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

Richard Hansen ,[1] Susanna Meade ,[2] R Mark Beattie ,[3] Marcus KH Auth ,[4] Nick Croft ,[5,6] Philip Davies ,[7] David Devadason ,[8] Conor Doherty,[9] Jenny Epstein ,[10] Lucy Howarth ,[11] Fevronia Kiparissi ,[12] Rafeeq Muhammed ,[13] Vinay Shivamurthy ,[14] Christine Spray ,[15] Michael P Stanton ,[16] Franco Torrente ,[17] Arun Urs ,[18] David Wilson ,[19,20] Peter M Irving ,[2] Mark Samaan ,[2] Jochen Kammermeier [21]

For numbered affiliations see end of article.

Correspondence to
Dr Jochen Kammermeier, Paediatric Gastroenterology, Evelina London Children's Hospital, London, London, UK; jochen.kammermeier@gstt.nhs.uk

RH and SM are joint first authors.
MS and JK are joint senior authors.

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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,

Significance of this study

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.

from asymptomatic carriage to fatal acute respiratory distress syndrome with resultant hyperinflammation and cytokine storm syndrome,[1] children have been relatively unaffected with low rates of morbidity or mortality. Encouragingly, paediatric IBD and its treatment does not appear to confer significant additional risk to children infected with SARS-CoV-2. A small case series of eight children with IBD and SARS-CoV-2 infection revealed that they had mild symptoms, even with concurrent immunosuppressant treatment.[2] In addition, of the 85 patients younger than 20 years of age reported to date on the Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE)-IBD database, none resulted in death and only one required admission for ventilation.[3 4]

While data are still emerging on the true impact of SARS-CoV-2, practitioners are more cautious about the risks of general anaesthetics, surgery and the use of immunosuppressants. The potential risks of these interventions however, need to be considered in the context of the likely increase of secondary morbidity from suboptimal assessment and treatment of IBD. Similarly, COVID-19 has generated an impetus for innovation within healthcare.

For these reasons, members of the British Society of Gastroenterology reviewed their own guidelines for managing acute severe UC (ASUC) by applying RAND appropriateness methodology to offer expert commentary and guidance on how management might need adaptation in light of SARS-CoV-2.[5] Subsequently and independently, we convened a RAND panel for the management of paediatric ASC using the current European Crohn's and Colitis Organisation (ECCO)/European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidance[6] as a reference point against which to highlight any changes to proposed current management.

While the ECCO/ESPGHAN guideline focuses on patients younger than 18 years of age, the adult RAND publication applies to patients 16 years of age or older presenting to an adult department. We acknowledge that, between different countries, there is significant variation of practice. Although our guidance is mainly aimed to young persons under the age of 16 and aligned with the adult RAND panel publication, we acknowledge that many patients between the ages 16 and 17 years are appropriately managed in an adult setting. The paediatric acute severe colitis (ASC) guideline differs from the adult version, for example, by recommending the paediatric ulcerative colitis activity index (PUCAI)[7] as a marker of disease severity, mandating sigmoidoscopy on day 3 rather than day 1 and second-line therapy escalation on day 5 instead of day 3.[6] Both paediatric and adult guidelines agree on initial management of ASC with first-line intravenous corticosteroids followed by second-line immunosuppressant therapy prior to colectomy unless surgical intervention is required as an emergency.

Significant variations were proposed in the recently published adaptation of management in adult ASUC in the context of COVID-19.[5] We therefore convened a RAND appropriateness panel to provide clarity on the management of ASC in children and adolescents, as defined by PUCAI,[6] 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.[7 8]

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.[6] 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.[7 8] 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.[8]

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[6] 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—temporally associated with SARS-CoV-2 (PIMS-TS).[9] 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.[10–12]

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, PMI) 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.[6] 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.[6] 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, RAND methodology mandates that decisions with regard to the appropriateness of interventions should not take into account treatment availability, practicalities or cost.

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.[8] 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.

$$DI = \frac{70\%ile - 30\%ile}{2.35 + \left(1.5 \times abs\left(5 - \frac{70\%ile + 30\%ile}{2}\right)\right)}$$

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 *Clostridium 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 multimatrix (MMX) or beclometasone) were also deemed inappropriate in all scenarios. The use of MADoV antibiotic combination[11] (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,

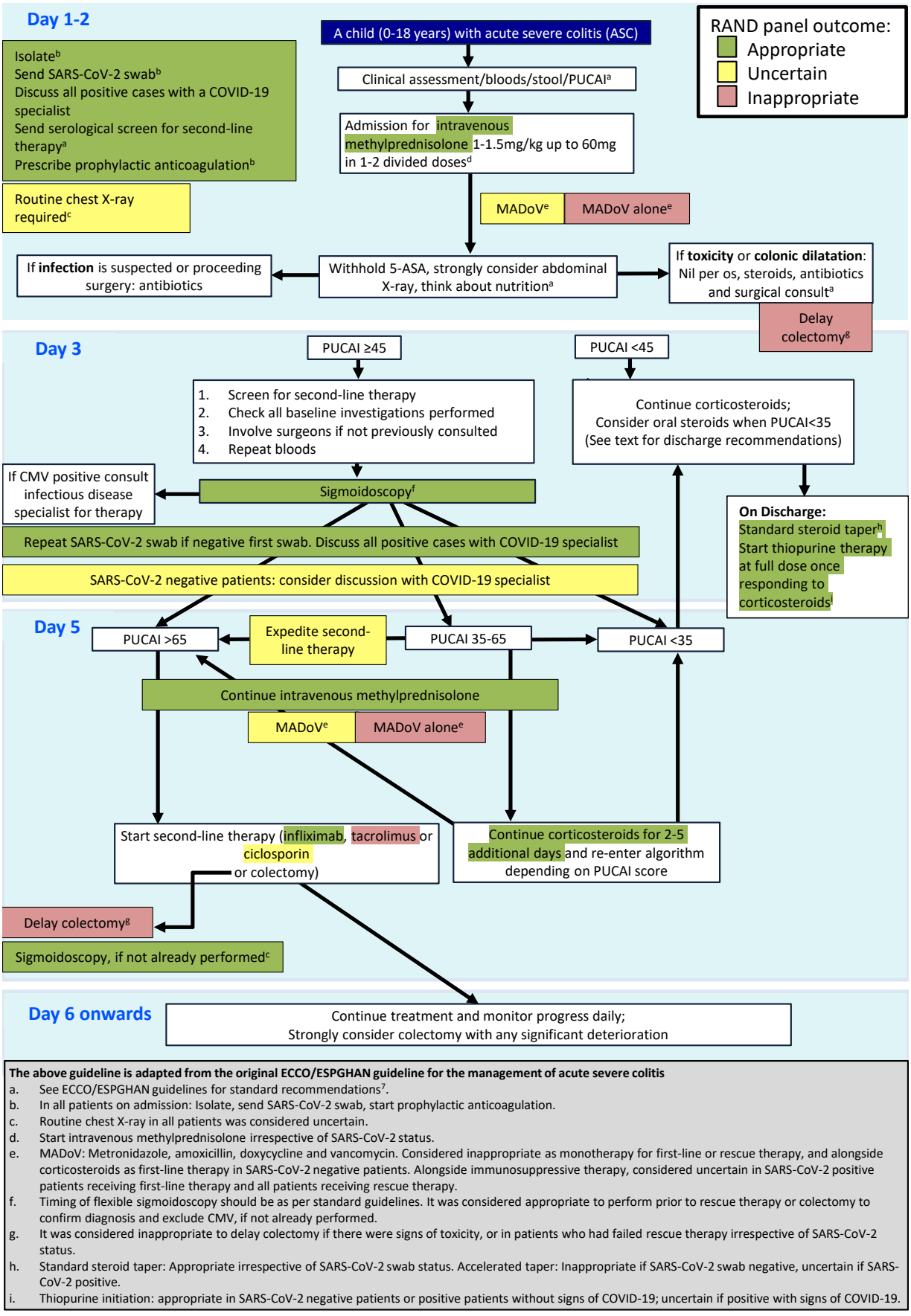

Figure 1 Variations to the current ECCO/ESPGHAN guidance as proposed by the RAND appropriateness panel. 5-ASA, 5-aminosalicylic acid; CMV, cytomegalovirus; ECCO, European Crohn's and Colitis Organisation; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition; PUCAI, paediatric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

Table 1 Appropriateness of patient isolation and investigation in paediatric patients admitted with acute severe colitis in the context of the COVID-19 pandemic

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

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.[6] 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.[13] We considered it appropriate to follow the current ECCO/ESPGHAN ASC guideline[6] 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.[14] In addition, patients with PIMS-TS have been regularly treated with corticosteroids.[9 15] Doubts regarding the

Table 2 Appropriateness of treatment options in acute severe colitis in the context of the COVID-19 pandemic: first-line medical therapy

	First-line medical therapy					
Negative SARS-CoV-2 swab without signs of COVID-19 infection	IP IV corticosteroids	Poorly bioavailable steroids*	IFX alone	Tacrolimus±corticosteroids	MADoV alone	Discussion with COVID-19 specialist†
	OP IV corticosteroids	IV corticosteroids+IFX	Ciclosporin±corticosteroids	MADoV as adjunctive therapy	Thromboprophylaxis	
Positive SARS-CoV-2 swab without signs of COVID-19 infection	IP IV steroids	Poorly bioavailable steroids*	IFX alone	Tacrolimus±corticosteroids	MADoV alone	Discussion with COVID-19 specialist†
	OP IV corticosteroids	IV corticosteroids+IFX	Ciclosporin±corticosteroids	MADoV as adjunctive therapy	Thromboprophylaxis	
Positive SARS-CoV-2 swab with signs of COVID-19 infection	IP IV corticosteroids	Poorly bioavailable steroids*	IFX alone	Tacrolimus±corticosteroids	MADoV alone	Discussion with COVID-19 specialist†
	OP IV corticosteroids	IV corticosteroids+IFX	Ciclosporin±corticosteroids	MADoV as adjunctive therapy	Thromboprophylaxis	

Green is considered appropriate, yellow uncertain and red grey inappropriate
*Budesonide MMX/beclometasone.
†Discussion with appropriate COVID-19 specialist as per local availability.
IFX, infliximab; IP, inpatient; IV, intravenous; MADoV, metronidazole, amoxicillin, doxycycline, vancomycin or equivalent; methylprednisolone, corticosteroids; MMX, multimatrix; OP, outpatient.

Table 3 Appropriateness of treatment options in acute severe colitis in the context of the COVID-19 pandemic

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
			IV corticosteroids+IFX	Ciclosporin+corticosteroids	Tacrolimus±corticosteroids	MADoV alone	Discussion with COVID-19 specialist*
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 alone	MADoV as adjunctive therapy	Colectomy
			IV corticosteroids+IFX	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 alone	MADoV as adjunctive therapy	Colectomy
			IV corticosteroids+IFX	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.
IFX, infliximab; MADoV, metronidazole, amoxicillin, doxycycline, vancomycin or equivalent; methylprednisolone, corticosteroids.

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.[4] 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.[16 17] Reassuringly, international paediatric studies consistently report a milder disease phenotype in children particularly in terms of respiratory complications.[15] In addition, it has become evident that a delay in initiating therapy is likely to have a detrimental effect on paediatric patients with IBD.[2]

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.[6] 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.[13] 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.[18] The risk for COVID-19-related kidney injury is significantly smaller in children; approximately 20% of children with PIMS-TS develop acute kidney injury.[9] 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.[19 20] Biologics including anakinra and infliximab may also be beneficial in the management of PIMS-TS.[9]

Maintenance therapy

The ECCO/ESPGHAN guideline[6] 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 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§
	Accelerated corticosteroid taper 4–6 weeks	Thiopurine‡	Vedolizumab‡	
Positive SARS-CoV-2 swab without signs of COVID-19 infection	Standard corticosteroid taper	Poorly bioavailable steroids†	Anti-TNF‡	Thromboprophylaxis§
	Accelerated corticosteroid taper 4–6 weeks	Thiopurine‡	Vedolizumab‡	
Positive SARS-CoV-2 swab with signs of COVID-19 infection	Standard corticosteroid taper	Poorly bioavailable steroids†	Anti-TNF‡	Thromboprophylaxis§¶
	Accelerated corticosteroid taper 4–6 weeks	Thiopurine‡	Vedolizumab‡	

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/beclometasone.
‡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.[6 21] 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 outcome[5] 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.[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[15] as well as in children with IBD on immunosuppressant therapy.[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/ESPHAGN guidelines, it was deemed feasible that at the onset of the pandemic immunosuppressant-sparing approaches may be relevant or preferable. Although data are limited,[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).[2] Notably, the median score was highest for SARS-CoV-2-positive patients with signs of COVID-19 infection and all panellists 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 panellists 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,[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.[5] 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.[10] The cumulative incidence of thrombotic complications in critically ill adult patients with COVID-19 is nearly 50%.[24] Even in critically ill adult patients with COVID-19 on standard prophylactic regimen, thromboembolic events were reported in 20%–30% of cases.[25] This has led to the implementation of more intensive anticoagulation strategies.[23] Despite the paucity of literature to support anticoagulation in paediatric patients with COVID-19, the favourable side-effect profile of LMWH[26] and the clear prothrombotic effect of COVID-19 in adults[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.[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 immunosuppressive 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,[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, panellists 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.[29] The inclusion of questions regarding CT chest scanning were generally considered inappropriate 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 tofacitinib 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.[3] 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 anticoagulation.

Author affiliations
[1]Department of Paediatric Gastroenterology, Royal Hospital for Children, Glasgow, UK
[2]Department of Gastroenterology, Guy's and Saint Thomas' NHS Foundation Trust, London, UK
[3]Department of Paediatric Gastroenterology, Southampton Children's Hospital, Southampton, UK
[4]Department of Paediatric Gastroenterology, Alder Hey Children's NHS Foundation Trust, Liverpool, UK
[5]Blizard Institute, Queen Mary's University of London, Barts and the London School of Medicine, London, UK
[6]Department of Paediatric Gastroenterology, Royal London Children's Hospital, Barts Health NHS Trust, London, UK
[7]Department of Paediatric Respiratory Medicine, Royal Hospital for Children, Glasgow, UK
[8]Department of Paediatric Gastroenterology, Queen's Medical Centre Nottingham University Hospital NHS Trust, Nottingham, UK
[9]Department of Paediatric Infectious Diseases and Immunology, Royal Hospital for Children, Glasgow, UK
[10]Department of Paediatric Gastroenterology, Chelsea and Westminster Hospital NHS Foundation Trust, London, UK
[11]Department of Paediatric Gastroenterology, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[12]Department of Paediatric Gastroenterology, Great Ormond Street Hospital for Children, London, UK
[13]Department of Paediatric Gastroenterology, Birmingham Children's Hospital, Birmingham, UK
[14]Department of Paediatric Rheumatology, Evelina London Children's Hospital, London, UK
[15]Department of Paediatric Gastroenterology, Hepatology & Nutrition, Bristol Royal Hospital for Children, Bristol, UK
[16]Department of Paediatric Surgery, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[17]Department of Paediatric Gastroenterology, Addenbrookes Hospital, Cambridge, UK
[18]Department of Paediatric Gastroenterology, Sheffield Children's Hospital NHS Foundation Trust, Sheffield, UK
[19]Child Life and Health, University of Edinburgh, Edinburgh, UK
[20]Department of Paediatric Gastroenterology and Nutrition, Royal Hospital for Sick Children, Edinburgh, UK
[21]Department of Paediatric Gastroenterology, Evelina London Children's Hospital, London, UK

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Twitter Mark Samaan @SamaanMark

Contributors 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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ORCID iDs
Richard Hansen http://orcid.org/0000-0002-3944-6646
Susanna Meade http://orcid.org/0000-0002-8283-6148
R Mark Beattie http://orcid.org/00000003-4721-0577
Marcus KH Auth http://orcid.org/0000-0002-9381-6994
Nick Croft http://orcid.org/0000-0002-1519-6435
Philip Davies http://orcid.org/0000-0001-7487-5115
David Devadason http://orcid.org/0000-0003-3376-3795
Jenny Epstein http://orcid.org/0000-0003-1380-465X
Lucy Howarth http://orcid.org/0000-0002-6963-8745
Fevronia Kiparissi http://orcid.org/0000-0003-1545-8893
Rafeeq Muhammed http://orcid.org/0000-0001-6107-8109
Vinay Shivamurthy http://orcid.org/0000-0003-2174-3439
Christine Spray http://orcid.org/0000-0002–2885–9156
Michael P Stanton http://orcid.org/0000-0003-1130-9778
Franco Torrente http://orcid.org/0000-0003-0060-5141
Arun Urs http://orcid.org/0000-0002-8776-565X
David Wilson http://orcid.org/0000-0003-0879-1129
Peter M Irving http://orcid.org/0000-0003-0972-8148
Mark Samaan http://orcid.org/0000-0002-4057-9200
Jochen Kammermeier http://orcid.org/0000-0002-6046-8727

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