Original research

Adaptations to the current ECCO/ESPGHAN guidelines on the management of paediatric acute severe colitis in the context of the COVID-19 pandemic: a RAND appropriateness panel

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ABSTRACT

Objective Paediatric acute severe colitis (ASC) management during the novel SARS-CoV-2/COVID-19 pandemic is challenging due to reliance on immunosuppression and the potential for surgery. We aimed to provide COVID-19-specific guidance using the European Crohn’s and Colitis Organisation/European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines for comparison.

Design We convened a RAND appropriateness panel comprising 14 paediatric gastroenterologists and paediatric experts in surgery, rheumatology, respiratory and infectious diseases. Panellists rated the appropriateness of interventions for ASC in the context of the COVID-19 pandemic. Results were discussed at a moderated meeting prior to a second survey.

Results Panellists recommended patients with ASC have a SARS-CoV-2 swab and expedited biological screening on admission and should be isolated. A positive swab should trigger discussion with a COVID-19 specialist. Sigmoidoscopy was recommended prior to escalation to second-line therapy or colectomy. Methylprednisolone was considered appropriate first-line management in all, including those with symptomatic COVID-19. Thromboprophylaxis was also recommended in all. In patients requiring second-line therapy, infliximab was considered appropriate irrespective of SARS-CoV-2 status. Delaying colectomy due to SARS-CoV-2 infection was considered inappropriate. Corticosteroid tapering over 8–10 weeks was deemed appropriate for all. After successful corticosteroid rescue, thiopurine maintenance was rated appropriate in patients with negative SARS-CoV-2 swab and asymptomatic patients with positive swab but uncertain in symptomatic COVID-19.

Conclusion Our COVID-19-specific adaptations to paediatric ASC guidelines using a RAND panel generally support existing recommendations, particularly the use of corticosteroids and escalation to infliximab, irrespective of SARS-CoV-2 status. Consideration of routine prophylactic anticoagulation was recommended.

Significance of this study

What is already known on this subject?
► Paediatric acute severe colitis management has been standardised by evidence-based guidelines from European Crohn’s and Colitis Organisation and European Society for Paediatric Gastroenterology, Hepatology and Nutrition.
► The management of acute severe UC during the COVID-19 pandemic in adults has been supported by specific new guidance generated through RAND panel methodology based on the British Society of Gastroenterology IBD guidelines.
► The management of acute severe colitis relies heavily on immunosuppressive therapy, posing specific concerns during the current COVID-19 pandemic.

What are the new findings?
► This RAND panel process has supported existing practice in the context of paediatric acute severe colitis, particularly the use of intravenous corticosteroids and second-line infliximab.
► Delaying colectomy was considered inappropriate in those who require this, irrespective of COVID-19 status.
► The RAND panel considered anticoagulation appropriate in all paediatric patients admitted with acute severe colitis, irrespective of COVID-19 status.

INTRODUCTION

All aspects of healthcare have been impacted in recent months by the novel SARS-CoV-2 pandemic, with rapid and fundamental shifts occurring in clinical services as a result. While infection has been seen to cause variable phenotypes of clinical disease,
How might it impact on clinical practice in the foreseeable future?

- This process enabled rapid review of existing guidance with specific reference to the risk:benefit of established acute severe colitis management in the context of an emerging pandemic.
- Our recommendations have the potential to increase clinician confidence and may be of considerable benefit as new challenges occur during the continued pandemic.

Significance of this study

Significant variations were proposed in the recently published adaptation of management in adult ASUC in the context of COVID-19. We therefore convened a RAND appropriateness panel to provide clarity on the management of ASC in children and adolescents, as defined by PUCAl, in the context of the COVID-19 pandemic. RAND appropriateness methodology is a widely used, iterative, evidence-based process that combines the best available evidence with expert opinion. It is ideally suited to providing greater clarity in circumstances where genuine uncertainty and clinical equipoise exist.

METHODS

Study overview

RAND/University of California, Los Angeles methodology was used to assess the appropriateness of following the standard ECCO/ESPGHAN guidelines for the management of ASC during the COVID-19 pandemic. It follows a modified Delphi panel approach which combines expert opinion with the best evidence to determine the appropriateness of interventions in specific clinical scenarios. We assembled a 14-person panel of British Society of Paediatric Gastroenterology, Hepatology and Nutrition IBD experts comprising consultants from the IBD working group and medium-sized to large-sized paediatric gastroenterology departments across the UK to ensure a geographically balanced representation (online supplementary table 1). The chosen number of panellists was based on RAND recommendations stating that panels should ideally include no more than 15 participants.

An online survey was created, iteratively improved and subsequently sent to all panellists to complete before the moderated online meeting. Panellists were provided with the current ECCO/ESPGHAN guidelines on the management of ASC as well as a list of relevant publications on COVID-19 in general and specifically in relation to paediatric IBD (PIBD) ahead of the meeting. Of particular relevance to paediatric COVID-19 infection were articles relating to the paediatric inflammatory multisystem syndrome—temporarily associated with SARS-CoV-2 (PIMS-TS). Some of the scenarios and interventions considered were not part of current guidelines but were proposed to aid comparison to the adult RAND panel (eg, timing of sigmoidoscopy) or proposed based on evidence from the literature review, to assess the appropriateness of immunosuppressant-sparing intervention (metronidazole, amoxicillin, doxycycline, vancomycin (MADoV also known as the Jerusalem cocktail) and use of thromboprophylaxis which may be of particular relevance during the pandemic.

Panellists rated the appropriateness of specific interventions at various time points during a patient’s admission with ASC (admission, first-line therapy, rescue therapy, continued medical therapy on discharge and surgery) in the context of their SARS-CoV-2 swab status and the presence or absence of symptoms or signs of COVID-19 infection. The appropriateness of each intervention was graded on a scale of 1–9, where 1–3 is inappropriate, 4–6 is uncertain and 7–9 is appropriate. The anonymised results were presented at a virtual meeting in June 2020. This enabled the moderators to ensure a common understanding of the questions and also enabled focused discussion on areas of disagreement, without trying to force consensus. Also present at the meeting were non-voting specialists who provided expert opinion with regard to IBD surgery (MS), rheumatology (VS), respiratory medicine (PD) and infectious diseases (CD). In practice, several specialists may provide expert opinion on COVID-19 management, including intensivists, respiratory
physicians and infectious disease physicians. We used the encompassing term ‘COVID-19 specialist’ to represent this group. The moderators (MS, PMJ) are experts in the management of IBD and RAND panel methodology but neither gave opinions during the meeting nor took part in either survey. Following the panel meeting, minor adjustments were made to the initial questionnaire and a second online survey of 113 questions was re-distributed for completion.

A number of assumptions were made to add clarity to the clinical scenarios. Patients were assumed to have a diagnosis of ASC, as defined by a PUCAI ≥65, with GI infection having been excluded. It was assumed patients had received optimised 5-aminosalicylic acid therapy prior to admission (except when admission was an index presentation). Where calcineurin inhibitors were proposed patients were assumed to be thiopurine-naïve. When discussing corticosteroid weaning or cessation, it was assumed that patients could discontinue corticosteroids without the risk of Addisonian crisis. Management decisions not discussed in the survey were presumed to be in line with ECCO/ESPGHAN guidance. Particular to rescue therapy, patients were assumed to have ongoing ASC despite 5 days of intravenous corticosteroid therapy and had reached standard criteria for rescue therapy. When discussing medical therapy after discharge, patients were assumed to have responded to intravenous corticosteroids, to have been successfully switched to oral prednisolone and were medically fit for discharge. Finally, when discussing corticosteroid therapy and had reached standard criteria for rescue therapy. It was the only first-line treatment deemed appropriate irrespective of SARS-CoV-2 status. It was considered inappropriate to delay colectomy, if required, in all patients. Expedited biological screening on admission was considered appropriate. In patients who had received broad-spectrum antibiotics (in the context of COVID-19), it was considered appropriate to repeat Closstrium difficile testing at day 5 if patients were failing first-line therapy. The appropriateness of referral to a COVID-19 specialist at various time points during admission was considered. In patients with a positive swab and no symptoms or signs of COVID-19 infection, this was deemed inappropriate if receiving first-line therapy but uncertain in patients requiring rescue therapy. It was however considered appropriate in all patients with a positive swab, irrespective of the presence of symptoms or signs of COVID-19 infection.

Analysis
Median scores were calculated for each clinical question. A score of <3.5 was considered inappropriate, ≥3.5 but<6.5 uncertain and ≥6.5 appropriate. We used the validated RAND disagreement index (DI) to define disagreement among panellists using the equation outlined below. A DI ≥1 denotes disagreement. Where disagreement was present for any scenario, the final outcome for that scenario was uncertain irrespective of the median score.

\[
DI = \frac{70\%ile - 30\%ile}{2.35 + (1.5 \times \text{abs}(5 - \frac{\text{median score}}{10}))}
\]

RESULTS
Overall results
All 14 panellists completed the prepanel and postpanel meeting questionnaires. Of the 113 clinical scenarios, panellists rated 30 as appropriate, 22 as uncertain and 61 as inappropriate. After the second round of voting, agreement was present for all scenarios (DI=1) except two, both relating to SARS-CoV-2-positive patients with symptoms or signs of infection; the use of ciclosporin with corticosteroids as rescue therapy and the use of prophylactic anticoagulation after discharge A detailed list of all scenarios, complete with median score, appropriateness rating and DI is shown in online supplementary table 2. The key findings are summarised in this chapter (overall results) and their relationship to current ECCO/ESPGHAN guidance is highlighted in figure 1.

Indications for investigations, inpatient isolation and specialist referral
It was rated appropriate that all patients admitted to hospital with ASC should have a SARS-CoV-2 swab performed on admission. If the result was negative it was felt appropriate to repeat the swab at the point of requiring rescue therapy and/or surgery. It was also considered appropriate to isolate all patients throughout their admission, irrespective of their SARS-CoV-2 status. It was considered inappropriate to expedite flexible sigmoidoscopy within 24 hours of admission from the current guideline recommendation of day 3. It was, however, considered appropriate that a flexible sigmoidoscopy should be performed prior to rescue therapy or colectomy had it not occurred already. Repeating this test during a single admission (eg, prior to rescue therapy and again prior to colectomy) was considered inappropriate (table 1).

The appropriateness of a routine chest X-ray in all patients admitted with ASC was rated as uncertain but this was considered appropriate as a preoperative investigation in all patients who require colectomy. It was deemed inappropriate to delay colectomy, if required, in all patients. Expedited biological screening on admission was considered appropriate. In patients who had received broad-spectrum antibiotics (in the context of COVID-19), it was considered appropriate to repeat Closstrium difficile testing at day 5 if patients were failing first-line therapy.

The appropriateness of referral to a COVID-19 specialist at various time points during admission was considered. In patients with a negative swab and no symptoms or signs of COVID-19 infection, this was deemed inappropriate if receiving first-line therapy but uncertain in patients requiring rescue therapy. It was however considered appropriate in all patients with a positive swab, irrespective of the presence of symptoms or signs of COVID-19 infection.

Initial treatment of ASC
As per ECCO/ESPGHAN guidance, inpatient intravenous methylprednisolone was rated appropriate as the initial management of patients presenting with ASC irrespective of SARS-CoV-2 infection or its sequelae. It was the only first-line treatment deemed appropriate; all other agents (infliximab, ciclosporin and tacrolimus) were deemed inappropriate irrespective of SARS-CoV-2 status. Outpatient treatment with intravenous methylprednisolone or inpatient treatment with poorly absorbed bioavailable steroids (budesonide matrix (MMX) or beclometasone) were also deemed inappropriate in all scenarios. The use of MADoV antibiotic combination (metronidazole, amoxicillin, doxycycline, vancomycin or equivalent) concurrently with corticosteroids was deemed inappropriate in SARS-CoV-2-negative patients but uncertain in patients with a positive swab. MADoV therapy alone was considered inappropriate in all scenarios. It was considered appropriate to prescribe prophylactic anticoagulation in all patients with ASC, irrespective of their SARS-CoV-2 status (table 2).

Rescue therapy
In patients with a PUCAI 35–65 at day 5 of first-line therapy it was deemed appropriate, irrespective of SARS-CoV-2 status, to continue intravenous corticosteroids for a further 2–5 days (as per ECCO/ESPGHAN guidelines). Expediting second-line therapy at this juncture was considered uncertain in all scenarios. Conversely, in patients with a PUCAI >65 it was considered inappropriate to continue monotherapy with intravenous corticosteroids, irrespective of SARS-CoV-2 status. Instead, the panellists deemed that following standard ECCO/ESPGHAN guidance by initiating infliximab and continuing corticosteroids was appropriate. ECCO/ESPGHAN guidelines also recommend ciclosporin or tacrolimus as alternatives to infliximab. Despite this,
COVID-19

Day 1-2
- Isolate
- Send SARS-CoV-2 swab
- Discuss all positive cases with a COVID-19 specialist
- Send serological screen for second-line therapy
- Prescribe prophylactic anti-coagulation

Routine chest X-ray required

If infection is suspected or proceeding surgery: antibiotics

A child (0-18 years) with acute severe colitis (ASC)
- Clinical assessment/bloods/stool/PUCAI
- Admission for intravenous methylprednisolone 1-1.5mg/kg up to 60mg in 1-2 divided doses
- MADoV
- MADoV alone

If toxicity or colonic dilatation: Nil per os, steroids, antibiotics and surgical consult

Day 3
- PUCAI >45
  - Screen for second-line therapy
  - Check all baseline investigations performed
  - Involve surgeons if not previously consulted
  - Repeat bloods

- PUCAI <45
  - Continue corticosteroids

Day 5
- PUCAI >65
  - Expedite second-line therapy
  - Continue intravenous methylprednisolone

- PUCAI 35-65
  - Start second-line therapy (infliximab, tacrolimus or ciclosporin or colectomy)

- PUCAI <35
  - Continue corticosteroids for 2-5 additional days and re-enter algorithm depending on PUCAI score

Day 6 onwards
- Continue treatment and monitor progress daily; strongly consider colectomy with any significant deterioration

The above guideline is adapted from the original ECCO/ESPGHAN guideline for the management of acute severe colitis

a. See ECCO/ESPGHAN guidelines for standard recommendations.
b. In all patients on admission: Isolate, send SARS-CoV-2 swab, start prophylactic anti-coagulation.
c. Routine chest X-ray in all patients was considered uncertain.
d. Start intravenous methylprednisolone irrespective of SARS-CoV-2 status.
e. MADoV: Metronidazole, amoxicillin, doxycycline and vancomycin. Considered inappropriate as monotherapy for first-line or rescue therapy, and alongside corticosteroids as first-line therapy in SARS-CoV-2 negative patients. Alongside immunosuppressive therapy, considered uncertain in SARS-CoV-2 positive patients receiving first-line therapy and all patients receiving rescue therapy.
f. Timing of flexible sigmoidoscopy should be as per standard guidelines. It was considered appropriate to perform prior to rescue therapy or colectomy to confirm diagnosis and exclude CMV, if not already performed.
g. It was considered inappropriate to delay colectomy if there were signs of toxicity, or in patients who had failed rescue therapy irrespective of SARS-CoV-2 status.
h. Standard steroid taper: Appropriate irrespective of SARS-CoV-2 swab status. Accelerated taper: Inappropriate if SARS-CoV-2 swab negative, uncertain if SARS-CoV-2 positive.
i. Thiopurine initiation: Appropriate in SARS-CoV-2 negative patients or positive patients without signs of COVID-19; uncertain if positive with signs of COVID-19.

Figure 1 Variations to the current ECCO/ESPGHAN guidance as proposed by the RAND appropriateness panel. 5-ASA, 5-aminosalicylic acid; CMV, cytomegalovirus; ECCO, European Crohn’s and Colitis Organisation; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition; PUCAI, paediatric ulcerative colitis activity index.
COVID-19

### TABLE 1

| On admission | Prior to rescue therapy | Prior to colectomy |
|--------------|-------------------------|--------------------|
| **Inpatient isolation** | All patients | Repeat swab if initial swab negative | Repeat swab if initial swab negative |
| SARS-CoV-2 swab | Perform in all patients | Repeat if initial test negative and patient has received broad-spectrum antibiotics | |
| **Clostridium difficile toxin** | ≤24 hours admission | If not performed | If not performed |
| **Flexible sigmoidoscopy** | If already performed | | If already performed |
| Chest X-ray | Perform in all patients | | Perform in all patients |
| Biological screen | Perform in all patients | | |

Green is considered appropriate, yellow uncertain and red inappropriate.

### Discussion

Treatment with ciclosporin concurrently with corticosteroids was deemed uncertain (irrespective of SARS-CoV-2 status) and the use of tacrolimus was deemed inappropriate irrespective of swab status or concurrent corticosteroid use. Commencing any second-line immunosuppressive therapy (infliximab, ciclosporin or tacrolimus) with simultaneous discontinuation of intravenous corticosteroid therapy was deemed inappropriate irrespective of SARS-CoV-2 status. In all scenarios, the appropriateness of MADoV alongside immunosuppressive therapy was considered uncertain, whereas MADoV alone was deemed inappropriate. Management by colectomy after failed first-line therapy was considered inappropriate in all patients with ASC irrespective of SARS-CoV-2 status (excluding cases where complications indicating the need for surgery were present such as toxic megacolon, perforation or severe haemorrhage) (table 3).

### Continuing medical therapy

On discharge from hospital, irrespective of SARS-CoV-2 status, it was deemed appropriate to use a standard corticosteroid taper as per ECCO/ESPGHAN guidance. An accelerated corticosteroid taper over 4–8 weeks was considered inappropriate in patients with a negative SARS-CoV-2 swab but uncertain in patients with a positive swab. It was considered inappropriate in all scenarios to use poorly bioavailable oral steroids as an alternative to prednisolone. Initiation of additional maintenance therapy during corticosteroid weaning to prevent disease relapse, was also considered. Following ECCO/ESPGHAN guidance by initiating a thiopurine was rated appropriate in patients with negative SARS-CoV-2 swab and asymptomatic patients with positive SARS-CoV-2 swab but uncertain in symptomatic patients with a positive swab (table 4).

Use of antitumour necrosis factor (anti-TNF) maintenance was considered uncertain irrespective of SARS-CoV-2 swab status. The use of vedolizumab was considered uncertain in asymptomatic patients with positive SARS-CoV-2 swab and inappropriate in symptomatic patients with positive swab and patients with negative swab.

Lastly, the appropriateness of the use of prophylactic anticoagulation for a period after discharge was considered. This was deemed inappropriate in patients who had a negative SARS-CoV-2 swab and uncertain in patients with a positive swab regardless of whether they had displayed signs or symptoms of COVID-19 infection.

### DISCUSSION

Our COVID-19-specific adaptations to paediatric ASC guidelines using a RAND panel generally support existing recommendations, particularly the use of corticosteroids and escalation to infliximab.

### The role of corticosteroids as first-line therapy

The use of intravenous corticosteroids constitutes the mainstay therapy for children with ASC. More than 70% respond to daily methylprednisolone according to the ‘Outcome of Steroid therapy in Colitis Individuals’ study published by Turner et al in 2010. We considered it appropriate to follow the current ECCO/ESPGHAN ASC guideline and initiate therapy with intravenous methylprednisolone irrespective of the SARS-CoV-2 screening result and without delay. Despite initial concerns regarding the safety profile of corticosteroids in the context of COVID-19 in adult patients, emerging evidence for the use of dexamethasone suggest that it is safe and might positively influence the disease course. Preliminary results from the RECOVERY trial revealed that dexamethasone treatment led to a significant reduction of mortality in hospitalised patients requiring respiratory support. In addition, patients with PIMS-TS have been regularly treated with corticosteroids. Doubts regarding the
safety of immunosuppressant medications including corticosteroids during the COVID-19 pandemic persist, particularly in light of preliminary data published from SECURE-IBD which suggested corticosteroids were associated with worse disease outcomes. However, the median age was 41 years, 59.4% of patients had Crohn’s disease and none of the reported 29 paediatric SARS-CoV-2 cases was classified as severe. The obvious confounder with regard to corticosteroid use is underlying moderate-to-severely active UC, which in itself has been associated with the risk of viral infection and worse outcomes in SARS-CoV-2 infection. Reassuringly, international paediatric studies consistently report a milder disease phenotype in children particularly in terms of respiratory complications. In addition, it has become evident that a delay in initiating therapy is likely to have a detrimental effect on paediatric patients with IBD.

The role of infliximab as rescue therapy

We also concluded that infliximab in combination with corticosteroids was an appropriate therapy, ciclosporin in combination with corticosteroids was considered uncertain and tacrolimus was deemed inappropriate regardless of SARS-CoV-2 status. None of these treatments was considered appropriate as monotherapy. Infliximab and ciclosporin are equally effective in achieving clinical remission in paediatric patients with ASC. Infliximab has, however, emerged as the preferred option due to its favourable risk:benefit profile, demonstrating the importance of safety considerations over efficacy alone in therapy selection. Ciclosporin use in adult patients with ASUC and COVID-19 has been considered inappropriate due to the combined risk of drug toxicity and COVID-19-related kidney injury. The risk for COVID-19-related kidney injury is significantly smaller in children; approximately 20% of children with PIMS-TS develop acute kidney injury. The risk of infliximab therapy in adult and paediatric patients with ASC and COVID-19 remains unknown. There is some evidence, however, that biologics, including infliximab, may have a beneficial effect by counteracting the hyperinflammatory response seen in COVID-19.

Maintenance therapy

The ECCO/ESPGHAN guideline recommends tapering corticosteroids over 8–10 weeks which was deemed appropriate by our RAND panel in all three clinical scenarios with uncertainty regarding an accelerated taper over 4–6 weeks in SARS-CoV-2-positive patients. ECCO/ESPGHAN guidance suggests to initiate azathioprine maintenance therapy in combination

### Table 3

| Day 5 (rescue therapy) | PUCAI 35–65 | PUCAI >65 |
|------------------------|------------|-----------|
| Negative SARS-CoV-2 swab without signs of COVID-19 infection | IV corticosteroids 2–5 days | Expedite second-line therapy | Continue IV corticosteroids alone | IFX alone | Ciclosporin alone | MADoV as adjunctive therapy | Colectomy |
| Positive SARS-CoV-2 swab without signs of COVID-19 infection | IV corticosteroids 2–5 days | Expedite second-line therapy | Continue IV corticosteroids alone | IFX alone | Ciclosporin+corticosteroids | Tacrolimus+corticosteroids | MADoV alone | Discussion with COVID-19 specialist* |
| Positive SARS-CoV-2 swab with signs of COVID-19 infection | IV corticosteroids 2–5 days | Expedite second-line therapy | Continue IV corticosteroids alone | IFX alone | Ciclosporin+corticosteroids | Tacrolimus+corticosteroids | MADoV alone | Discussion with COVID-19 specialist* |

Management at day 5: (Green is considered appropriate, yellow uncertain and red inappropriate).
*Discussion with appropriate COVID-19 specialist as per local availability.
†Disagreement index >1.
‡Corticosteroid taper and start additional therapy at or soon after discharge.
§Continue IV corticosteroids alone if clinical remission not achieved.
¶Disagreement index >1.

| Table 4 | Appropriateness of treatment options in acute severe colitis in the context of the COVID-19 pandemic: continuing medical therapy |
|---------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Continuing medical therapy in patients who have responded to intravenous steroid therapy* |
| Negative SARS-CoV-2 swab without signs of COVID-19 infection | Standard corticosteroid taper | Poorly bioavailable steroids† | Anti-TNF† | Thromboprophylaxis§ |
| Positive SARS-CoV-2 swab without signs of COVID-19 infection | Accelerated corticosteroid taper 4–6 weeks | Thiopurine‡ | Vedolizumab† |
| Positive SARS-CoV-2 swab with signs of COVID-19 infection | Accelerated corticosteroid taper 4–6 weeks | Poorly bioavailable steroids† | Anti-TNF† | Thromboprophylaxis§ |

Medium grey is considered appropriate, light grey uncertain and dark grey inappropriate.
*Patient has responded to intravenous corticosteroid therapy sufficiently to convert to oral prednisolone; standard or accelerated taper; switch methylprednisolone to prednisolone with taper as described.
†Switch from methylprednisolone to budesonide MMX/becloethasone.
‡Corticosteroid taper and start additional therapy at or soon after discharge.
§Continue for a period after discharge.
¶Disagreement index >1.

MMX, multimatrix; TNF, tumour necrosis factor.
with mesalazine for the majority of patients following ASC to decrease the likelihood of relapse.\textsuperscript{6} The RAND panel considered it appropriate to initiate azathioprine except in patients with signs of COVID-19 infection when it was deemed uncertain. This is in contrast to the adult RAND panel\textsuperscript{7} in which azathioprine treatment was more likely to be considered inappropriate. Reasons for concerns were possible side effects such as pancreatitis which might require hospital admission and lymphopenia potentially mimicking acute SARS-CoV-2 infection as well as the need for regular blood monitoring.\textsuperscript{22} This is likely to become less of a concern as services start to resume and areas and systems to manage patients without COVID-19 are put in place. The paediatric RAND panel considered azathioprine appropriate which might be explained by the rapidly evolving experience with COVID-19 confirming an overall favourable disease course in the general paediatric population\textsuperscript{3} as well as in children with IBD on immunosuppressant therapy.\textsuperscript{2} As per current guidance, patients who underwent rescue therapy with infliximab are recommended to continue this treatment as maintenance. Initiating an anti-TNF as maintenance treatment was considered uncertain in first-line (corticosteroid) responders regardless of SARS-CoV-2 status, which perhaps suggests a desire to avoid escalation to anti-TNF purely for the purposes of maintenance in those who have not required it as a rescue.

**MADoV therapy**

Although MADoV is only mentioned as a side note in the ECCO/ESPGHAN guidelines, it was deemed feasible that at the onset of the pandemic immunosuppressant-sparing approaches may be relevant or preferable. Although data are limited,\textsuperscript{11,12} we felt it important to explore the use of MADoV in this context. MADoV was considered inappropriate as a single agent in all contexts and uncertain as an adjunct in SARS-CoV-2-positive patients. This demonstrates that conventional therapy with agents known to be efficacious in preventing morbidity and mortality were considered more appropriate despite the potential risks of immunosuppression.

**Anticoagulation**

One of the most interesting and compelling findings of this RAND panel was that prophylactic anticoagulation was deemed appropriate in all patients, irrespective of COVID-19 status. This is distinct from the current ECCO/ESPGHAN guideline which recommends anticoagulation with low molecular weight heparin (LMWH) in adolescents with one or more risk factors for venous thromboembolic events (VTE).\textsuperscript{2} Notably, the median score was highest for SARS-CoV-2-positive patients with signs of COVID-19 infection and all panelists scored this scenario as appropriate. For SARS-CoV-2-positive patients without signs of COVID-19 infection and SARS-CoV-2-negative patients, the DI remained <1 but not all panelists voted anticoagulation as appropriate likely reflecting the need to weigh up thrombotic risk in individual patients. Adult guidelines advise thromboprophylaxis in all inpatients with ASUC,\textsuperscript{23} whereas this is not currently the case in paediatric ASC. The adult RAND panel therefore explored prophylactic anticoagulation postdischarge and recommended this in patients with a positive SARS-CoV-2 swab.\textsuperscript{3} While we considered routine thromboprophylaxis at presentation appropriate in all paediatric patients, there was uncertainty about continued therapy on discharge in SARS-CoV-2-positive patients and it was considered inappropriate in patients with negative swab. One limitation of our survey with regard to anticoagulation was that our clinical scenarios did not take into consideration specific patient factors such as age or thrombotic risk profile. It is likely that more nuanced guidance would emerge if clinical scenarios were more refined. Data from the safety registry in the PIBD-SETQuality (Safety, Efficacy, Treatment and Quality Improvement of Care) project suggest that VTEs are rare in PIBD but are 10 times more likely to occur compared with the general paediatric population. Most reported cases were seen in the context of UC or IBD-unclassified and during acute relapse.\textsuperscript{10} The cumulative incidence of thrombotic complications in critically ill adult patients with COVID-19 is nearly 50%.\textsuperscript{24} Even in critically ill adult patients with COVID-19 on standard prophylactic regimen, thromboembolic events were reported in 20–30% of cases.\textsuperscript{25} This has led to the implementation of more intensive anticoagulation strategies.\textsuperscript{23} Despite the paucity of literature to support anticoagulation in paediatric patients with COVID-19, the favourable side-effect profile of LMWH\textsuperscript{26} and the clear prothrombotic effect of COVID-19 in adults\textsuperscript{27} suggest to adopt a low threshold to use anticoagulation in paediatric COVID-19.

**Further comparisons with adult RAND panel data**

Several comparisons can be made between our results and those from the recent adult RAND panel.\textsuperscript{5} There was agreement that all patients should be isolated, tested for SARS-CoV-2 on admission and subsequently re-swabbed prior to rescue therapy or colectomy. Results were also similar with regard to the decision to refer to a COVID-19 specialist in all SARS-CoV-2-positive patients. These findings are perhaps unsurprising given the risk of nosocomial infection, particularly in a population being treated with immunosuppressant therapy. Similar to the adult RAND panel, it was considered appropriate to perform a flexible sigmoidoscopy at the point advised in the respective guidelines (day 1 for adults, day 3 for paediatrics) and it was not deemed necessary to repeat this test prior to treatment escalation or colectomy. Although SARS-CoV-2 can present with GI symptoms,\textsuperscript{28} it was considered that expediting endoscopy would not alter management but was required at the advised time point to confirm the diagnosis and, in particular, to exclude cytomegalovirus infection ahead of colectomy. Practical issues are not considered in the RAND process, but unlike in adult practice, most endoscopies in paediatrics are performed under general anaesthetic.

In the adult RAND panel, panelists were asked whether all patients should undergo a CT chest on admission and prior to colectomy which were deemed uncertain and appropriate respectively. The majority of adult patients undergo a routine chest X-ray on admission to hospital. However, there have been reports of improved sensitivity of CT chest compared with SARS-CoV-2 PCR for the diagnosis of COVID-19 infection.\textsuperscript{29} The inclusion of questions regarding CT chest scanning were generally considered inappropiate in paediatric patients due to the irradiation exposure and the additional requirement for a general anaesthetic to obtain adequate studies in some patients. The appropriateness of a routine chest-X-ray was posed instead and deemed appropriate prior to colectomy but only considered appropriate on a case-by-case basis on admission, leading to an outcome of uncertain.

The panel did not believe that SARS-CoV-2 status affected their decision to arrange an abdominal X-ray and therefore this question included in the first survey was removed from the second. The appropriateness of ustekinumab and tocilizumab use were considered during the adult RAND panel. Although discussed during the paediatric panel meeting, both
therapies are not licensed in paediatrics at present and are not mentioned in the ECCO/ESPghan guideline. Although it was appreciated that these therapies may be considered in individual paediatric cases, the focus of the RAND panel was to explore how practice might change when compared with standard practice. In both panels, there was a clear message that, if indicated, colectomy should not be delayed due to SARS-CoV-2 positivity.

With regard to the use of intravenous corticosteroids first-line and infliximab monotherapy as first-line or rescue therapy, there was less uncertainty in our results compared with the adult RAND panel. This likely reflects evolving decision-making processes during a period of rapidly emerging evidence and the fact that children have been relatively spared of severe sequelae from COVID-19 when compared with adults. In the adult panel, there were only six questions (6%) where all panellists voted the same appropriateness category as the final outcome category compared with 42 scenarios in our results (37%), whereas the number of scenarios reaching disagreement were similar 0/92 and 2/113, respectively.

**Strengths and limitations**

Our study has several strengths. We assembled a panel of IBD experts from multiple UK centres, evenly distributed across the country. We used RAND methodology, a validated and evidence-based technique to aid decision making, in an area with significant clinical uncertainty. We invited non-gastroenterology specialists with experience in managing children with COVID-19 and PIMS-TS to enable informed discussions during the panel meeting and provide specialist insight where uncertainty or disagreement existed, particularly with regard to the risks and benefits of immunosuppression. Although the aforementioned adult RAND panel has recently been published, our data provide new guidance on the management of ASC specific to children. Furthermore, by comparing our RAND panel with the adult version we have demonstrated how, despite the short time interval, decision making can change as data emerges, highlighting the need for us to be prepared to perpetually adapt our clinical practice. To our knowledge, this is the first study in paediatric IBD applying RAND appropriateness methodology to provide guidance in an area of clinical uncertainty. Given its successful application and positive feedback from panellists and experts within the field, this approach should be considered more often in the future.

Our study also has limitations. We made a number of assumptions with regard to the clinical scenarios considered and nuances in clinical decision making in specific clinical circumstances could not be brought to the fore. We broadly reviewed the use of individual agents to demonstrate themes with regard to the risks and benefits of therapy. We did not, for example, discuss continuing medical therapy in patients who required rescue with infliximab, in whom the potential risk of concomitant therapy needs to be weighed-up with the risks of immunogenicity if omitted. Rather, the outcomes discussed should serve as a guide and as an adjunct to clinical judgement and multidisciplinary decision making. It is possible that treatment-related considerations may change as new data come to light.

**Conclusions**

This process was undertaken during a period of great uncertainty with a rapidly emerging evidence base. The process enabled rapid review of existing guidance with specific reference to the risk:benefit of established ASC management in the context of an emerging pandemic. Our recommendations have the potential to increase clinician confidence and may be of considerable benefit as new challenges occur during the continued pandemic. The process also raised new issues for consideration including the timing of investigations, specifics of therapy and use of anti-coagulation.

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**Correction notice**

This article has been corrected since it published Online First. The author’s name Conor Doherty has been corrected and ORCID IDs have been added for all authors.

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All authors approved the final version. Study concept and design: RH, SM, RMB, MS, PMI and JK. Development of questionnaire: RH, RMB, SM, MS, PMI and JK. Data analysis: SM, MS and PMI. Interpretation of data and drafting of manuscript: RH, RMB, SM, MS, PMI and JK. Panellists, experts and moderators: all authors. Contributions to literature review and critical revision of the manuscript for important intellectual content: all authors.

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**Competing interests**

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All data relevant to the study are included in the article or uploaded as supplementary information. This is not a clinical trial, hence no patient identifiable data generated. Any other data generated in this study is included in the article.

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