

## ESPS PEER REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 13115

**Title:** Human cytomegalovirus and epstein-barr virus infection in inflammatory bowel disease: Need for mucosal viral load measurement

**Reviewer code:** 00041288

**Science editor:** Ya-Juan Ma

**Date sent for review:** 2014-08-06 13:42

**Date reviewed:** 2014-08-22 04:39

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

### COMMENTS TO AUTHORS

Congratulations on a well written and thought provoking study and manuscript. Comments below.

Abstract - Change "the risk factors" for "its risk factors". - Should it be ...endoscopic colon mucosal sample? - Would change to: No correlation between peripheral blood values and immunohistochemistry was identified. - Would change to: Steroid use was identified as a significant risk factor for both HCMV (P=0.018) and EBV (P=0.002) colitis. - Change to ...of mucosal specimens (throughout the manuscript). Key words - Change refractoriness for refractory. Core tip - Change "among" for "between". - Delete "Moreover". - Change to: ...loads, which correlated... - Change to: ...activity. EBV infection was most prevalent. - Change to: Steroid therapy was identified as a significant risk factor for viral colitis. Introduction - Change to: ...localized to the gastrointestinal tract. - Change to: ...majority of studies. Methods - Please change "blind pathologist" to "pathologist blinded to patient diagnosis and clinical disease status". - Was a power analysis performed? Results - Simply placing "(Table 1)" would suffice. - The tables should be placed at the end of the manuscript, not embedded in the text. - In table 1, an extra column should be added for the respective P values. - The "mucosal viral load" section is confusing. Please use more periods and avoid long and confusing sentences. - I would try to shorten and focus the results section and place most of the numbers and statistics in the tables. At times, I would get lost amongst the P and correlation values, scores, etc. Try to keep it easy to digest for the reader. - Were there any



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correlations between viral loads and the diseased anatomic site (i.e. ascending, descending, rectum, etc)? - Were both HCMV and EBV positive cells and DNA load >103 copies/105 cells considered as positive markers for active viral colitis? - What is the significance of positive serology and DNA load >103 in asymptomatic, healthy patients? This should be clarified in the discussion. - Replace "both viruses" with "HCMV/EBV colitis". - I would suggest replacing "Systemic steroids emerged as the main risk factor for" for "Systemic steroid use was identified as a significant risk factor for". - Replace "biological agents and topical steroids resulted positively related only to EBV" for "biologic agent and topical steroid use were significantly related to EBV colitis". - In general, data not shown should not be part of the results nor the discussion. - Why did only 1 patient receive Rituximab? - Change to: "worsening of the patient's". - What were the indications for colectomy? Discussion is good. Figures are great!



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**Title:** Human cytomegalovirus and epstein-barr virus infection in inflammatory bowel disease: Need for mucosal viral load measurement

**Reviewer code:** 00503587

**Science editor:** Ya-Juan Ma

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<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

**COMMENTS TO AUTHORS**

This manuscript focuses on the presence of viral agents in patients with and without IBD. Specific Comments: 1.The first sentence of the Abstract could be more precise. Do the authors mean in the pathogenesis of IBD or in the exacerbation of disease or other? 2. The word correspondence in the Abstract may be better replaced with correlation 3. There are some errors of English language use in the Abstract and elsewhere that should be corrected 4. in the Methods why is the word habitus in italics? 5. On page 6 (Methods) the word macroscopic is used incorrectly. This should read endoscopic - as the authors did NOT look at the surface of the bowel with their naked eyes, rather via the endoscope. 6. The definition of refractory is difficult to follow, and may incorporate many variables. 7. The authors define taking biopsies from involved and non-involved areas - how did they manage confluent disease (with no non-involved areas)? 8. Further, how did the authors consider pure ileal CD (with no colonic involvement)? 9. The Results should have subheadings throughout (the first sections lack these) 10. The details of the control subjects could be added to the Table 1 and taken from the text area 11. According to Table 1, patients were assessed as to their L4 involvement - yet according to the Methods no patients underwent upper endoscopy. This should be corrected/clarified 12. Did the authors consider a role for stool testing for these viral agents? This would be more rapid and less invasive. Similarly, were there any changes on peripheral bloods that were helpful (lymphocyte count etc)?



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**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 13115

**Title:** Human cytomegalovirus and epstein-barr virus infection in inflammatory bowel disease: Need for mucosal viral load measurement

**Reviewer code:** 00034127

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
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<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
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### COMMENTS TO AUTHORS

Excellent original work on the role of human CMV and EBV in mucosal lesions in refractory IBD.



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**Title:** Human cytomegalovirus and epstein-barr virus infection in inflammatory bowel disease: Need for mucosal viral load measurement

**Reviewer code:** 00503513

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input checked="" type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
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**COMMENTS TO AUTHORS**

The authors investigated CMV and EBV in tissue specimens of refractory and non-refractory mixed IBD patients by quantitative real-time PCR and immunohistochemistry. Additionally, the whole colon was mapped in order to correlated viral loads to endoscopic lesions. The main findings are: all refractory patients had viral loads over 1000 copies/10000 cells At least in INTRO additional risks of primary infections in immunocompromised subjects such as EBV-related lymphomas or the macrophage activation syndrome for both, CMV and EBV should be mentioned The paper is well written and, despite the small numbers of patients, should be published Minor points Page 6, line 17: I would prefer the term smoking habits Page 15, line 30: ...target is T cells should read target are T-cells