, adults EL3] (*100% agreement).

Practice points:

1. Bowel perforation or TM should be considered in cases of severe or escalating abdominal pain (*100% agreement).
2. No analgesic medication has demonstrated proven efficacy in improving abdominal pain in IBD. Paracetamol/acetaminophen and conservative measures such as hot packs could be attempted for initial pain management (*100% agreement).
3. Opioid analgesics should be used with caution due to limited reported efficacy, along with the risk of adverse events, including compromised bowel peristalsis that may increase the risk of colonic perforation [EL5, adults EL5] (*100% agreement).

Despite limited data, opioids have been reported as potential precipitating factors to TM in adults due to their antimotility effect.[60] In a paediatric case-control study, 20% of patients with TM were found to have received opiates.[61] Still, it is unclear whether opiates are a marker of disease severity or a true predisposing factor for TM. Moreover, opioids have been associated with severe infections and mortality among adults with IBD.[80,81] The mechanism behind these associations is unknown but may involve intestinal hypomotility, increased intestinal exposure to pathogenic bacteria, and masking of early symptoms of infection.[81] A recent Danish nationwide cohort study reported tramadol to be associated with lower odds of infection, bowel obstruction/ileus, and mortality compared to traditional opioids among patients with IBD.[82]

NSAIDs have been associated with exacerbation or new onset disease.[61,83] Thus, their use is not recommended in adult guidelines,[84] while preliminary evidence suggests that short-term therapy with selective cyclooxygenase-2 (COX-2) inhibitors is safe.[85] However, a recent systematic review and meta-analysis found no consistent association between acetaminophen, NSAIDs or COX-2 inhibitor use and risk of UC exacerbation.[85] A few reports describe the use of ketamine for pain management also in children with TM.[86] The use of cannabinoids is not recommended in the management of acute abdominal pain in patients with UC due to the lack of benefit reported in a recent systematic review and meta-analysis.[87]

5.3 | 5-aminosalicylic acid (5-ASA) preparations

Recommendations:

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, adults EL5] (*100% agreement).

The efficacy of oral or rectal mesalamine preparations may be compromised by the severity of the disease in ASC, thus it is advisable to discontinue them during this phase. There have been documented cases of exacerbation of colitis symptoms in patients with mesalamine intolerance, reported in approximately 2%–10% of cases.[88–90] Additionally, recent data from an adult RCT indicated that the combination of 5-ASA with corticosteroids during hospitalization for ASC did

not provide additional benefits compared to corticosteroids alone.[91]

5.4 | Nutritional support

Recommendations:

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

Practice points:

1. Body weight, caloric intake and hydration status should be monitored daily. Dietary assessment and access to a dietitian is recommended for all patients (*100% agreement).
2. In nonseptic patients, standard oral or enteral 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 refeeding syndrome under the guidance of a dietitian (*100% agreement).
3. There is no evidence to recommend a specific diet in children with ASC (*100% agreement).
4. Electrolyte imbalance (especially hypokalaemia and hypomagnesemia) can promote colonic dilatation. Thus, electrolytes should be monitored (and subsequently corrected), at least every 1–3 days, according to the degree of the baseline values and clinical status (*100% agreement).

RCTs conducted in adults have demonstrated no benefit for bowel rest in ASC. In one adult trial focusing on ASC, enteral polymeric nutrition showed similar remission and colectomy rates compared to total parenteral nutrition (TPN), but it resulted in a higher increase in serum albumin (17% vs. 5%, $p = 0.019$), fewer adverse events (9% vs. 35%, $p = 0.046$), and fewer postoperative infections ($p = 0.028$).[92] In a retrospective case series involving 15 children with ASC who underwent bowel rest and received TPN, 33% required colectomy, a rate identical to that reported in other studies.[93] Therefore, TPN is not indicated in children with ASC unless prolonged ileus or severe malnutrition with intolerance to oral feeds are present.

In the prospective OSCI study of 128 children admitted for ASC, 58% were not consuming solid foods by the third day of admission; however, multivariate analysis did not associate this with improved outcomes even after controlling for disease activity (personal communication from D.T.).[94]

In an adult open-label RCT, patients with ASC ($n = 62$) received IVCS with EEN (semielemental formula) for 7 days along with the standard of care (SOC) versus IVCS + SOC alone.[95] Corticosteroid failure was lower on EEN compared to SOC (intention-to-treat analysis 25% vs. 43%, $p = 0.051$; per protocol analysis 19% vs. 43%, $p = 0.04$), without a difference in colectomy rate (9% vs. 13%; $p = 0.41$). Patients on EEN had a shorter hospital stay, higher albumin level on Day 7, greater reduction in serum CRP and faecal calprotectin levels, and a lower composite outcome of colectomy/hospitalization at 6 months compared to SOC.

6 | VTE PROPHYLAXIS

Recommendations:

1. Pharmacological thromboprophylaxis for reducing the risk of VTE should be considered in all inpatient children with ASC (Figure 1) [EL5, adults EL2] (*100% agreement).

Practice points:

1. Adequate mobilization, hydration, correct use and proper care of central venous catheters should always be promoted as a broad VTE reduction strategy (*100% agreement).
2. Clinicians should be aware of VTE symptoms to diagnose and manage VTE complications as early as possible. VTE-specific treatment and investigations should be discussed case by case with haematologists and clinicians appropriate to the VTE location (*100% agreement).
3. Pharmacological thromboprophylaxis with low molecular weight heparin (LMWH) is the current mainstay. Subcutaneous enoxaparin 1 mg/kg once daily (max 40 mg daily) is advised with 0.5 mg/kg twice daily to be considered, according to compliance, in younger patients under 40 kg due to faster renal clearance. Monitoring with anti-Xa activity levels should be performed in children with significant renal impairment (*100% agreement).
4. Pharmacological thromboprophylaxis should be maintained until discharge. Extended prophylaxis after discharge is not routinely indicated and should only be considered in selected specific clinical situations (e.g., discharge after major surgery or previous VTE) in consultation with haematologists, surgeons and other clinicians involved (*100% agreement).
5. Mechanical thromboprophylaxis should be added to pharmacological thromboprophylaxis according to local availability and age-related feasibility (*100% agreement).
6. Risk factors for VTE should be investigated in all UC patients and regularly re-evaluated when clinical condition changes. Patients should not be routinely screened for genetic or acquired thrombophilia,

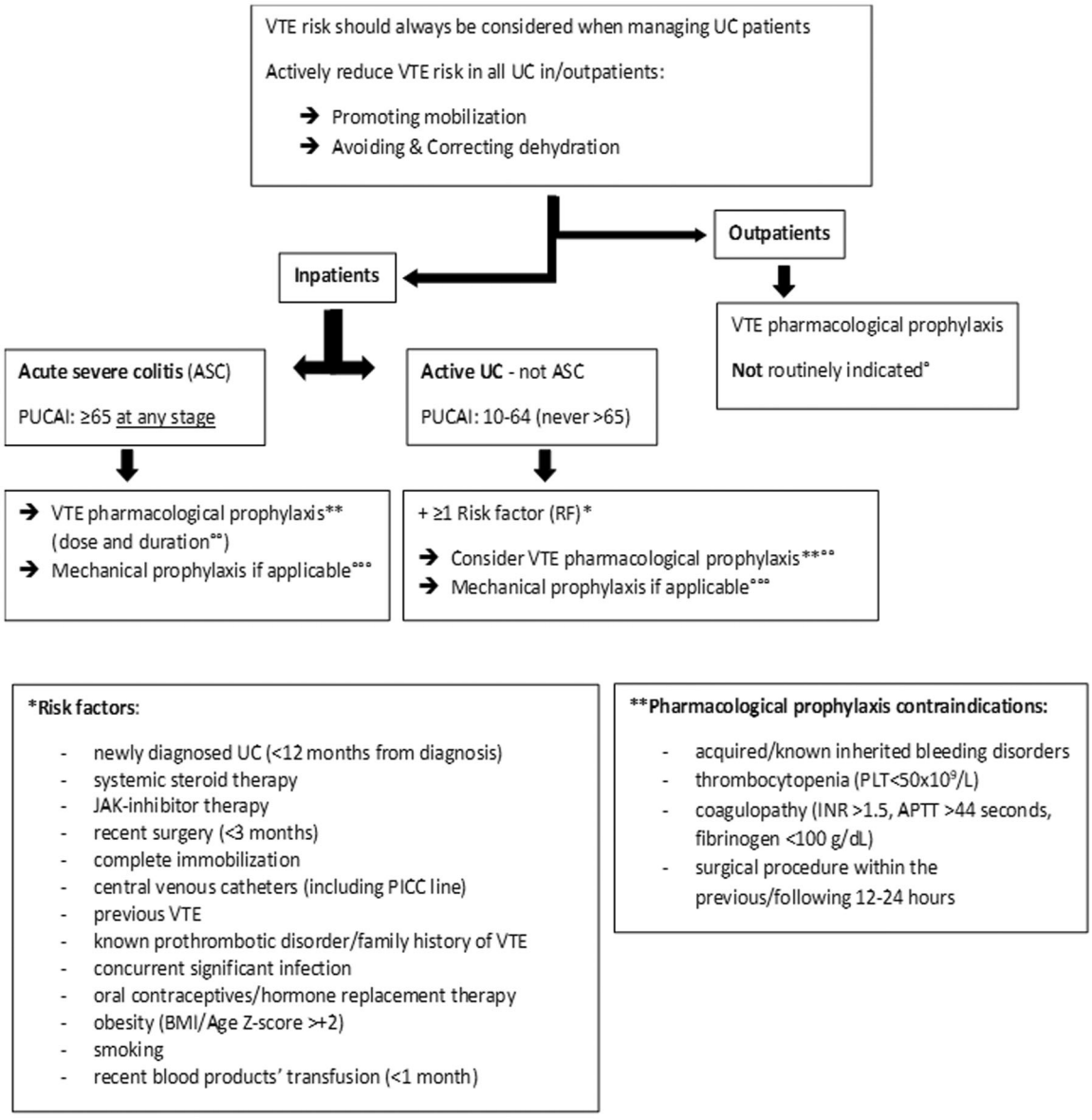

FIGURE 1 VTE prophylaxis management algorithm for paediatric patients with UC. APTT, activated partial thromboplaspin time; ASC, acute severe colitis; BMI, body mass index; INR, international normalized ratio; JAK, Janus kinases; NPO, nothing per os; PCR, polymerase chain reaction; PICC, peripherally inserted central catheter; PLT, platelets; PUCAI, Paediatric Ulcerative Colitis Activity Index; RF, risk factors; UC, ulcerative colitis; VTE, venous thromboembolism.

except for patients experiencing unprovoked VTE events in the absence of risk factors and active disease (*100% agreement).

VTE represents a serious IBD complication, which can lead to prolonged hospital stay and intensive care unit admission.[96–98] Although patients with paediatric IBD (PIBD) have a lower incidence rate of VTE compared to adults, they have a substantially increased absolute risk (VTE incidence rate ranging from 3.7 to 31.2 per 10,000 patient-years) compared to general paediatric population either hospitalized or

ambulatory (VTE incidence rate ranging from 0.18 to 0.78 per 10,000 patient-years).[99–103] Moreover, although the absolute risk of VTE increases with age, the relative risk is higher in younger patients due to the lower background risk.[101,103,104]

In addition to the well-known IBD-unrelated prothrombotic risk factors, VTE aetiology in IBD is multifactorial with inflammation playing a central role.[105–107] Disease activity was shown to increase VTE risk with most children with IBD having concomitant intestinal, particularly colonic, inflammation, with a greater risk in UC compared to Crohn's disease (CD) (VTE incidence rate in UC ranging from 12.4 to 49.6 per 10,000 patient-years).[99,100,102,104,108] VTE risk is reported to be increased in children newly diagnosed with IBD (VTE incidence rate within 12 months from diagnosis ranging from 18.0 to 81.2 per 10,000 patient-years)[99,100] and hospitalizations (estimated VTE incidence rate in hospitalized patients 1144 per 10,000 patient-years in the PIBD-SET Quality Safety Registry).[99,109] Systemic corticosteroids, but not biologics, have been independently associated with VTE risk in adult and children with IBD.[99,100,102,110–113] Up to 40% of VTE cases in children with IBD were reported in prepubertal patients.[99,103]

VTE location is heterogeneous (and so therefore are its symptoms), including most frequently deep venous thrombosis (29%–73%), cerebral sinus venous thrombosis (0%–50%) and pulmonary embolism (8%–23%).[98,99,102–104,108,110,114–117] While the majority of patients fully recover, VTE may result in significant morbidity, such as persistent or recurrent thrombosis, post-thrombotic syndrome or persistent neurological deficits, and mortality (ranging from 5% to 10%).[96,98,99,102,104]

The most commonly used anticoagulant in paediatric pharmacological thromboprophylaxis is LMWH, which has a longer half-life, a more predictable pharmacokinetic profile and lower rates of adverse events compared to unfractionated heparin.[118,119] In a recent systematic review prophylactic LMWH proved to be safe and effective in reducing VTE risk in the general paediatric population with a rate of major haemorrhage of 0.6%.[120] In PIBD, as described in adult IBD, LMWH does not increase the risk of IBD-related gastrointestinal bleeding even in hospitalized patients with ASC, with no difference in haemoglobin levels or need for blood transfusions whether or not prophylactic LMWH is administered.[114,121–124] Although specific evidence that LMWH necessarily prevents thrombotic events in children with IBD is lacking, in adult patients it is recognized to reduce VTE episodes.[125–129] Lack of data on direct oral anticoagulant use as thromboprophylaxis in children with IBD prevents them from being recommended at the moment.

Overall, currently available quality data on VTE both in adult and paediatric patients are sparse with a 2024 meta-analysis concluding a significant reduction in VTE (number needed to treat, NNT = 35) in IBD patients treated with VTE prophylaxis, if considering lower-risk-of-bias studies, with the caveat being intrinsic limitations/biases in data collection.[96,99–103,109,114,130–132] While there is an increased incidence rate of VTE, the absolute numbers remain low, balanced with the practical and ethical impossibility of a RCT to prove the efficacy and safety of thromboprophylaxis in the PIBD cohort and obtain a precise NNT and number needed to harm (NNH). All this considered, based on the current available evidence, we opted to recommend medical thromboprophylaxis in all patients with ASC and in selected hospitalised patients with UC that is not acute severe, in contrast with adult consensus and guideline on the topic, where VTE pharmacological prophylaxis is recommended in all IBD patients hospitalized for any cause.[133,134]

We therefore acknowledge the limitations of the available paediatric literature, but note the severity of the VTE events reported with potential acute and chronic morbidity, particularly the strikingly higher occurrence of cerebral thrombosis in children with IBD compared to the general paediatric population.[99,109,135] While acknowledging that the risk of VTE in the young age group (<12 years) may not be lower than in adolescents,[99] in selected mobile young subjects, therapeutic decisions on thromboprophylaxis should be individualized while weighing the potential emotional stress caused by the frequent subcutaneous injections, the rarity of the events and the limited paediatric evidence (Figure 1).

7 | CORTICOSTEROIDS

Recommendations:

1. Intravenous methylprednisolone 1 mg/kg/day (up to 40 mg/day) once daily is the first-line treatment in ASC and should be promptly started [EL2, adults EL1]. A higher dose of 1.5 mg/kg/day (up to 60 mg/day) can be used at the clinician's discretion (e.g., in patients on oral corticosteroids at admission and/or with a more severe spectrum of ASC) [EL4, adults EL4] (*100% agreement).

Practice points:

1. A rapid reduction of methylprednisolone to 1 mg/kg/day (40 mg/day) should be performed once response has been observed if started on a higher dose (*100% agreement).
2. Intravenous methylprednisolone should not be extended beyond 7–10 days of total course, since it carries no additional benefit and increases toxicity. In corticosteroid-refractory patients in whom second-line therapy is initiated, there is no need for corticosteroid tapering if corticosteroids are given as an isolated short course (up to 10 days) (*100% agreement).

3. Second-line therapy should be considered in place of initial intravenous methylprednisolone in patients with contraindications/significant side effects to IVCS (e.g., uncontrolled hyperglycaemia in diabetic patients) (*100% agreement).

There is limited new evidence on IVCS in ASC since the previous guideline, and thus associated advice remains largely unchanged.[5]

IVCS are long established as the first-line treatment for ASC.[136–138] In a systematic review and meta-regression of 32 adult and paediatric studies, the corticosteroids response rate was 67% with a short term colectomy rate of 27% and a mortality rate of 1%.[139] A subsequent paediatric multi-centre study on long-term outcomes in ASC reported a lower rate of corticosteroid failure, with 22.6% of patients requiring a second-line therapy, and a lower rate of colectomies before discharge and at long-term follow-up.[11] In a 2023 prospective paediatric inception cohort of ASC patients at initial presentation, 51% escalated to infliximab before discharge following corticosteroid-refractoriness, and 74% escalated to infliximab by 1 year of follow-up, reflecting contemporary practice of prompt escalation in corticosteroid refractory/dependent patients associated with improved colectomy rates.[9]

Concerning corticosteroid dosage, no updated RCT has been performed to clarify the optimal therapeutic window. Briefly, in a retrospective study among children with ASC, corticosteroid response did not vary within the standard dosing range (1–1.5 mg/kg/day up to 40–60 mg/day).[136] In addition, a propensity score analysis in a large paediatric ASC cohort failed to find significant superiority of the higher IVCS doses (cutoff 2 mg/kg/day).[140] Anecdotal evidence for the effectiveness of very high-dose or pulse corticosteroids is inconsistent.[141,142] A single-centre retrospective study, reporting a strikingly low colectomy rate at 1 year with the suggestion of a high-dose benefit (11% total; 5% in high dose vs. 23% in standard dose, $p = 0.09$), was performed in a paediatric cohort of both moderate and severe UC patients extensively treated at admission with intravenous antibiotics.[143]

Concerning corticosteroids withdrawal in corticosteroid-refractory patients, although dosage and duration of corticosteroid treatment are imperfect predictors of adrenal suppression, patients being on corticosteroids for less than 2 weeks or on high-dose corticosteroids (e.g., ≥40 mg prednisone) for less than 1 week can be considered as less likely to develop adrenal suppression, unless they have recently received frequent short corticosteroids courses; in these cases there is no need of tapering after initiation of second-line therapy.[144–148] However, in corticosteroid-refractory patients initiated on second-line therapy, who have been on corticosteroids for longer (e.g., previous oral course) or have undergone repeated courses within the last 12 months (e.g., ≥3 short courses via any route), a rapid taper to a physiological corticosteroid dose (prednisone 0.2 mg/kg/day up to a maximum of 20 mg/day, or equivalents) may be considered, followed by gradual reduction to support recovery of endogenous adrenal function, maintaining a low threshold for the assessment of the hypothalamic-pituitary-adrenal (HPA) axis.[146,147,149] Regardless, a high level of vigilance should be maintained during and after corticosteroid withdrawal for recognizing adrenal insufficiency and corticosteroids withdrawal symptoms.[144,150] Corticosteroid administration in divided daily doses increases the probability of HPA axis suppression with evening doses having the potential of inhibiting peak adrenocorticotropic hormone secretion in the early morning.[146,147,151] Therefore, once daily morning doses of corticosteroids should be preferred.

A small observational prospective study, comparing oral corticosteroids to standard infliximab regimen as induction treatment in moderately to severely active paediatric UC, suggested that infliximab and corticosteroids were equally effective in short-term outcomes, with infliximab being superior in the long term.[152] However, given the limitations of the above-mentioned study and the absence of published literature directly comparing IVCS to second or third-line therapies in ASC, evidence to change the current ASC management paradigm for the vast majority of patients is not justified. Nevertheless, in specific clinical situations where corticosteroids are contraindicated, a case-by-case evaluation to start a second-line therapy as first should be undertaken by the clinician. A recent meta-analysis demonstrated that adults with IBD receiving anti-TNF medication had significantly less VTE than patients treated with corticosteroids (OR: 0.42; 95% CI: 0.25–0.71), suggesting a potential role of anti-TNF over corticosteroids in remission induction in IBD flare-ups in patients at risk for VTE.[113] Failure of oral corticosteroids before admission should not discourage IVCS as up to 80% of nonresponders to oral formulation may benefit of IVCS. However, this needs to be balanced against evidence that prolonged use of corticosteroids before admission can predict need for rescue therapies.[153–155] Finally, to maximize response, intensive approaches combining IVCS with additional medications (such as mesalamine) are more commonly attempted but without clear signs of benefit.[156]

8 | SECOND- AND THIRD-LINE THERAPIES

Recommendations:

1. Second-line therapy should be initiated on the 5th day of IVCS treatment in children with a PUCAI ≥ 65 [EL2, adults EL2] (*100% agreement).
2. Infliximab is recommended as the preferred second-line medical therapy for anti-TNF naive children failing IVCS [EL3, adults EL1] (*100% agreement).

3. CNIs (tacrolimus or cyclosporine) can be considered as an alternative second-line medical therapy in centres experienced with its use, particularly following previous infliximab failure [EL4, adults EL1] (*100% agreement).
4. To reduce unnecessary immunosuppression, corticosteroids (when ineffective) should be rapidly weaned following introduction of second-line therapy or decision to proceed to colectomy (stopped if in use ≤10 days and reduced to prednisone ≤0.2 mg/kg or equivalent to 10 mg adult dose with gradual tapering thereafter if >10 days) [EL5, adults EL5] (*100% agreement).
5. Third-line sequential rescue therapies (CNIs after infliximab, infliximab after CNI or a JAK inhibitor after either) may be considered in stable patients, in specialised centres and in those whose corticosteroids were weaned off or nearly weaned off as stated above [EL5, adults EL2] (*100% agreement).

Practice points:

1. Cyclosporine or tacrolimus should be considered as a rescue therapy and mainly as a bridge to long-term maintenance therapy such as a thiopurine (in thiopurine naïve patients) or to vedolizumab (in patients who failed thiopurines) (*96% agreement).
2. Dosing and target levels (where relevant) for infliximab, cyclosporine, tacrolimus, tofacitinib and upadacitinib are given in tab. 2 of the ambulatory chapter (*96% agreement).
3. Drug clearance is significantly enhanced in children with ASC, particularly in patients younger than 10 years and in the presence of hypoalbuminemia. Therefore, infliximab induction should be initiated with 10 mg/kg per dose and given more frequently than usual (e.g., Weeks 0, 1 and 3–4), in most cases (*88% agreement).
4. Infliximab therapeutic drug monitoring (TDM) may be used before the second and third infusions to guide subsequent infusions dosing and intervals. Higher doses and shorter intervals during induction may be considered according to trough concentrations (TC), clinical and biochemical response (*100% agreement).
5. Among responders to intensified induction, subsequent doses of infliximab during maintenance phase can often be gradually lowered (and intervals prolonged), guided by TDM, clinical and biomarkers response (*100% agreement).
6. Response to infliximab or CNIs 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 7–14 days with either therapy (*96% agreement).
7. 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 (*100% agreement).
8. If sequential therapy is used, *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis with trimethoprim-sulfamethoxazole should be considered especially if triple immunosuppressive treatment is used. Trimethoprim-sulfamethoxazole dosing: 450 mg/m^2 twice daily for 3 days each week, (maximum daily dose 1.92 g) either consecutive or alternate day dosing (*100% agreement).
9. Tofacitinib has been shown to be effective in small cohorts of adults and children with acute severe corticosteroid-refractory UC but should only be considered in specialised centres. A dose of 10 mg three times daily for 7 days was reported in adults, however, there are no data to support specific dosing regimens in children. Upadacitinib has demonstrated efficacy in small cohorts of adults and children with ASC using the label dose of 45 mg once daily (*96% agreement).
10. Fourth line treatment should be generally discouraged but may be considered in specialized centres and in selected nonfulminant cases only, after a surgical consultation (*100% agreement).
11. There is currently no evidence to support the use of vedolizumab and ustekinumab as a primary third-line agent in ASC, but these could be considered after using CNI rescue as a bridging strategy (*100% agreement).

8.1 | Infliximab

In the prospective multicentre OSCI study of ASC in children, 33 subjects 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).[94] Other case series have reported the use of infliximab in children with ASC, with pooled short-term response rate of 75% (95% CI: 67%–83%) ($n = 126$, six studies) and a pooled 1-year response of 64% (95% CI: 56%–72%).[157] In another prospective paediatric study of 52 subjects who received infliximab (half with ASC) the corticosteroid-free remission rates at 1 and 2 years were 38% and 21%, respectively, and the likelihood of avoiding colectomy by 2 years was 61%.[158] In a multicentre prospective paediatric cohort study of ASC at initial presentation from the Canadian Children IBD Network, infliximab was the first advanced therapy initiated in all patients. Of 379 children with new onset UC/IBD-unclassified, 105 (28%) presented with ASC.[9] Fifty-four (52%) children were corticosteroid-refractory and given infliximab (87% intensified regimen); corticosteroid-free remission at 1 year was achieved by 34 (63%) of the corticosteroid-refractory patients (all on infliximab).[9]

Different factors can affect pharmacokinetic features in paediatric patients treated with anti-TNF antagonists, especially in ASC. In the setting of severe inflammation, drug clearance is enhanced due to increased faecal loss, mucosal barrier damage, high concentrations of tissue TNF and increased proteolytic degradation of TNF-anti-TNF immune complexes (sink effect).[159–162] In addition, hypoalbuminemia observed in some patients with ASC exacerbates infliximab loss, since the drug is bound to albumin in the serum.[163] These features decrease serum level of anti-TNF drugs and ultimately may predispose to development of anti-drug antibodies.[164] Young children are even more vulnerable: Jongsma and colleagues demonstrated that infliximab-treated patients with IBD aged <10 years achieved lower TC during maintenance and required higher doses, leading to higher rates of development of anti-drug antibodies, compared to children >10 years.[165] When drugs are administered in mg/kg, such as done with infliximab, the discrepancy between the nonlinear weight-related clearance and the linear total dose calculated according to weight results in underdosing of patients with low weight, resulting in lower TC in children.[166] This might even be enhanced in very-early-onset IBD patients, who sometimes require ultrahigh doses of infliximab during induction to induce remission and achieve suitable TCs.[167]

Data on ASC aligns with the observation that higher inflammatory burden is associated with lower infliximab serum concentrations. A small retrospective study comparing adults with severe versus moderate UC exacerbations showed that infliximab TC at week 2 was significantly lower in the former (7.2 ± 5.3 vs. 14.4 ± 11.2 µg/mL, $p = 0.007$).[168] Indirect data support applying TDM during induction in ASC: Papamichael et al. showed that a TC of <16.5 mg/mL at Week 2 was significantly associated with colectomy (hazard ratio [HR]: 5.6, 95% CI: 1.1–27.8).[169] A single paediatric prospective noninterventional study in patients with ASC showed that high infliximab clearance at Day 3 after drug initiation, but not total exposure, was associated with colectomy (HR: 58.2; 95% CI: 6.0–568.6; $p < 0.001$).[170] While these data support modifying infliximab therapy already during induction, based on TDM, no trial was performed to define whether proactive TDM during induction improves outcomes.

Although the association between serum infliximab concentrations and clinical and endoscopic outcomes is well defined, data regarding accelerated infliximab dosing in ASC are contradictory. Several observational studies suggested a benefit from intensive infliximab dosing. A retrospective study conducted by Gibson et al. compared standard dosing (5 mg/kg at Weeks 0, 2 and 6) to accelerated dosing (three doses within a median period of 24 days) in 50 adults with ASC.[171] The colectomy rate during induction was lower in the accelerated group (7% vs. 40%, $p = 0.039$), but similar between the groups after induction. A short-term advantage of accelerated regimen was also observed in a propensity score-matched cohort of 52 patients (30-day colectomy rate of 57% in standard dosing vs. 27% in the accelerated group, $p = 0.048$). No difference was observed, however, in the overall colectomy rate.[172] Other studies have not shown a benefit of intensified dosing in ASC.[173–176] A propensity score-based analysis that included 42 hospitalized patients with ASC showed that the dose during the first infusion (5 vs. 10 mg/kg) did not affect 30 days colectomy rate but acceleration after an initial standard dose was associated with significantly higher colectomy rates (probably reflecting an association between refractoriness to first infusion and colectomy).[177] In a systematic review of seven retrospective studies (181 patients receiving accelerated infliximab dosing and 436 receiving standard dosing), the colectomy rate was similar between the groups.[174] Two meta-analyses ($N = 705$ and $N = 2158$) reported similar results.[178,179] Srinivasan et al. suggested that dose intensification strategy may influence infliximab pharmacokinetics but not clinical outcomes.[180] Importantly, many of these studies are limited by selection bias of patients with more severe disease being allocated to the accelerated dosing group. The most recent data comes from an open-label Australian RCT in which 138 patients with ASC were randomly assigned to receive either an upfront accelerated regimen (three infusions of 10 mg/kg within 3 weeks), gradual acceleration if not responding (first infusion of 5 mg/kg and two more infusions of up to 10 mg/kg within 3 weeks) and a standard induction (5 mg/kg at Weeks 0, 2, 6 with an allowed extra infusion during the first week if not responding). All endpoints, including clinical response, clinical remission, corticosteroid-free clinical remission, endoscopic remission and colectomy rate did not differ between the groups either at Day 7 or at the 3 months timepoint. However, it should be noted that ultimately only 28 patients (20%) received a conventional standard induction (5 mg/kg, Weeks 0, 2 and 6) while the rest were accelerated either according to their allocation or as salvage therapy.[181]

The data on accelerated infliximab dosing in the paediatric population are more limited. In 125 children with corticosteroids-refractory UC, intensified induction (a mean induction dose of ≥7 mg/kg or an interval of ≤5 weeks between doses 1 and 3) was associated with a higher rate of remission (HR = 3.2) and a lower rate of colectomy (HR = 0.4).[182] These outcomes were not improved by intensified induction in children that were corticosteroid dependent.

8.2 | Cyclosporin

In an RCT among adults with ASC, 73 patients (however, not all failing IVCS) were randomized to either 2 or 4 mg/kg of intravenous cyclosporin.[183]

Response rates at Day 8 were similar in both groups (83% and 82%, respectively), with 9% requiring 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%–85% of patients respond to intravenous cyclosporin and avoid colectomy in the short term, with a median time to response of 4 days.[184] In a systematic review of paediatric nonrandomized studies, the pooled short-term success rate with cyclosporin was 81% (95% CI: 76–86).[157]

8.3 | Tacrolimus

Tacrolimus has been studied in two double-blind RCTs in adult UC. In the first study, 60 corticosteroid-refractory UC patients were randomly assigned to receive oral tacrolimus targeting high (10–15 ng/mL; $n = 19$) or low (5–10 ng/mL; $n = 21$) serum trough levels, or placebo ($n = 20$).[185] Clinical response rates were 68% and 38% in the high and low trough groups, respectively, and 10% with placebo. Another RCT treated 62 patients with corticosteroid refractory, moderate-to-severe UC with tacrolimus to trough levels of 10–15 ng/mL.[186] 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 combined the data of these two trials and other observational studies and demonstrated that clinical response at 2 weeks was significantly higher with tacrolimus compared with placebo (RR = 4.61, 95% CI: 2.09–10.2), especially in those treated with thiopurines in parallel. Colectomy-free rates at 1, 3, 6 and 12 months were 86%, 84%, 78% and 69%, respectively.[187]

Paediatric studies of tacrolimus as rescue therapy in ASC have been limited to retrospectively reported single-centre case series and one small multicentre prospective study. In the latter, of 14 children with ASC, 69% responded to tacrolimus, but 44% of responders underwent colectomy by 1 year.[188] Short-term response rates, meaning hospital discharge without colectomy, ranged between 60% and 90% in the retrospective case series, with at least 40%–50% requiring surgery by 1–2 years.[189–192]

A recent paediatric systematic review including the five previous studies and two others, with a total number of 166 patients, the majority naïve to biologics, demonstrated an initial response to tacrolimus therapy in 84% (95% CI: 73%–93%). At 1 year follow-up, 15% had sustained response on only tacrolimus while the pooled frequency of 1 year colectomy free survival in children treated with initial oral tacrolimus was 64%; 7% of patients required cessation of therapy because of side effects.[193–195]

8.4 | Infliximab Versus CNI

Infliximab and CNI are equally effective in inducing clinical remission in ASC in both children and adults.[157,196–198] At present, most of corticosteroid-refractory children receive infliximab as second-line therapy. Besides the greater familiarity with infliximab and better risk-benefit profile, the ability to continue it as maintenance is an advantage.[157] In a retrospective multicentre study from the Porto IBD working group of ESPGHAN (2009–2011), reflecting the practice at 25 different centres, the outcomes of 141 children with ASC were reported; 31 (22%) escalated to second-line therapy, 19 (13%) to infliximab and 12 (8%) to cyclosporin; 16 (11%) of patients had colectomy before discharge.[11] Colectomy-free survival rates were significantly lower in patients requiring escalation to second-line agents versus those who did not, including 65% versus 95% at discharge, 42% versus 80% at Year 1, 42% versus 73% at Year 3, and 38% versus 70% at Year 5 ($p < 0.001$ for all comparisons).

Comparable efficacy of infliximab (with standard dosing) and cyclosporin has been demonstrated in two randomized comparative trials in adults and in a meta-analysis of retrospective studies.[196–198] The open-label CYSIF trial showed that treatment failure at Day 98 was reported in 60% patients with cyclosporin versus 54% with infliximab ($p = 0.49$). The colectomy rate by Day 98 was 18% versus 21%, respectively ($p = 0.66$).[196] Similarly, the randomized controlled comparison of infliximab and cyclosporin in corticosteroid resistant ulcerative colitis (CONSTRUCT) trial found no significant difference regarding colectomy, mortality rates or the occurrence of serious infections in 270 patients with corticosteroid-resistant ASC treated with cyclosporin or infliximab.[197]

In contrast, tacrolimus has never been included in a comparative trial with biologic therapy. In a retrospective study, the clinical outcome of children with ASC who did not respond to IVCS and were subsequently treated with infliximab or tacrolimus was evaluated; 170 patients were included and the rate of colectomy 6 months from rescue therapy was similar between both groups (23% infliximab versus 27% tacrolimus, $p = 0.53$). About half of corticosteroid-refractory patients failing tacrolimus or infliximab as initial rescue therapy required colectomy at 6 months, even if they switched to the alternative agent.[199]

Of note, close monitoring of cyclosporin and tacrolimus levels is required, given the narrow window between therapeutic and toxic levels. CNI 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 azotaemia, given the potential for renal toxicity.

8.5 | Third-line and sequential medical therapies for paediatric ASC

Third-line medical therapy in ASC arises when a steroid-refractory patient has failed second-line therapy in the initial ASC hospitalization. Such a sequential medical therapy is used when the choice is made not to proceed to colectomy. By far, sequential therapy was reported when infliximab follows or is followed by a CNI (cyclosporin or tacrolimus) and almost exclusively in adult ASC. There have been very few reports of third-line therapy in paediatric ASC. This is a separate scenario from sequential therapy in the ambulatory chronic active UC patient, who is steroid-dependent or refractory with a course of months and often multiple hospitalizations (discussed in the ambulatory paper). In the largest published prospective cohort study of ASC at initial presentation to date, by the Canadian Children IBD Network, no patient received tacrolimus after infliximab; a small number progressed to vedolizumab but not during the initial ASC episode.[9] A systematic review of sequential therapy in adult ASC included 10 case series or cohort studies (314 participants), of which only one was prospective and none were RCTs.[200] It should be noted that many of the source studies contained a mixture of chronically active UC and ASC cases. The review concluded that the risk of sequential therapy seemed lower than initially reported. In nonurgent and stable cases, deferral of colectomy to the elective setting, which is associated with significant improvement in patient outcomes, could also be considered a successful outcome of sequential rescue therapy.[201]

However, an earlier report noted that sequential third-line therapy is associated with significant adverse events and mortality.[202] Therefore, third-line sequential rescue therapies (CNI after infliximab, infliximab after CNI or a JAK inhibitor after either) may be considered in stable patients and only in specialised centres. Fourth-line therapy, meaning any treatment following three lines of therapy (e.g., CNI after corticosteroids, infliximab and JAK inhibitors or any other different order) should be generally discouraged due to prolongation of a high risk, refractory condition amenable for surgical treatment, but may be considered in specialized centres and in selected nonfulminant cases only, after a surgical consultation. Successful use of dual biologic therapy in IBD has suggested that we do not need to ensure that the levels of the second-line medication have cleared or nearly cleared before starting the third-line therapy in paediatric ASC. Nevertheless, due to lack of data concerning combinations of infliximab and JAK inhibitors, caution should be employed when initiating anti-JAK agents adjacent to an infliximab infusion. Multiple studies of IBD therapies have demonstrated that infectious complications are highest with concomitant corticosteroid therapy, so rapid weaning of corticosteroids is needed if not previously performed at second-line therapy introduction.

Slower onset of action of ustekinumab and vedolizumab limits their efficacy in ASC, but CNIs may be used as a bridge to their planned introduction as maintenance therapies.[193,203] The favourable safety profile of ustekinumab and vedolizumab makes the use of CNI as bridge therapy attractive, especially if there has been previous thiopurine and anti-TNF failure.[201]

Tofacitinib is an attractive third-line option in biologic-experienced ASC patients due to its rapid effect, although its use has not yet been approved in children.[201] A placebo-controlled RCT of tofacitinib in adult ASC showed that the addition of tofacitinib to IVCS improved corticosteroid responsiveness and decreased the need for rescue therapy (infliximab or colectomy).[204] A review of tofacitinib for treatment of ASC in paediatric and adult UC found 21 studies including 11 cases of refractory paediatric UC (many with chronic active disease with acute hospitalisation).[205,206] The 30- and 90-day colectomy-free survival rates were 85%, even among refractory patients who were deemed to require colectomy.[205] A further case series of six children with ASC requiring tofacitinib salvage reported a rapid response with few complications and four gaining complete remission.[207] The dose in adult studies has been the intensified dose of 10 mg orally three times daily and the paediatric series have mostly used 10 mg orally twice daily; however, most paediatric studies have been in the chronic active UC patient who is corticosteroid-refractory and has an episode of ASC during a hospitalization.

Upadacitinib may also be effective for corticosteroid-refractory chronic active UC, but the registration trials of upadacitinib excluded ASC. A recent systematic review including 11 adult studies ($n = 55$) reported 80% corticosteroid-free clinical remission of 80% and a colectomy rate of 16% at 3 months.[208] In a subanalysis of a multicentre cohort including 100 children with refractory UC treated with upadacitinib, 22 patients with ASC following IVCS and infliximab failures demonstrated clinical response of 82% (18/22) and corticosteroid-free clinical remission of 55% (12/22) patients by the end of the 8-week induction period. Six patients underwent colectomy after a median of 4.5 (1–8) weeks of therapy.[209] A smaller paediatric cohort ($n = 20$), reported a corticosteroids-free clinical remission rates of 75% and 65% at Weeks 8 and 24, respectively.[210]

IBD patients are at increased risk of PJP (HR: 2.96; 95% CI: 1.75–4.29),[211] which is associated with significant morbidity and mortality, especially in children and also in patients receiving triple immune suppression, although the absolute risk is very low.[211–213] PJP has been described in IBD patients receiving corticosteroids, immunomodulators, biologics and CNI, although a systematic review showed that 76% of patients who developed PJP were receiving corticosteroids at the time of

diagnosis.[214] The ECCO Guidelines on infections in patients with IBD recommend that standard prophylaxis with trimethoprim-sulfamethoxazole should be strongly considered in patients receiving triple immunosuppressive therapy, and may be considered in patients on double immunosuppression, especially if one of the drugs is a CNI.[215] In addition, it may also be considered for any combination of high-dose corticosteroids, low lymphocyte count, or JAK inhibitors.[215]

9 | MONITORING DISEASE DURING ADMISSION AND THERAPEUTIC DECISIONS

Recommendations:

1. A PUCAI > 45 on the 3rd day of IVCS treatment should dictate planning for second-line therapy between Days 3–5 [EL2, adults EL2] (*100% agreement).
2. IVCS should be continued in children with a PUCAI of 35–65 on Day 5 with close daily monitoring for response; a decision on second-line therapy should be made in most cases within a total of 7–10 days of IVCS [EL2, adults EL2] (*100% agreement).

Practice points:

1. Management of ASC may be initiated in local paediatric centres. Transfer to referral paediatric IBD centres should take place as needed but certainly by Day 3 of IVCS in patients with a PUCAI > 45 (*100% agreement).
2. Recommended planning for second line therapy between Days 3–5 in nonresponders includes sigmoidoscopy (to detect severity of inflammation as well as ruling out the presence of granulomas and infectious colitis, most notably CMV), surgical consultation, exclusion of latent tuberculosis, infectious serology as indicated before biologic therapy, and/or blood tests required before treatment with CNI (e.g., creatinine, lipids and magnesium levels) (*100% agreement).
3. Frequent monitoring of laboratory tests (including complete blood count, CRP, ESR, albumin and electrolytes) is advisable as needed but at least at admission and on Days 3 and 5 thereafter (*100% agreement).
4. Transabdominal intestinal ultrasound assessment of the bowel wall thickness (BWT) may be performed on admission to help predict IVCS failure. Repeating the ultrasound 3–5 days later to assess the degree of improvement in BWT may also help predict IVCS response (*100% agreement).

A step-by-step monitoring algorithm is provided in Figure 2. Clinical guidelines for adults recommend that second-line therapy should be initiated if no response to IVCS is achieved within 3–10 days of admission as further corticosteroid treatment in nonresponders is associated with complications.[216] In adults, various prediction rules (Oxford, Lindgren), based on stool frequency and CRP were shown to be associated with IVCS failure and colectomy.[217] Other adult tools for predicting corticosteroid refractoriness included CRP, ESR, haemoglobin, albumin, transverse colon diameter on AXR, Ulcerative Colitis Endoscopy Index of Severity (UCEIS) score ≥ 7, and physician global assessment of severe endoscopic activity on admission.[218–222] CRP, albumin, and UCEIS on Day 3 were also found to predict IVCS refractoriness among adult patients.[220,223] Endoscopy during admission not only stages the severity of inflammation, but can also assess for infectious colitis, most notably CMV.

PUCAI score at Days 3 and 5 is the best validated predictive and decision-making tool in children.[224] In a retrospective study of 99 children with ASC, the PUCAI performed better than the adult indices to differentiate responders from nonresponders on Days 3 and 5 of IVCS treatment.[224] These findings were then validated in the prospective OSCI cohort study of 128 children with ASC.[94] A PUCAI > 45 on Day 3 predicted nonresponse to IVCS with a sensitivity of 92%, specificity of 50%, NPV of 94% and a PPV of 43%, indicating that complete response is anticipated in those with PUCAI ≤ 45. A PUCAI > 70 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 a PUCAI > 70. A cut-off score of >65 had a specificity of 96%, PPV 82%, sensitivity 49% and NPV 82%. Likewise, in a retrospective multicentre study of 153 adults, a PUCAI > 45 on Day 3 had a NPV of 83% and PPV of 54% for salvage therapy (anti-TNF, cyclosporine or colectomy), whereas a PUCAI > 65 on Day 5 had a PPV of 100% and NPV of 73%.[225] Although a small minority of children with a Day 5 PUCAI > 65 may eventually respond, delaying second-line therapy has the potential of increasing morbidity in ASC as shown both in children and adults.

The PUCAI performed better than four faecal markers (calprotectin, lactoferrin, M2-pyruvate kinase [M2-PK] and S100A12) in predicting IVCS failure in paediatric ASC, and faecal calprotectin had low area under the ROC curve reflecting limited sensitivity and specificity.[226] Although some studies, mainly among adult patients, showed significant association with baseline faecal calprotectin and IVCS outcomes, these studies did not report sensitivity, specificity and predictive values, which are important figures in utilizing predictors.[227,228] Indeed, one of the studies quoted a low AUROC of 0.65, similar to the paediatric OSCI prospective study.[229] Attempts to associate stool microbiome pattern at time of hospital admission in

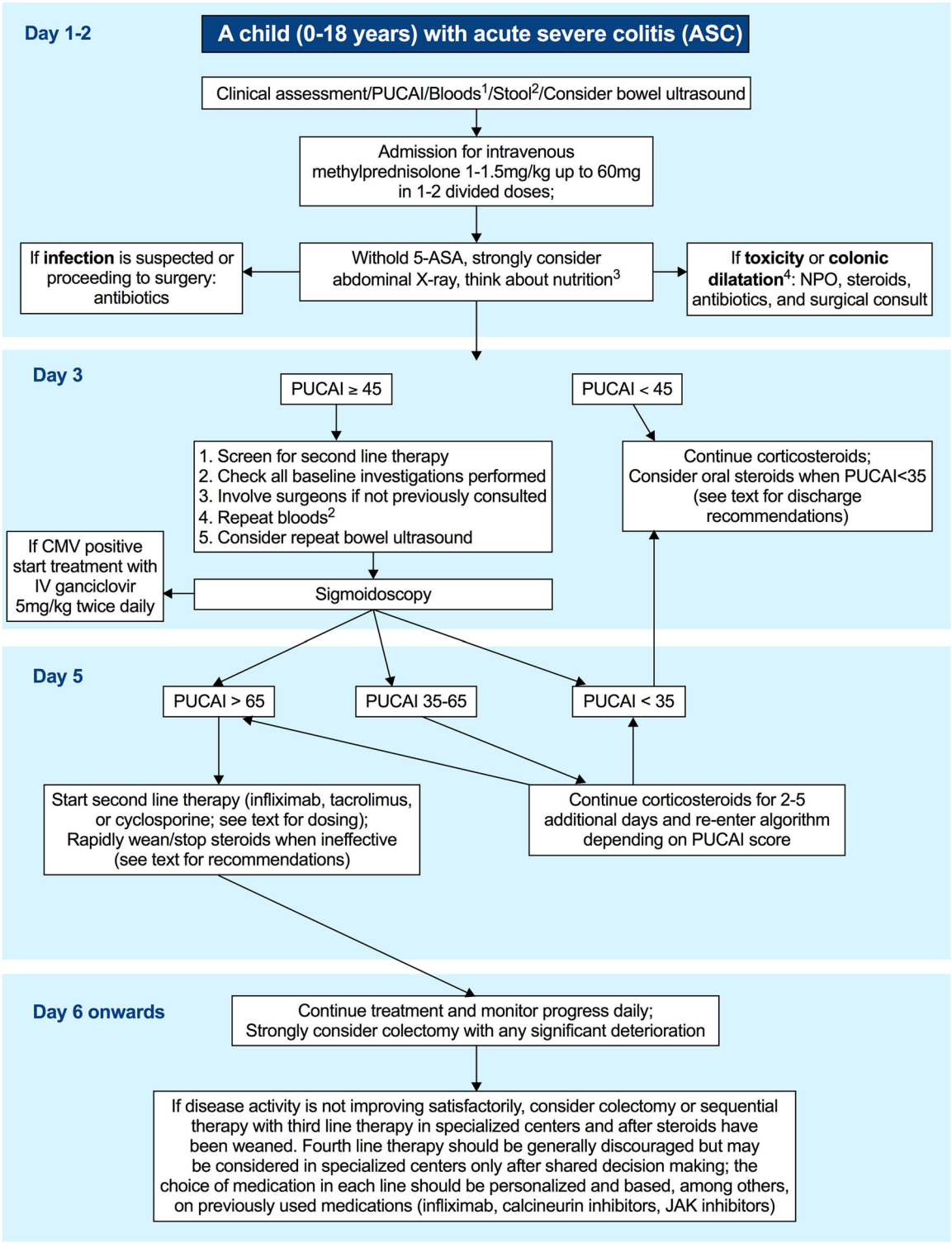

FIGURE 2 Monitoring and therapeutic management algorithm for children with ASC. Abbreviations: 5-ASA, 5-aminosalicylic acid; ASC, acute severe colitis; CMV, cytomegalovirus; JAK, Janus kinases; PUCAI, Paediatric Ulcerative Colitis Activity Index.

paediatric ASC patients with IVCS response yielded conflicting results.[9,230]

Livshits et al. reported that mucosal ulcerations on AXR performed on 56 children with ASC during the first 3 days of admission were significantly different between IVCS responders and nonresponders (mucosal ulcerations: 3% vs. 30%, $p = 0.006$). AXR mucosal tags (9% vs. 30%, $p = 0.073$) and megacolon (0% vs. 13%, $p = 0.064$) were only numerically different between groups.[231] Thickened bowel wall on bowel

ultrasound >3.4 mm ($p = 0.007$, OR: 88, 95% CI: 3.5–2227) and loss of bowel wall stratification ($p = 0.046$, OR: 15.3, 95% CI: 1.1–222) at admission has been found to predict IVCS failure in paediatric ASC.[232] Ilvemark et al. found that a decrease of >20% in BWT from admission to 24–72 h later predicted IVCS response (OR: 22.6, 95% CI: 4.2–201.2, $p = 0.001$) in adults with ASC.[233]

Hypoalbuminemia has also shown an association with IVCS nonresponse. The Canadian prospective paediatric ASC cohort demonstrated that baseline albumin <26 g/L had an aHR of 2.57 (95% CI: 1.6–4.1, $p < 0.001$) of needing to start infliximab due to corticosteroid nonresponse.[9] Generally, there is no need to correct hypoalbuminemia by albumin infusion unless the reduced oncotic pressure is associated with clinically significant complications (e.g., pulmonary oedema, pleural infusions or dyspnoea). Hypoalbuminemia is associated with a decreased infliximab TC and thus should dictate an increased infliximab dose when used. Nonetheless, there are no published data to suggest that infusing albumin before infliximab administration improves the therapeutic outcomes.

10 | PREOPERATIVE MANAGEMENT (FOR BOTH ELECTIVE AND URGENT COLECTOMY)

Recommendations:

1. Children with ASC not improving on first-line therapy (IVCS) should receive care from a highly specialized multidisciplinary team, which includes a colorectal surgeon [EL5, adults EL4] (*100% agreement).
2. In children with ASC, the possibility of no response and therefore the need for colectomy should be discussed early in the course of admission. The start of second-line therapy should trigger a consultation with the surgical team [EL5, adults EL4] (*96% agreement).
3. In a nonurgent setting, if time and clinical status allow, optimized enteral nutrition is advised preoperatively. There is evidence that adding nutritional supplementation including exclusive enteral nutrition may reduce peri-operative complications [EL5, adults EL2] (*100% agreement).
4. When iron-deficiency anaemia is present, correction of anaemia with either RBC transfusion in severe anaemia (<7–8 gr/dL, especially with significant bleeding or rapid Hb drop) or IV iron in milder anaemia, is recommended [EL4, adults EL1] (*100% agreement).
5. In children with ASC undergoing colectomy, VTE thromboprophylaxis with LMWH should be recommended to be continued postoperatively. Post-discharge thromboprophylaxis (for not more than 3–6 weeks from discharge) should be considered based on risk factors and in consultation with a haematologist [EL5, adults EL4] (*100% agreement).

Practice points:

1. In both elective and urgent scenarios, surgeons should be introduced to paediatric patients and families at an early stage, ideally not when surgery is imminent. This would ensure that patients and relatives are prepared for surgery (should that be necessary) and allow adequate time to discuss surgical options, reducing the anxiety and stress associated with a surgical procedure at a young age (*100% agreement).
2. In an elective setting, when colectomy is considered, a complete diagnostic workup is necessary, making sure to exclude CD. Preoperative assessment should include ileocolonoscopy, upper GI endoscopy and intestinal imaging. When doubts exist before surgery, performing a subtotal colectomy and waiting for the pathology of the specimen may be considered (*96% agreement).
3. Treatment with corticosteroids (prednisone >0.25 mg/kg per day or >20 mg/day) is associated with an increased risk of short-term surgical complications. Following a decision for surgery, the corticosteroids taper strategy should be individualized based on prior exposure and clinical status (100% agreement).
4. Delaying surgery to optimize nutrition and taper corticosteroids may be considered in stable patients with malnutrition. A diverting ileostomy should be considered in severely malnourished cases (*100% agreement).
5. Preoperative biologics (anti-TNF) use should not delay the decision to perform colectomy, when indicated. Patients on biologics may be at increased risk of developing early and late pouch-specific complications: three- or two-stage modified approaches with deferred pouch construction should be performed under these circumstances in both elective and urgent settings (*100% agreement).
6. It is currently unclear whether preoperative exposure to JAK-inhibitors is associated with increased rates of adverse postoperative outcomes notably thromboembolism (*100% agreement).
7. Multidisciplinary perioperative optimisation and management are pivotal to reduce adverse events and enhance postoperative recovery (*100% agreement).

When medical management is no longer sufficient to control disease activity or if complications occur (in cases of ASC indications include uncontrolled bleeding, TM, perforation, infections, thromboembolism; indications in cases of chronic refractory disease include dysplasia, complicated nutrition status and growth impairment), colectomy may be required.[61,234–237] In the nonurgent

setting, CD must be excluded before surgery, through a diagnostic workup including ileocolonoscopy, gastroscopy, and small bowel imaging, as clinical status allows. It must be noted that a change of diagnosis to CD may occur after colectomy even if a diagnosis of UC is certain, with increasing proportions with longer periods of follow-up.[238–241]

Perioperative management decisions can markedly influence surgical outcome.[242–245] Timely consideration of colectomy is recommended to avoid the perioperative complications associated with emergency procedures.[243,246–248] To facilitate judicious treatment escalation, children with ASC not improving on first-line therapy (IVCS) should receive care from a highly specialized multidisciplinary team which includes a colorectal surgeon. The possibility of no response and therefore the need for colectomy should be discussed at or before the start of second-line therapy.

Once the decision for surgery is made, the corticosteroids tapering regimen should be individualized based on prior corticosteroids exposure and the clinical status. Corticosteroids use (equal to or greater than 20 mg) preoperatively is associated with higher risk of both postoperative infectious and noninfectious complications.[234,249–251]

Preoperative biologics are not significantly associated with postoperative complications, but in any case, their use should not delay the decision to perform colectomy.[252,253] Specifically, anti-TNF exposure was not associated with postoperative infectious complications, but historical data are conflicting.[253,254] In the PUCCINI trial, a prospective cohort study of patients with UC and CD undergoing intra-abdominal surgery, preoperative exposure to anti-TNF was not associated with a higher risk of postoperative infections.[254] Data regarding postoperative complications with exposure to newer drugs in adults such as vedolizumab (including infections and ileus) are conflicting with more recent data showing no increase in postoperative complications.[243,255–260] Limited data on ustekinumab showed no difference in postoperative complications as compared with other second-line therapy.[251,261] Older cohort data[241,262] have suggested that patients on biologics might be at increased risk of developing early and late pouch-specific complications: three-stage or two-stage modified approaches with deferred pouch construction should be considered under these circumstances. Single-stage restorative proctocolectomy should be avoided in patients receiving biologics.

Delaying surgery to optimize nutrition and taper corticosteroids should be considered in patients with malnutrition in the nonurgent setting. A diverting ileostomy may be considered in severe cases.[263,264] Poor nutritional status affects the risk of postoperative infectious complications, irrespective of the use of biologics, and postoperative length of stay.[261,265]

An additional reduction of peri-operative risks can be achieved by enteral nutrition (if necessary, using nasogastric or nasoduodenal feeds), correcting malnutrition and avoiding the need for parenteral nutrition (and its associated risk of thrombosis). A wider approach to preoperative rehabilitation to address malnutrition and/or altered body composition through nutrition and exercise has been shown to improve surgical outcomes.[266–269]

In active disease and severe anaemia, IV iron supplementation is preferred.[268–271] In severely active colitis, judicious use of blood transfusions may be required when haemoglobin drops below 8 g/dL.[270,272,273]

When colectomy is considered in ASC, consultation with the surgeon should take place to determine whether, and during which interval, thromboprophylaxis should be temporarily discontinued. Post colectomy, thromboprophylaxis should be reintroduced until discharge. In selected cases, thromboprophylaxis may need to be extended beyond discharge in consultation with a haematologist. Paediatric literature is scarce, but adult colectomy literature suggests up to one-third of thrombotic events occur following discharge and are influenced by body mass index (BMI), preoperative corticosteroid use, albumin, sepsis, operation time, length of hospital stay, race, smoking status, IBD (as compared with malignancy as a reason for colectomy), return to the operating room and postoperative ileus.[99,103,274] In large (mostly adult) series, postoperative complications were the strongest risk factor for in-hospital and postdischarge VTE.[275]

11 | ELECTIVE AND URGENT SURGERY

Recommendations:

1. Subtotal colectomy with terminal ileostomy is recommended in children with ASC, on high dose or prolonged corticosteroids treatment, or severe malnutrition. Subsequent surgical options include completion of proctectomy and pouch formation with ileal pouch anal anastomosis either with (three-stage) or without (two-stage modified) a covering ileostomy (loop ileostomy). [EL4, adults EL3] (*100% agreement).
2. In elective settings, total proctocolectomy with ileal pouch formation and ileal pouch anal anastomosis (restorative proctocolectomy) is recommended in paediatric patients with medically refractory UC. This should ideally be performed with a covering ileostomy (loop-ileostomy, two-stage procedure). [EL3, adults EL3] (*100% agreement).
3. Minimally invasive surgery (laparoscopic approach) should be favoured over open surgery in paediatric patients with medically refractory UC (in both

elective and urgent settings), having been associated with a smoother postoperative course in the short and long term plus better cosmetic outcomes [EL3, adults EL2] (*100% agreement).

Practice points:

1. If colectomy is indicated in medically refractory patients with ASC, it should be performed within 24–48 h. In such cases, evidence from adult cohorts recommends that reconstruction is performed after adequate time to ensure full recovery and that adhesions are easier to deal with. This has been historically set at 3–6 months, favouring longer waiting times. In the era of minimally invasive surgery, shorter waiting times (3 months) could be used, depending on patient conditions and choice (*100% agreement).
2. Similar outcomes have been reported for stapled versus hand-sewn ileal pouch anal anastomosis. Regardless of the anastomotic technique, it is important that a true pouch-anal anastomosis is performed, avoiding pouch-rectal anastomosis (*100% agreement).
3. Postponing pouch surgery after subtotal colectomy until after puberty has not been associated with improved long-term outcomes or reduced revisional surgery but might reduce the rate of reclassification to CD. Topical treatment, preferably based on proctoscopy, when indicated, may be required to maintain the rectal stump in remission (*100% agreement).
4. An ileorectal anastomosis (IRA) may be offered to select female patients who are concerned about fertility, on condition that adequate information is provided concerning the need of long-term cancer surveillance and the potential risk of disease recurrence, which might require medical treatment or further surgery (*100% agreement).
5. Pouch surgery in children with UC should be performed in high-volume centres (≥10 IPAAs per year) by paediatric or adult surgeons with expertise in pouch surgery, where multidisciplinary teams are available (*100% agreement).

Despite advances in medical therapy, up to 15% of patients with UC will require a colectomy within 10 years after diagnosis.[276] Within the paediatric setting, a single centre retrospective study of 217 paediatric patients demonstrated that 13% required colectomy even within the era of advanced therapy, with a median follow-up of 5 years.[277] In paediatric patients, there are typically two clinical scenarios that culminate in colectomy. The first is the outcome of medically refractory ASC. This may be an emergent consequence of a catastrophic event, such as TM, perforation or massive haematochezia. More commonly, colectomy in ASC is the semielective endpoint of a lack of adequate response to salvage therapies. Indeed, after several days without significant improvement, surgical intervention should be strongly considered to prevent perioperative complications more significantly associated with emergency procedures and prolonged corticosteroids use. Second, a colectomy may be the outcome of medically refractory or corticosteroids dependent disease in the ambulatory setting. In adults with UC, colectomy may be undertaken to manage dysplasia, especially if multifocal or high grade, although this is extremely uncommon in children.[278]

Colectomy can be a daunting prospect for patients and families alike. In addition to concerns regarding surgical risk, there may be concerns about temporary or permanent ostomy formation and impact on quality of life, fecundity or body image. The prospect of future surgeries, if a restorative proctocolectomy with ileal pouch with anal anastomosis (IPAA) is to be considered, is also potentially daunting. Therefore, young people and their families should meet surgeons and stoma nurses early in their journey. In the case of medically refractory disease in the outpatient setting, this may be considered when second- or third-line advanced therapy is being suggested. In patients with ASC, surgical referral should be considered when refractoriness to IVCS is apparent, with view to consult taking place early during the course of hospital stay. It is ideal, if possible, for patients to be given the opportunity to meet others who have lived with a stoma. Patients and families can be reassured that quality-of-life (QoL) outcomes with both IPAA and ileostomy are good, often better than life with chronic refractory colitis.[279]

When possible, colectomy should be undertaken in a high-volume centre; patients who undergo colectomy in centres who undertake 10 or more procedures per year have fewer postoperative complications than patients who undergo the procedure at low volume centres (adjusted OR: 0.7; 95% CI: 0.5–0.9).[280,281] Data from 129 children in centres affiliated with the Porto group showed that performing IPAA in centres with at least 10 annual procedures is associated with better pouch outcomes than in smaller centres.[282] A laparoscopic approach to colectomy is recommended, when a surgeon with necessary expertise is available. Within the adult UC population, the evidence for this is strong, with meta-analysis data demonstrating shorter recover times, improved cosmesis and improved QoL outcomes.[283,284] There is also an association between laparoscopic approach and improved fecundity in female patients, with a shorter time to conception when pregnancy is desirable.[285] Within the paediatric setting, a laparoscopic approach is often also feasible, with a low conversion rate to open surgery noted[286] and superior cosmetic outcome. However, reports of peri- and postoperative complications have been variable.

One cohort described these as comparable to open surgery,[286] whereas a national referral centre reported lower complication rates in 38 patients undergoing laparoscopic compared with open procedures (42.1% vs. 75%).[287]

It is anticipated that most, but not all, patients who undergo a colectomy for either ASC or medically refractory UC will eventually want to consider regaining continuity. This is typically achieved by formation of ileoanal pouch with anal anastomosis, by means of a J pouch (forming a reservoir), and is associated with lower failure rates (8% vs. 15%) and lower rates of perianal sepsis (10% vs. 20%) than direct ileo-anal anastomosis.[288] It is generally accepted that one-step surgery of colectomy and IPAA creation should be avoided, due to worse surgical outcomes in many cohorts, including an increased risk of anastomotic leak (17% vs. 0%, $p = 0.002$ in a single centre paediatric study).[289,290] This is particularly important in the emergency setting, or with prolonged corticosteroids use, nutritional depletion and potentially a prolonged catabolic period. The second surgery should be delayed (typically for 3–6 months) until initial healing is in progress and following the reversal of the above factors, which may predispose to adverse outcomes. Traditionally, a three-stage approach was adopted to undertake a subtotal colectomy and IPAA formation, an approach still widely accepted for unwell patients (mostly with ASC). This approach should also be preferred when a diagnostic doubt exists about CD. The first stage entails a subtotal colectomy with end ileostomy, the second, the restorative proctectomy with ileal pouch formation and IPAA plus loop ileostomy, and the third, the closure of the covering ileostomy. The theoretical advantage of a three-stage procedure is a lower complication rate, as the IPAA is delayed, giving the inflammation time to decrease, and the patient time to recover before and after the IPAA creation. In the adult population, there are emerging data to support the use of a modified two-step approach, whereby proctectomy and IPAA formation take place in a single second surgery without loop ileostomy formation. The advantage of a two-stage procedure is fewer procedures and a supposedly shorter time with a stoma. A meta-analysis with 10 observational studies, which included 1727 patients (38% of whom underwent modified two-stage approaches), showed that among paediatric patients (4 studies, 146 patients), modified two-stage approaches had higher rates of anastomotic leakage than three-stage approaches ($p = 0.03$).[291] In children undergoing colectomy in the elective or ambulatory setting, a restorative proctocolectomy and IPAA with a covering ileostomy can be performed, with the covering ileostomy subsequently reversed, typically within 6–12 weeks. The creation of the loop ileostomy should protect the newly formed IPAA from complications, reducing the risk of infectious complications and anastomotic leak.[243] Even in the ambulatory setting, the three-stage approach may be indicated in children with significant corticosteroids exposure or a high PUCAI (>45), or in those on high-dose preoperative corticosteroids (prednisone ≥ 0.20 mg/kg/day).

Regarding the anastomotic configuration, similar outcomes have been reported for stapled versus hand-sewn IPAA. Stapled IPAA is being more widely adopted globally because of its simplicity and the advantage of preserving the anal transition zone, associated with better pouch function. In a nonpaediatric specific meta-analysis, hand-sewn IPAA with mucosectomy was compared with stapled IPAA. Stapled IPAA carried a lower risk of stricture, small bowel obstruction, pouch failure and achieved better functional outcomes with less use of pads and less nocturnal incontinence.[292] When fashioning the IPAA, special attention should be paid to the transection point of the rectum, being of outmost importance that a truly ileoanal anastomosis is performed. A long rectal cuff (>2 cm) predisposes to kinking and obstruction and can be avoided by checking the position of the stapler by digital rectal examination before the stapler is fired.[293] A long rectal cuff may also confer a future malignancy risk.[278] Incontinence is another common long-term complication of IPAA in children with an overall incidence of 20% (95% CI: 14%–28%) at a median follow-up (range) of 67 (3–182) months.[294]

Postponing pouch surgery until after puberty seems to have no significant effect on the rate of complications or long-term outcome after IPAA in paediatric patients.[282] The three-stage IPAA has been used to reduce the rates of change of diagnosis from UC to CD in children with IBDU. However, even if this might be a prudent strategy, colectomy specimen histology or preoperative diagnosis of IBD unclassified have been reported to poorly predict the long-term outcomes of IPAA in adults with UC.[295,296]

With regard to fertility concerns, colectomy is associated with reduced fertility in women, with the highest risk associated with proctectomy and IPAA formation.[297] A meta-analysis from 2011 reported an increase of average infertility rates from 20% pre-IPAA to 63% post-IPAA. The relative risk of infertility after IPAA was 3.91 (95% CI: 2.06–7.44).[298] Limited evidence suggests that this risk is reduced when IPAA is performed laparoscopically.[299] In selected cases, particularly in the elective setting, IRA may be considered as an option to preserve fertility but this decision needs to be balanced by some of the challenges of IRA, including risk of retained rectal inflammation and need for future surveillance, as well as the associated increased stool frequency, itself known to be associated with adverse QoL outcomes in children.[300] Patients should also be made aware of and accept the risk of a potential repeated major surgery to remove the rectum.

12 | POUCH RECOMMENDATIONS INCLUDING POUCHITIS AND CUFFITIS

Recommendations:

1. Pouchoscopy with mucosal biopsies is recommended in patients after proctocolectomy and IPAA with symptoms suggestive of pouchitis [E4, adults EL2] (*100% agreement).
2. A 14-day course of ciprofloxacin or metronidazole is recommended as first-line therapy for acute pouchitis [E4, adults EL2] (*100% agreement).
3. Combined ciprofloxacin with metronidazole or oral/topical budesonide can be used for recurrent or persistent pouchitis [E4, adults EL4] (*100% agreement).
4. Anti-TNF-α therapies are recommended as first-line biologic agents for Crohn's-like disease of the pouch. Current evidence supports vedolizumab as the most effective biologic agent for chronic antibiotic-refractory pouchitis, but anti-TNFs may be also effective [E4, adults EL1] (*96% agreement).
5. Topical mesalamine is recommended for induction and maintenance treatment of cuffitis following pouch surgery [E4, adults EL4] (*100% agreement).
6. The common antibiotic dosing strategies for pouchitis are ciprofloxacin (30 mg/kg/day up to 1 g/day in two divided doses) and/or metronidazole (20–30 mg/kg/day in three divided doses up to 1.5 g/day) for 14 days. Budesonide may be administered either orally (9 mg once daily for 8 weeks) or topically (enema of 2 mg/100 mL at bedtime for 4 weeks) (*100% agreement).
7. Rotation of antimicrobials should be considered for patients with chronic antibiotic-dependent pouchitis, to reduce the potential for developing resistance (*100% agreement).
8. Biologic therapy should be considered for inducing and maintaining remission in chronic antibiotic-refractory or dependent pouchitis, although paediatric data are limited. Precolectomy biologic failure does not preclude their use for pouchitis (*100% agreement).
9. The rectal 'cuff' refers to residual rectal tissue in patients following continuity surgery, whereas the term rectal 'stump' refers to the oversewn rectal remnant formed following subtotal colectomy. Rectal 5-ASA suppositories (up to 1 g/day) may be used as first-line treatment of symptomatic inflammation of the cuff or stump (*100% agreement).

Practice points:

1. A diagnosis of pouchitis is based on a combination of clinical, endoscopic and histologic findings (*100% agreement).
2. Pouchitis encompasses a disease spectrum. It may be described as *acute pouchitis* (responsive to antibiotics within 2 weeks; <4 episodes/year), *chronic pouchitis* (>4 weeks of symptoms despite treatment), *chronic antibiotic-dependent pouchitis* (≥4 acute episodes per year, or persistent symptoms, which require long-term antibiotic therapy to maintain remission), and *chronic antibiotic-refractory pouchitis* (inadequate response to 4 weeks of antibiotics; requiring ≥4 weeks of an alternative antimicrobial and/or anti-inflammatory, corticosteroids or immunomodulator therapy to induce remission) (*100% agreement).
3. Alternative diagnoses should be considered in patients with recurrent, refractory or chronic pouchitis, including infectious, mechanical, functional and inflammatory conditions (*100% agreement).
4. A diagnosis of CD of the pouch (CDP) requires a combination of clinical, laboratory, endoscopic, histologic and radiological evaluations. It may be classified as inflammatory, fibrostenotic or penetrating phenotypes (*100% agreement).
5. Faecal calprotectin may be used to assess pouch inflammation, to minimize repeated pouchoscopy in recurrent pouchitis, and to monitor response to treatment, even though a validated cut-off is absent (*100% agreement).

Pouchitis is the most common complication following IPAA. Its diagnosis relies upon a combination of clinical, endoscopic and histological findings.[301] Pouchitis may be classified as acute or chronic pouchitis, with chronic pouchitis further categorized as chronic antibiotic-dependent pouchitis or chronic antibiotic-refractory pouchitis.[302]

Symptoms include increased stool frequency, urgency, tenesmus, incontinence, abdominal pain and rectal bleeding. Pouchitis rates of 33%–86% are described in retrospective paediatric studies.[282,303–310] Almost half of patients with pouchitis eventually develop chronic pouchitis, being more likely following early pouchitis.[306–309] The median time to the first episode of pouchitis in a retrospective Porto Group study was 8.4 months (IQR: 3.2–21)—43% occurring within 6 months, 60% by 1 year, 79% by 2 years and 90% by 4 years.[282]

Putative risk factors for pouchitis in children include higher PUCAI score at UC diagnosis, moderate-to-severe appendiceal inflammation of the surgical specimen, backwash ileitis, precolectomy neutrophilia, vitamin D deficiency post-IPAA, extra-intestinal manifestations, precolectomy anti-TNF exposure, high cumulative corticosteroids dose and low-volume surgical IPAA caseload.[282,305,308,309,311–313] Older age at colectomy and early BMI improvement had lower pouchitis risk.[303,306] The development of pouchitis is associated with an increased hospitalization rate.[304]

Endoscopic and histological evaluation of the pouch should be performed at the first episode of pouchitis

and periodically thereafter. Endoscopic features of pouchitis include oedema, hyperaemia, diminished vascular pattern, friability, erosions, ulceration and fistulae. The 'Chicago classification' of pouch findings in adults proposes seven endoscopic phenotypes, based on location and distribution of findings.[314] Macroscopic findings may be focal or diffuse, and involve any part of the pouch, its limbs or the rectal cuff. Robust validated pouch activity indices are lacking, but a standardized reporting of descriptors has been proposed in the interim, including location, length and surface area involvement of findings.[315–317]

Two mucosal biopsies should be taken from the pouch body, pouch limbs and rectal cuff, but not from the staple line, as erosions and/or ulcers along the staple line do not necessarily indicate pouchitis.[316,318] The histological spectrum of pouchitis includes mucosal atrophy, crypt hyperplasia, infiltrates of mononuclear cells and eosinophils in the lamina propria, crypt abscesses, erosions and ulceration. Pouchitis is not defined by histopathological abnormalities alone—they poorly correlate with symptoms and were found in 53% of adults with normal pouchoscopy.[319]

CD of the pouch (CDP) is a distinct entity from pouchitis, and may be classified into inflammatory, fibrostenotic or penetrating phenotypes.[301] Low preoperative BMI was associated with developing de novo CDP, occurring in 17% of 111 children with IPAA, after a median follow-up time of 25 months.[320] Cross-sectional imaging is advised to identify potential surgical mimics of CDP.[321] Mild or short-segment terminal ileitis, or 'prepouch ileitis,' in children does not necessarily imply CDP.[322] Other mimics of pouchitis include infection (e.g., CMV), anastomotic ulceration, stenosis, pouch dysfunction and irritable pouch syndrome, and should be considered during evaluation.

The first-line treatment for acute pouchitis is a 14-day course of antibiotic monotherapy. Without high-quality head-to-head studies, systematic reviews and network meta-analyses of low certainty adult evidence favour metronidazole and ciprofloxacin over placebo, with slightly higher remission with ciprofloxacin than metronidazole (relative risk [RR]: 2.68, 95% CI: 1.13–6.35).[323–325] A combination of ciprofloxacin with metronidazole or oral/topical budesonide can be used for recurrent acute pouchitis.[301]

Chronic pouchitis requires treatment to both induce and maintain remission. Prolonged courses (>4 weeks) of combination antibiotics or biologics effectively induced remission in 74% (95% CI: 56%–93%) and 53% (95% CI: 30%–76%), respectively in adult studies including both chronic antibiotic-dependent pouchitis and chronic antibiotic-resistant pouchitis.[326,327] Rotation of antimicrobials should be considered to reduce the potential for developing resistance. Low quality case-series data reported 15/20 patients in remission at 8 weeks with budesonide.[328]

Vedolizumab was more effective than placebo at inducing remission by Weeks 14 (31% vs. 10%) and 34 (35% vs. 18%) in adults with chronic antibiotic-resistant pouchitis in the EARNEST RCT, irrespective of concomitant antibiotic use.[329] Previous studies totalling 44 patients reported clinical (75%) and endoscopic improvement (73%) following vedolizumab therapy.[330] Paediatric data are limited, but anti-TNF therapy in adults has shown pooled clinical remission rates of 51%–66% and 31%–33% for infliximab and adalimumab respectively.[331,332] Anti-TNF-induced remission was higher in CDP (0.64, 95% CI: 0.5–0.77) than chronic antibiotic-resistant pouchitis (0.10, 95% CI: 0.00–0.35) on meta-analysis, but high-quality studies are lacking.[327] Probiotics are not discussed in these guidelines due to limited and conflicting evidence and have been reviewed elsewhere.

Residual rectal tissue remains following subtotal colectomy. The 'rectal stump' is the oversewn rectal remnant which may cause intermittent symptoms, but more informative data are lacking. In cases in which IPAA is not eventually performed and the rectal stump develops chronic inflammation, topical therapy with 5-ASA or corticosteroids is usually indicated.[333] The 'rectal cuff' refers to the very short rectal segment (typically <3 cm) between the dentate line and pouch. Rectal cuff inflammation, 'cuffitis', may mimic pouchitis symptoms, causing urgency, tenesmus, bleeding and negatively impact quality of life. It was reported in 12% of 129 children in a retrospective study of IPAA outcomes.[282] Treatment of the rectal stump or cuff inflammation should follow UC guidelines, beginning with first-line topical mesalamine (up to 1 g/day), while refractory inflammation may need escalation to systemic therapies.[301,334–336]

During follow-up, faecal calprotectin may be used to monitor treatment response or to assess for recurrent pouchitis, minimising pouchoscopy. Calprotectin levels exceeding thresholds ranging from 40 to 460 μg/g in adult studies have shown sensitivities and specificities for significant endoscopic disease ranging from 57% to 92% and 19% to 83% respectively, although lower levels do not preclude pouchitis.[337] Cuffitis may also cause elevated calprotectin levels.

13 | DISCHARGE RECOMMENDATIONS

Recommendations:

1. Children should not be discharged from hospital unless their disease is at least mild (i.e., PUCAI < 35) under stable therapy, but preferably closer to remission (PUCAI < 10) [E2, adults EL2] (*96% agreement).
2. Following a first episode of ASC, maintenance treatment with a thiopurine in combination with

5-ASA is recommended in children who responded to IVCS. Less commonly, exclusive 5-ASA maintenance treatment could be considered based on the patient's individual characteristics at presentation, and response to corticosteroid treatment [E2, adults EL2] (*100% agreement).
3. Children responding to infliximab or JAK inhibitors commenced during ASC should continue these drugs as a maintenance treatment postdischarge [E2, adults EL2] (*100% agreement).

Practice points:

1. The following should be ensured before discharge: stable vital parameters, adequate oral nutrition, tolerance of oral medications, stable haemoglobin, an improving trend in inflammatory markers and albumin, and discontinuation of pain-control medications at least 24 h before discharge. In children who have required a colectomy, a stable stoma output <20 mL/kg/day, appropriate stoma care and a healthy stoma site upon assessment by the paediatric surgeon and/or the paediatric stoma nurse are also essential (*100% agreement).
2. Before discharge, when switching IV methylprednisolone to oral prednisone, it should be considered that 1 mg of methylprednisolone is equivalent to 1.25 mg of prednisone (i.e., 40 mg is equivalent to 50 mg, respectively) (*100% agreement).
3. Thiopurines should be introduced once the patient is responding to corticosteroids, as it can take up to 10–14 weeks to reach full therapeutic effect (*100% agreement).
4. If cyclosporine or tacrolimus is commenced during ASC treatment, this should be weaned within the following 4–6 months as a bridge to thiopurine or other maintenance medication, to minimize adverse drug events (*100% agreement).
5. Children should be reviewed clinically within 2–3 weeks of discharge post-ASC. The frequency of future follow-up appointments will depend on the maintenance treatments in place and on the disease behaviour (*100% agreement)

The timing of discharge and the tight postdischarge monitoring following an episode of ASC are crucial to avoid early recurrence. Previous studies have elucidated the importance of achieving clinical remission (PUCAI < 10) at Week 4 and at Week 8 from the time of admission for ASC, with regard to achieving corticosteroid-free remission at 1 year and the risk of further treatment escalations or colectomy.[338–341]

The rate of hospital readmission postdischarge is a measure of the patient's health outcome. A retrospective analysis identified about one in seven hospitalizations of patients with IBD leading to a 30-day readmission. The use of corticosteroids and the presence of chronic pain were significantly associated with readmission within 90 days. Younger age and a short length of hospital stay were additional predisposing factors identified in patients who had five or more readmissions.[342] A systematic search of 17 cohort studies with meta-analysis identified IBD flare, infection, or complications from unplanned surgeries during hospitalizations as the most common reasons for readmission. Consistent risk factors for 30-day readmission were admission for pain control, need for TPN on discharge, and prior or unplanned surgery during admission.[343]

In adult patients, VTE is one of the serious complications of a severe IBD flare. A study based on a national IBD registry identified prior VTE, longer length of hospital stay, comorbidities, having a flexible sigmoidoscopy or colonoscopy at index admission, CDI at index admission and age older than 18 years as risk factors associated with readmission to the hospital for VTE. Most readmissions with VTE occurred within 60 days of discharge.[344] Paediatric data on post discharge VTE is lacking.

In IVCS responders, IV therapy should be switched to oral prednisone at least 48 h before discharge to allow adequate monitoring of response. Oral corticosteroids should be weaned following discharge, according to the tapering algorithm illustrated in the ambulatory chapter, to limit corticosteroids exposure to the minimum necessary. Thiopurines have been shown to be effective in maintaining remission post IVCS. Evidence suggests that a combination of a thiopurine with 5-ASA is associated with more favourable medium-longer term outcomes compared to 5-ASA alone.[345,346] This has guided our recommendation favouring the combination of a thiopurine and 5-ASA for maintenance treatment following an episode of ASC, over 5-ASA monotherapy. The latter may be considered for patients who responded to IVCS within Day 3 and achieved clinical remission before discharge. CNI should be used only as a bridge to thiopurines or biologics for several months to avoid toxicity.[347] If cyclosporine or tacrolimus are commenced during ASC treatment, they should be weaned once the patient has achieved remission when they can be replaced with a thiopurine or alternative maintenance treatments, to minimize adverse drug events. Maintenance with vedolizumab post induction with CNI could be considered in those who failed thiopurines before the admission.[348]

PJP prophylaxis is recommended after discharge as-long-as the patient is on triple immunosuppression with one of these being either a CNI or anti-TNF therapy, and may be considered in patients on double immunosuppression, especially if one of the drugs is a CNI or a JAK inhibitor.[349–352]

Oral iron supplements should be commenced after discharge or a recommendation for IV iron treatment should be made in cases of anaemia in accordance with the recommendations in the ambulatory chapter.

Colectomy during the first year after ASC episode is not a rare event, highlighting the importance of close follow-up in this sub-group of patients. A paediatric multicentre study ($N = 141$) described colectomy free rates of 71%, 66% and 64% at 1, 3 and 5 years after initial ASC admission, respectively, with similar rates across different age groups. In a multivariate analysis, the use of oral corticosteroids in the 3 months before admission, ESR > 70 mm/h, and albumin <2.5 g/dL, were significantly associated with a 5-year colectomy risk.[11]

QoL should be also addressed by a multidisciplinary team following discharge. A study by Alrubaly et al. assessed the long-term QoL of patients with ASC enroled in the CONSTRUCT trial following treatment of UC with infliximab or cyclosporine. Disease-specific scores showed a sharp improvement up to 2 years, with a gradual reduction in QoL up to 84 months. The study did not identify any significant difference between treatments with infliximab and cyclosporine, in any of the QoL scores.[353]

14 | CONCLUSIONS

Based on systematic review of the literature and a consensus process, we included 36 recommendations and 72 practice points. Given the scarcity of paediatric data we extrapolated from adult data where appropriate and, in rare cases, based our practical statements on common practice and expert's opinion. Some of the statements differ from adult guidelines reflecting the unique considerations that exist in children.

The monitoring and therapeutic recommendations are summarized in the algorithm which should be used in conjunction with the supporting text (Figure 2). We are aware that in some regions and particularly in low-resource countries, some of the recommendations are either not available or not feasible to perform but our aim was to set a high standard to which all practitioners should aspire. We also expect that changes in practice, including the approval of new medications, will evolve more rapidly in the upcoming years, thus, practitioners will have to adapt and adjust their practice accordingly. Nevertheless, the presented recommendations serve as an updated, practical framework for the management of ASC in children.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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