Peer Review File

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Reviewer A

Introduction (lines 48-79 in original submission)

The introduction contains only one citation – this should either have each statement cited, or none at all. It does seem odd as a reader to have such a long piece of factual text citation free but having included one it's hard to gauge if this was as intended. Please choose one option and be consistent.

The first sentence needs revising as doesn't make sense.
There are some long sentences that need breaking up.

Thank you for these comments regarding the structure and syntax of this section. Please see the revised version. The first sentence now reads "The global incidence of paediatric inflammatory bowel disease (IBD) has been steadily increasing over the past two decades, coinciding with advancements in the management of these diseases in children," for clarity.

Long sentences have been drastically altered within this section, for flow and clarity. Please see section "Introduction," from "The global incidence…" to "improved access to treatments as important avenues for future optimization."

Methods – (lines 80-82 in original submission)

It is insufficient to just put a table in here with no lead in sentence. It would be more pleasant flow-wise for readers if this was presented in text, not table form, but understand it may be required as part of the review format.

Thank you for this comment regarding the "Methods" section, a brief introductory paragraph is now presented – "A literature search was undertaken … UK and Europe."

Epidemiology - (lines 84-128 in original submission)

Please use a new paragraph for each theory, ie- a separate one for 'Support for dietary theories…' . Ideally add sub-headings as in subsequent sections.

Thank you for the suggested change in formatting, please see the revised Epidemiology

section, with subheadings “Support for dietary theories,” “Genetic and Genomic factors in pathogenesis,” “Environmental triggers and the microbiome” and “implications”

The word ‘however’ is redundant in the sentence starting ‘The pathophysiology of IBD however…’

Thank you for this suggestion, this has been removed from the original line 96.

Please break up the sentence beginning ‘For some patients the inadequate…’ it’s too long and convoluted.

Thank you for this comment, this sentence has now been divided, see “For some patients an inadequate immune response, related to hypomorphic variants in key bacterial sensing and signal transduction pathways - such as the NOD-signalling pathway - is the cause of disease. For other individuals, hyperinflammatory or autoinflammatory variation is the culprit.

The sentence ‘Multiple causes have been suggested for this increase, including westernisation of diet, genetic predisposition - though it is unlikely that such significant of a drift could have occurred over such a recent time period – and aseptic childhood upbringing’ would be better changed around to: ‘Multiple causes have been suggested for this increase, including westernisation of diet, aseptic childhood upbringing and genetic predisposition, although it is unlikely that such significant of a drift could have occurred over such a recent time period’

Thank you for the suggested revision to this sentence. The suggested wording has been added to the paragraph.

Please change ‘Although’ to ‘However, …’ (line 108)

Thank you for this suggested change which has been amended as requested.

Referral pathways - (lines 122-182 in original submission)

You already have Table 1 in the methods, subsequent ones will have to be re-numbered.

Thank you for this comment, the tables and figures have been renumbered accordingly.

There is very little on referral pathways and jumps almost instantly to FC. Seeing as your paper is on assessment and management you could either stick to what is done in tertiary care and take out the referral pathways part and stick to FC, or bilk out the referral section.
There is plenty to compare and contrast about alarm symptoms and recommended testing that should be added. It is not sufficient to just add in figure 1 and leave as is.

Thank you for this suggestion, we have sub-divided this into "initial presentation" and "faecal calprotectin" sections. This initial presentation section now integrates the content regarding presenting symptoms from the previous "faecal calprotectin" section for ease of reading/ cohesion and sets up the calprotectin section more effectively.

FC section

As in previous statement, you could condense this section to make relevant for children in tertiary care only undergoing testing/management for IBD and just make commentary on the levels in 'normal' populations without including them in the table.

Thank you for this comment – please see the above changes.

The table is incomprehensible anyway, due to the amount of information and size of text (see commentary below) so would help reduce this. This section also mixes up presenting symptoms with FC and seems disjointed.

Thank you for your comment regarding figure 1 – now renamed "table 2." We have made extensive changes to this table, reducing the volume of information presented as well as making wholesale formatting changes for ease of reading.

Best / gold standard section

There is a disproportionate amount of text discussing endoscopy vs capsule imaging. It makes more sense to bulk out the endoscopy part with details of how they are graded (SES etc) and used to define phenotype. There is nothing on the phenotyping, or difference between CD and UC, for example. There is too much on VCE that are used considerably less frequently!

Thank you for your comments regarding the balance of endoscopy and VCE in this section. The intention of this section had been to draw attention to and highlight trends in capsule endoscopy, the use of which has been increasing exponentially in recent years. We wanted to avoid going over too much old ground regarding endoscopy. This has been made reference to in the text and both sections extensively edited for flow, ease of reading and conciseness of content. The title of this section has been changed to "developments in specialist investigations" to highlight this. Subheadings have been introduced.

Line 255 has this in: 'In spite of this, t[NO_PRINTED_FORM]'. Please check your manuscript.

Thank you for noting this inclusion, the manuscript has been updated with this removed.

EEN section

You mention EEN being first line treatment in the UK but there is no discussion of use in other regions. Your manuscript should be generalisable/relatable to all regions.

Thank you for this comment regarding generalisability. The journal originally commissioned this article as a commentary on the contemporary UK management of IBD, which expanded due to the heavy influence of ESPGHAN and ECCO on UK practice. Here position papers from ESPGHAN have been included.

'Remission rates up to 80%' needs further definition of range as it could be 2-80% which is a big difference! The papers you get this data from should really be systematic reviews/meta-analyses/original data, and if SR's, MA's you should state this.

Thank you for this comment. The remission rate is now better defined, as are the sources "These statements, integrating several systematic reviews, have defined an overall combined remission rate of 73% for EEN, noting similar efficacy for this purpose as corticosteroids."

This sentence needs citations to back up your statement! 'There is limited scope for EEN for use in patients exhibiting extra-luminal symptoms or perianal disease. Use in ulcerative colitis is not supported.'

Thank for noting this – the sentence has been restructured and properly cited – "Conversely there are insufficient data to support the use of EEN for extraintestinal and perianal disease, or in ulcerative colitis (52)"

Corticosteroids section

There are no citations here… no commentary on remission rates, side effects, risks, comparable efficacy with EEN (as mentioned previously but important to note in some way), preference of one over another in terms of efficacy?

Thank you for these comments. This section has been cited accordingly. A short section regarding side effects has been included - The side effect profile of corticosteroids, particularly in prolonged and "supraphysiological" dosing is well documented, with weight gain, cushingoid features, osteoporosis, glaucoma, hypertension and mood disturbance being commonly seen." Comparable efficacy with EEN is noted in the EEN section and again referenced here, "with rates of 50-64% reported, which is comparable to EEN."

5-ASA section (induction and remission)

There are no citations here – remission rates for induction, data for CD to back up your statement as being no role. Is still included in NASPGHAN recommendations so this needs further commentary. It is still used in some regions as a step-wise treatment so please check this. Spelling check on aminosalycylates – should it be salicylates?

Thank you for these comments. Please see the amended version of this section, integrating induction and maintenance useage. Please see appropriate citation of this section. NASPGHAN recommendations are not included for focus on UK and European practice. Thank you for noting spelling error – this has been amended.

Immunomodulator section

Once again you mention the UK but no other regions, thereby limiting generalisability.

Thank you for this comment, this section has not been altered to continue focus on UK/ European practice.

Anti-TNF section

What are anti-TNF? You have added more info in the 'maintenance' section but it still lacks an overview sentence.

Thank you for this suggestion – an introductory sentence has been added – "Anti-TNF therapy, primarily infliximab - monoclonal chimeric anti-TNF antibody - and adalimumab – a fully humanised monoclonal anti-TNF antibody, have become mainstays of paediatric treatment"

Also - 'Increasingly there are recommendations for top-down therapy in paediatric IBD.' – where is the evidence for the benefit of this, is it regional? What about bio-similars?

Thank you for this comment, an appropriate citation has now been included for this statement.

As in commentary below, please consider combining the drug sections as there is very little in the 'induction' section and readers have to wait until this section for additional information.

Thank you for this suggestion, as visible in the revised version, sections for induction and maintenance for each class have been combined for ease for comparison/ flow.

Acute severe colitis section

Due to the ambiguous heading format (see commentary below) it is hard to tell how

this fits in to where it is placed after drugs. The addition of dosing regimens in this section seems out of place having not been discussed in other sections.

Thank you for your comments. The following sections have been restructured under "Key topics and practice points in disease management." This allows for some cohesion of these areas under a single banner. The section on dosing regimens has ben amended to be in keeping with other sections.

You have suddenly added in this statement with no basis 'A RAND appropriateness panel was conducted, evaluating the guidance provided by ECCO/ESPGHAN during the COVID-19 pandemic, which generally supported existing recommendations, in addition to adding the consideration of routine thromboprophylaxis [84].'

Thank you for this comment, this sentence has been rewritten in keeping with the rest of the paragraph – "Thromboprophylaxis should also be considered concurrently."

TDM section

Please lead in with which drugs this is use for. Which drugs do your citations refer to?

Thank you for this comment, the section now specifies the anti-TNF drugs to which we are referring – "Typically, therapeutic drug monitoring (TDM) refers to biologic therapies, such as infliximab and adalimumab."
This section now integrates the "loss of response section" as suggested.

Personalised and precision therapy section

More information is required to explain what this is, what it may be based on, any papers showing success?

Thank you for your comments. A definition of personalised medicine has been integrated into this section, as has a citation to Dr Ashton's paper reporting on personalised medicine in IBD. "In this way, the integration of genomic, biomarker and environmental data from an individual could provide them an optimised and specific diagnosis, and bring about targeted prevention and treatment of disease. For IBD, this personalised or precision medicine, could equate to improved understanding and prediction for an individual patient, allowing for the right therapy to be given at the right time, avoiding complications and side-effects, whilst maximising therapeutic benefits."

Complications of Crohn's disease section
You start using phenotype here without having explained it previously.

Thank you for this comment, classification of phenotypes in crohn's disease is now included in this section. "Crohn's disease behaviour is heterogenous, with phenotypes recognised as per the Paris modification of the of the Montreal classification of IBD."

Line 563 'in up r-50%'
Thank you for noting this, it has been amended to say "…disease behaviour changes to stricturing disease (B2) in up to 50%."

Loss of response to therapy section
Parts of this would fit better in with 'TDM'
This suddenly has extensive study results added, which doesn't fit with most of the rest of the paper.

Thank you for these comments, this section has been integrated with the TDM section and extensive study results amended to be in keeping with the rest of the article.

Transition care section

Using just UK again…
Provide some guidelines to demonstrate what should be involved, and papers showing what is lacking in other global regions.

Thank you for this comment. This section has been added to, noting guidance from NICE. We have continued to provide a UK specific slant in this section, in keeping with the articles original focus.

Tables

These are all, with the exception of the first Figure 1 in the methods, incomprehensible due to tiny text and far too much detail included. They will all need extensive revision before they can even be reviewed.

Thank you for noting this, both the original table 1 and table 2 have been streamlined and condensed for ease of reading. They have been renamed, and this has been updated in the "tables and figures section"
"Figure 1- Summary of a potential diagnostic and referral pathway for paediatric-onset inflammatory bowel disease, including integration of monitoring and drug dosing between primary, secondary and specialist care.
Table 1 - The search strategy summary employed by the authors for the compilation of relevant research works
Table 2- A summary of primary data 2017-2020 evaluating faecal calprotectin in a healthy paediatric population including average results by age and suggested threshold value if stated
Table 3- Long term outcomes of paediatric inflammatory bowel disease – specific

situations and key studies (2017-2022)”

Figures
Why is Figure 1 at the end of the document so readers have to scroll to after the conclusion to find it?
The text is very small and the figure cluttered and poorly organised due to lots of rather unnecessary pictures.

To be revised

Reference list
This seems corrupted in places, please check carefully

Thank you for noting this, corrupted entries have been removed

The writing is rather disjointed in many sections and reads like facts strung together. Please work on how the writing flows for the reader, with the primary aim of telling a ‘story’. However, some sections are written really well, flow, and are a great indicator of what I mean by my comments (Complications of CD and UC).

Thank you for this comment, significant re-structure and re-writing has been made throughout the article, as well as the integration of similar sections for ease. This has improved flow and structure.

Sections need to be moved around in order to ‘fit’ together as there is little flow though the whole paper.

Please see above comments.

It’s hard to tell what audience you are aiming this paper at as lack detail/descriptions in many places that would require if aimed at primary care, and have excessive detail in others that would indicate tertiary specialists.

Thank you for these comments, the extensive changes throughout, improving flow in particular should improve accessibility for all audiences.

There often seems to be text in sections that could be divided under additional sub-headings to make it easier to read, or should be in other sections. Please review.
Some sections seem overly long and complex compared to others that should be the primary focus.

Please see above changes and re-structure

Please consider combining sections – for example - drugs combined as

induction/maintenance as would avoid repetition and provide a more succinct overview.

Thank you, please see the combining of sections in the revised article, for example the integration of TDM and loss of response sections

Please expand your commentary past UK and ESPGHAN/ECCO to provide commentary on differences in any NASPGHAN guidelines, for example.

Thank you for this comment, we have specified the focus on UK and European practice, with reference to this made throughout.

The lack of continuity in your headings makes it hard to tell which are section, sub-sections etc. Please consider using a numbering system.

Please see numbering system

Reviewer B

Major comments

- Some newer data in adults supports even lower limits on calprotectin levels. This will likely be true in the pediatric population as well, with the exception of VEO-IBD as the authors mention briefly

Many thanks for this comment, we have expanded the section on thresholds for faecal calprotectin, including BSG guidance in adults – "British Society of Gastroenterology (BSG) guidance suggests that local referral to endoscopy should factor in local audit values for threshold value of calprotectin. They state that a balance must be found between higher thresholds, wherein fewer necessary tests will be performed, and some cases missed, and lower thresholds where fewer cases will go undetected, but unnecessary tests will be undertaken. BSG do not suggest that there is enough evidence to support repeat measurements, though in paediatrics, particularly in younger children where "normal" values may be higher or more variable, recent work has supported this.

- The authors should mention long-term steroid side effects, which children are disproportionately prone to in comparison to adults (and why steroid-sparing therapy is so important in this population)

Thank you for this comment, this section has been expanded upon, highlighting steroid side effects- "The side effect profile of corticosteroids, particularly in prolonged and "supraphysiological" dosing is well documented, with weight gain, cushingoid features, osteoporosis, glaucoma, hypertension and mood disturbance being commonly seen. As a result, after weaning, steroid sparing strategies are favoured for the maintenance of

remission to avoid these side effects, which can be particularly significant in a paediatric population – i.e. bringing about growth and pubertal delay."

- JAK inhibitors are rapidly being incorporated into pediatric IBD care. This section should be enhanced to cover more detail on tofacitinib and upadacitinib, which is likely to overtake tofacitinib in children due to improved safety profile seen in adults

Thank you for this comment – we have expanded on this section to highlight this point – "Promising efficacy data have been demonstrated with Tofacitinib for induction and maintenance of remission in UC, particularly in the adult population, however certain concerns regarding the safety profile, including risks of infections and venous thromboembolism must be considered [93]. Upadacitinib has also been shown to be effective for this purpose, with fewer safety concerns [94]. Few case reports have utilised Upadacitinib in the paediatric population, though contemporary work has noted efficacy and safety [95]."

- TDM is standard of care for anti-TNF therapy at most academic centers in the US. The fact that there are data to support it for anti-TNF while the data for other biologics are disheartening should be highlighted (eg vedolizumab). The information we have currently points to TDM being more important in children than in adults because of pharmacodynamic differences

Thank you, a should comment has been added regarding this. "Data supporting therapeutic monitoring with Vedolizumab and Ustekinumab are more lacking, although adult studies have demonstrated improved mucosal healing with higher trough levels [111]. Further work is required, particularly in a paediatric population, to support routine monitoring and the development of threshold values [112]."

- In the disease outcomes section, I might suggest a discussion on pain and mental health outcomes, as these are central in pediatric IBD. Pain in particular has proven to be a major issue in drug trials because many patients still report pain despite evidence of endoscopic remission. These pathways deserve more thorough molecular interrogation to determine how to better help IBD patients deal with chronic abdominal pain.

9.4 – Additional outcomes to consider
Measuring pain and mental health outcomes has been largely ignored in clinical trials but remains a central feature of disease burden for many patients. Addressing these measurables in future studies will be important to reduce overall disease burden