Peer Review File

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Reviewer Comments: This MS overviews aspects of IBD in children

SPECIFIC COMMENTS

Comment 1: The ABSTRACT is very long. In addition, it contains some excessively long sentences.
Reply 1: Thank you for pointing this out, abstract is now short and revised.

Comment 2: Several of the sentences in the ABSTRACT are repeated word for word in the main text of the MS
Reply 2: Again, the abstract is rewritten to avoid duplication.

Comment 3: There are numerous grammatical or typographical errors that need correction throughout the MS. As just two examples: Line 43, the word but is not appropriate Line 44, the sentence should start with The
Reply 3: Grammatical and typographical errors have been corrected

Comment 4: Line 49 and 50 is not a full paragraph
Reply 4: A careful attention is given and these sections have been revised to address grammatical and typographical errors.

Comment 5: The INTRO could also be more focused (to set the scene clearly) and shortened
Reply 5: Introduction have been revised to improve brevity.

Comment 6: The term indeterminate colitis and IBDU should be used correctly (they are not synonymous)
Reply 6: Traditionally, IBD is classified as CD, UC or IBD-unclassified (IBD-U) in those with overlapping features of CD and UC.

Comment 7: Abbreviations should be used correctly and consistently. CD and UC are introduced early, but are then used intermittently thereafter.
Reply 7: Abbreviations have been used correctly and consistently in the revised MS.

Comment 8: The sentence at lines 90-92 needs revision
Reply 8: Revision. It is important to consider IBD in children with chronic abdominal pain but it should be remembered that it is frequently encountered in other common GI conditions, such as functional abdominal pain, post-infectious irritable bowel syndrome, and coeliac disease in children. Non-voluntary weight loss is an important red-flag sign of serious organic pathology, a detailed record of weight, height, growth velocity and puberty are vital for diagnosis. In those with strong family history of IBD, weight loss a high index of suspicion should be maintained and laboratory tests should be ordered

for the screening purposes

Comment 9: Line 94 is missing some words
Reply 9: This section was rewritten: The presence of anemia, elevated serum inflammatory markers including ESR, CRP are supportive for a diagnosis of IBD in children presenting with symptoms of IBD, however a normal serum biochemistry can be seen in 21-50% of children with IBD (8).

Comment 10: The mention of a normal range for FC needs referencing
Reply 10: FCP is predominantly a neutrophilic protein that can be measured in stools, it is a highly accurate non-invasive test that differentiates between functional and inflammatory bowel disorder, with a normal value <50mcgm/gm of stool. Although it may be a cost-effective screening strategy when in doubt, it should be noted that elevated levels of fecal calprotectin can be seen in cases with infectious colitis, juvenile polyps, NSAIDS exposure and in healthy infants.

Comment 11: Line 111: the word macroscopic is not used correctly here. this should be replaced with the word endoscopic
Reply 11: This section was rewritten and reviewers' suggestions have been incorporated.
All children with suspicion of IBD, should undergo a complete endoscopic evaluation including upper gastrointestinal endoscopy and ileo-colonoscopy with multiple biopsies. There are typical endoscopic features that helps to differentiate CD with UC. In a child with classic UC, a continuous mucosal inflammation of the colon, starting from the rectum, without small intestine involvement (except backwash ileitis) is seen. On the other hand, a classic CD is non-continuous aphthous or linear ulcers, involving any part of the GI tract. UGI tract inflammation was previously considered a specific finding of CD but it can also be seen in children with UC, although serpiginous gastric or duodenal ulcers would favor a diagnosis of CD. 13 CD can also present atypically with continuous superficial inflammation involving colon, isolated oral or perianal disease without any bowel involvement. In those with atypical findings on endoscopy, with overlapping features of CD and UC, histology and small bowel imaging, can be helpful for a more accurate classification. Histological findings such as lymphocytic esophagitis, focal enhanced gastritis, epithelioid granulomas not associated with ruptured crypt favor a diagnosis of CD over UC.
On the other hand histological features can make differentiation difficult between colonic CD and UC difficult, such as endoscopic rectal sparing, isolated non-serpiginous gastric ulcers, transmural inflammation in acute severe colitis.

Comment 12: Line 123: revision here also
Reply 12: Cohort studies comparing the natural history of pediatric-onset vs. adult-onset IBD (CD and UC), confirms its more aggressive nature, with extensive anatomical involvement, rapid progression, and increased disease activity, despite greater immunosuppression use in children with IBD compared to adults

Comment 13: The term "IBD patients" must be replaced with the term "patients with IBD" **Reply 13:** Delay in diagnosis in patients with IBD should be avoided at all costs, as it associated with complicated disease behavior with and higher risk of surgery and linear growth loss 15.

Comment 14: The sentence at lines 135-7 needs correction to ensure clarity
Reply 14: Intestinal tuberculosis is the more frequently encountered in Asia compared to CD leading to widespread use of empirical anti-tubercular treatments leading to delay in diagnosis and complications such as stenosis, requiring intestinal. 22 Taken together increasing incidence of IBD in Asia, poor awareness, resource limitations and a higher prevalence of common IBD mimics, such as tuberculosis and amoebiasis are unique challenges facing pediatricians in Asia.

Comment 15: Lines 138-140 is repeated
Reply 15: Thanks for pointing that out, it is now omitted.

Comment 16: Lines 143-147 refers to immediate and medium goals but not long-term goals
Reply 16: Ultimately the long-term goals are to avoid complications such as growth failure, stricture, fistulae, surgery and hospitalization. Striving to achieve these goals have potential to prevent complications related to disease while minimizing adverse effects of the medications such as corticosteroids, that are not associated with deep remission.

Comment 17: Line 161: the first sentence appears to have a missing section
Reply 17: An appropriate treatment decision involves careful consideration of multiple prognostic factors. This includes the severity of disease at diagnosis, risk factors associated with disease progression, and the risk and benefits of treatments.

Comment 18: Bacterial names needs to written correctly (italicisied)
Reply 18: as Anti-Saccharomyces cerevisiae (ASCA) and Anti-flagellin (anti-CBir), early non-response to treatments were confirmed as poor outcome predictors in CD.

Comment 19: Lines 182/183 needs to be rewritten to ensure clarity
Reply 19: These lines have rewritten as per reviewers suggestion.. While the concept of MH is an intuitive and important but it is not a novel concept. Blood pressure targets in chronic hypertension and glycosylated hemoglobin in diabetes have been around for decades reinforcing the idea that a tight control of chronic disease, prevents end-organ damage. (Figure. 2)

Comment 20: lines 218/219: these doses are given without explanation. AZA would only be dosed at this level is TPMT activity was normal. MTX should only be dosed to a maximum of 25 mg weekly. Suggest to exclude specific doses to avoid confusion.

Further prednisone should only be dosed at 60 mg daily in the setting of IBD-associated liver disease. No data to support dosing above 40 mg daily in standard usage. Further, this summary is selective about the mention of immunomodulators: rather than implying that AZA and MTX are the only immunomodulators, the text should say something such as: Two examples are AZA and MTX. Also, MTX would traditionally be given as SC injection.

Reply 20: This section was rewritten incorporating suggested changes, Treatment options for CD can be divided into rapidly acting medicines, also known as induction therapies, and maintenance therapies First-line induction therapies in Pediatric CD include an exclusive liquid-based polymeric diet also known as exclusive enteral nutrition (EEN) for two months, or a two-month weaning course of oral prednisolone starting at 1 mg/kg with a maximum dose of 40 mg. EEN is widely accepted as the first-line therapy for pediatric Crohn's disease as it has no side effects, comparable clinical efficacy to control symptoms to that of corticosteroids and a greater ability to heal intestinal ulcers and nutritional benefits. 44,45 The two most common conventional maintenance therapies include immune-modulators such as azathioprine (2–2.5 mg/kg/day) and methotrexate 10−25 mg/m2 weekly). These agents are slow-acting and are primarily used to reduce the risk of relapses and minimize corticosteroid dependency.

Comment 21: Please correct line 225: this currently says that this drug should not be given in children with severe CD who also have perianal disease.

Reply 21: Thanks for pointing this out again, here is the revised version Anti-tumour necrosis factor (TNF) agents such as infliximab and adalimumab are fast-acting, highly efficacious agents used both for induction and maintenance therapy. Anti-TNF agents are currently used in children with CD after failing an adequate trial of steroids or exclusive enteral nutrition with or without concurrent use of conventional immune-modulators. Anti-TNF should be considered upfront in children with complex perianal fistula, deep colonic ulcerations, severe growth delay or in those with stricture or intestinal fistulising CD 44,46,47

Comment 22: line 238: does this drug act against multiple integrins or one specific integrin?

Reply 22: This is now corrected Vedolizumab (anti-α4β7 integrin) and oral small synthetic molecules such as Janus Kinas (JAK) inhibitors (Tofacitinib, Upadacitinib,Filgotinib) and oral sphingosine 1 phosphate 1 receptor (S1P) modulators

Comment 23: Line 256/257: an example might help here

Reply 23: Using trough drug levels of biological agents (pharmacokinetic monitoring) and combining them with surrogate biomarkers of mucosal inflammation such as CRP and FCP (Pharmacodynamics monitoring) are redefining how we can treat and manage IBD. For example, in a patient with CD who is on standard 5mg/kg/dose dosing of Infliximab(IFX) reporting GI symptoms suggestive of relapse, a good therapeutic decision would require both a pharmacodynamic and a pharmacokinetic information.

An elevated FCP provides a pharmacodynamic information about disease activity and a therapeutic trough level of IFX below < 3 μg/mL would suggest insufficient control of disease that could be related to pharmacokinetic failure. In these circumstances, increase dose of IFX is likely to benefit the patient. On the other hand, if the IFX trough levels were above 12 μg/mL it would be considered a pharmacodynamic failure and dose increase is unlikely to benefit the patient.

Comment 24: line 277-279: this sentence needs to be revised to ensure clarity.
Reply 24: Vaccination records, travel history and exposure to tuberculosis, should be checked prior to commencing biologics. All children newly diagnosed with IBD should have vaccination titers tested for hepatitis B and varicella. If the immunity to hepatitis B and varicella cannot be established, the child should have their vaccination schedule updated as soon as possible while on non-immunosuppressive treatments, such as EEN in Crohn's disease and 5-ASA in ulcerative colitis. Quantiferon for tuberculosis (TB) or tuberculin skin test should be performed prior to commencing immunomodulators and biologics due to higher risk of TB reactivation on anti-TNF's on all children with IBD regardless of history of non-exposure to TB. Once the child has started immunosuppressive agents and/or biologics, the use of live vaccinations (eg measles, mumps and rubella [MMR], varicella, yellow fever, BCG) is contraindicated and the response to non-live vaccinations, such as hepatitis B can attenuate. 57

Comment 25: It may be appropriate to refer to coronavirus in the infectious risk section (topical)
Reply 25: SARS-CoV-2 infection risk in patients with IBD is comparable to the general population. Outcomes of COVID-19-positive IBD patients are worse on steroids or 5-aminosalicylates but outcomes are better with biological agents.

Comment 26: A new paragraph could start at line 324
Reply 26: Accepted: Another important aspect of integrated care that is often forgotten is the emotional wellbeing of patients with IBD. Anxiety and depression are more common in patients with IBD when compared to the general population. Screening and prompt referrals to a psychologist should be considered at an early stage. Other aspects that affect patients with IBD are feelings of stress, poor self-image, drug-related side effects and dependent behaviors. It is important to equip patients with strategies to deal with some of these such as relaxation and breathing exercises, meditation, light exercise and also building a good support network around them. Finally, to achieve the best outcomes we should invest in a good quality of care that is inclusive, effective and integrated. 66

Comment 27: Table 1: This should comment that these are examples of conditions that could mimic IBD (rather a complete and exhaustive list). Italics for C diff
Reply 27: This is now reflected both in figure and text that these are some examples rather than a complete list

Comment 28: Figure 1: this implies that one can have patchy right sided disease in UC.
Reply 28: Authors was trying to explain milder disease gradient in the right colon but as this can be confused with patchy disease a new figure was created.

Comment 29: Figure 2 is hard to follow. Acknowledgements of the figures also required?
Reply 29: This figure was deleted as there are sufficient details in the text

Comment 30: Figure 3: the title is misleading and should be enhanced. The figure needs appropriate acknowledgement
Reply 30: This figure was original and not reproduced from any previous text, to avoid confusion it was simplified.