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Dear Editor,

Please find enclosed the revised manuscript in Word format

Comparison of the use of Wireless Capsule Endoscopy with Magnetic Resonance Enterography in Children with Inflammatory Bowel Disease

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Reviewer#02917331 comments

This is an interesting study written by Hijaz NM et al. The authors could show the performance of Wireless Capsule Endoscopy (WCE) with Magnetic Resonance Enterography (MRE) to detect the inflammatory lesions in Children on Inflammatory Bowel Disease. Several revisions are needed as follows.

Major comments 1. In Methods paragraph, details of PCDAI should be described.

I will enclose new table to be added in supplemental material for Pediatric Crohn's Disease Activity Index and to the end of the manuscript page 41.

Pediatric Crohn Disease Activity Index (From most recent visit)				
Score per element	0	5	10	Individual score
Abdominal pain	Abdominal pain: None	Mild- brief, does not interfere with activities	Mod/severe-daily, longer lasting, affects activities, nocturnal	
Stools per day	1-2 Formed or liquid stools, no blood	Up to 2 semi-formed with small blood, or 2-5 liquid	Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea	

Patient Functioning, General Well-being	No limitations of activities; well	Occasional difficulty in maintaining age appropriate activities; below par	Frequent limitation of activity; very poor	
Albumin	≥3.5	3.1-3.4	≤3.0	
Weight	Weight gain or voluntary weight stable/loss	Involuntary weight stable, weight loss 1-9%	Weight loss ≥ 10%	
Height	Height velocity ≥ -1SD	Height velocity < -1SD, > -2SD	Height velocity ≤ -2SD	
Abdomen Exam	No tenderness, no mass	Tenderness, or mass without tenderness	Tenderness, involuntary guarding, definite mass	
Perianal disease	None, asymptomatic tags	1-2 indolent fistula, scant drainage, no tenderness	Active fistula, drainage, tenderness, or abscess	
Extra-intestinal Manifestations (Fever ≥ 38.5 for 3 days over past week, definite arthritis, uveitis, E. nodosum, P. gangrenosum)	None	one	≥ Two	
Score per element	0	2.5	5	
HCT (%) Male 11- 14 years 15-19 years	≥35 ≥ 37	30-34 32-36	<30 <32	
HCT (%) Female <10 years 11-19 years	≥33 ≥34	28-32 29-33	<28 <29	
ESR	<20	20-50	>50	
Total PCDAI score				

PCDAI: Pediatric Crohn's disease activity index, HCT: hematocrit, ESR: erythrocyte sedimentation rate, SD : standard deviation.

2. Not all the enrolled patients received pathological examination. The methodology of pathological examination should be described.

I have included the pathological methodology table below in the in the supplemental material and to the end of the manuscript page 40.

The content of Histology section is changed to include epithelial damage in the active disease part and not chronic changes. This change is in section of histology page 11,Para 3, line 25. The histology grading table is included in supplemental material.

This histology grading is extracted from the NASPGHAN guidelines for diagnosing Crohn's disease and from adapted definition of mucosal healing and diagnosis guidelines. [27, 2]

Positive Histology		Negative Histology
1. Final impression: chronic active ileitis or duodenitis.		No chronic active ileitis or duodenitis.
2. At least one of chronic changes plus at least one of active disease:		Having chronic changes without active disease features
Chronic changes	Active disease	Having active changes without chronic disease features
Architectural changes of mucosal surface	Intraepithelial PMNs in surface epithelium	Acute focal changes
Crypt atrophy (shortened, widely spaced crypts)	Neutrophils in crypt epithelium or cryptitis	Eosinophilia of tissue alone
Distorted, dilated, branching crypts	Crypt abscess	
Moderate or severe lamina propria mononuclear cells	Focal or extensive epithelia damage	
Moderate or severe lamina propria PMNs	Granuloma or excess histiocytes in lamina propria or basal cell giant cells	
Basal plasmacytosis, increase in cells in basal third of lamina propria	Erosions/ulcers/microulcerations	

The histology grading in the available tissue in small bowel (ileum and duodenum).[2,27]

3. In Results paragraph, page 8 line 2, "DC or ID" should be corrected.

The change has been corrected to CD or IC in page 12 in the first line of results section.

Reviewer# 04025483 comments:

In this work, Hijaz and co-workers compared the diagnostic performance of magnet resonance enterography (MRE) and wireless capsule endoscopy (WCE) for the assessment of small bowel involvement in pediatric IBD patients. For this purpose, a total of 27 children, of which 20 had a diagnosis of Crohn's disease, were prospectively included and underwent MRE and WCE within a maximum of 7 days of each other. WCE was analyzed by two blinded readers and in 15 patient's histology from the terminal ileum and the duodenum was available. For analysis WCE and MRE findings and concordance between clinical disease activity (as assessed by the PCDAI) and histology was assessed. As their major finding, the authors found a sensitivity of MRE and WCE of 100% and 83% and a specificity of MRE and WCE of 57.14% and 78.6% for diagnosis of small bowel involvement in CD patients with clinical disease activity (PCDAI>10) Further, if the histology in ileum or/and duodenum was used as the reference for active small bowel involvement, WCE had a higher specificity as compared to MRE (83.3% vs. 50%) and WCE had an excellent concordance between the different readers. Minor concerns

- 1. The authors state that a PCDAI of >10 was used as an indicator for small bowel involvement. Can the authors provide some data/references to support their assumption that PCDAI>10 is indeed a marker of SB involvement and not only of disease activity in general (irrespective of disease location).**

We appreciate the limitation implied in our attempt to characterize the PCDAI as a surrogate marker for SI involvement, we expand on this limitation and provide our rationale in the discussion page 15, para 3 line 14.

"Because of the lack of standard criteria for confirming proximal SB CD activity that is feasible and less invasive in children, this study used two different references to compare MRE with WCE. The first was the PCDAI as a global clinical standard for overall disease activity may be associated SB involvement (SBI) and the second was pathological findings in the ileum and duodenum as histological standards for SBI. We have used PCDAI because the evidence suggested its moderate correlation with pediatric CD activity and endoscopic scores. [29,30]. PCDAI < 10 is the standard definition of inactive CD that is used in clinical trials for clinical response to medical therapies [29,30]. Pediatric onset CD runs a more aggressive active disease course, including more extensive disease location, more upper GI involvement and increased need for more aggressive medical therapy, in pediatric studies. [31,32,33] This is also replicated in adult studies; proximal small bowel involvement should be considered as high risk in terms of CD-related surgery. [34,35,36] In particular L4 (proximal SB not including TI) disease phenotype was associated with stricturing disease, and significantly increased risk for multiple surgeries [37,38]. Pediatric phenotypes of CD at the time of diagnosis showed 50.9% were affected by CD proximal to the terminal ileum in United Kingdom. [39.] In Europe, isolated ileal disease(L1) is reported to be 16% in CD children, or proximal to terminal ileal (L4) in 24% and esophagogastroduodenal (EGD) involvement in 30% [33] If pediatric CD mostly runs an aggressive and extensive course involving small bowel either in more than half of children, then using PCDAI can arguably be justified to reflect active small bowel disease. However, this is still a limitation in this study because it does not exclude the possibility of bowel disease activity overall and it is not validated to accurately reflect SBI compared to other invasive reliable standards."

Therefore and because of this limitation, we have provided the histology reference in the available small bowel disease biopsies that is accessible by endoscopy and available to subgroup of patients is additionally described in this manuscript.

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2. **The manuscript would benefit from figures showing a) concordant findings between WCE and MRE and b) disparate findings between MRE and WCE (e.g. positive MRE and negative WCE and also negative MRE but positive WCE). Please add.**
Images are enclosed and added in the manuscript page 33 at the end of the manuscript for All patients (CD and IC) and page 20 for CD only.

Thank you for your kind consideration of this manuscript, critical review and potential recommended acceptance.

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