

ANSWERS TO REVIEWERS

Manuscript ID: ESPS Manuscript NO: 31367

Manuscript Title: Pseudopolyps in inflammatory bowel diseases: Have we learned enough?

Dear Editor,

We submit our revised manuscript, and we provide a point-by-point response to the comments made by the reviewers and we highlight the additions made in revised manuscript using colored text. We are very grateful to you for your valuable comments and to the reviewers for their valuable contribution.

Kind Regards,

Politis Dimitrios, MD

Department of Gastroenterology, University Hospital of Ioannina, Faculty of Medicine, School of Health Sciences, University of Ioannina

Answers to Reviewers' Comments to Author:

Reviewer 00043819:

Thank you very much for your so valuable comments that have helped to substantially improve our manuscript.

Please see below our point-by-point answers to your suggestions:

1) Following your suggestion we added the following paragraph at the end of the section of **Long term management** page 13 line 335 of the revised manuscript “*In the same context, the discovery of PP in a patient with IBD, without evidence of suspicious lesions in endoscopy and in which the presence of PP does not obstruct adequate endoscopic surveillance of the mucosa, should not urge gastroenterologists towards more intense endoscopic follow-up. Neither should it discourage them from the use of chromo-endoscopy for surveillance in any manner other than those proposed in the various guidelines (with an approximate 3-year interval), and certainly not in a different way than would be performed in patients without PPs^[54-56]. As mentioned before, CRC derived from PP is a rare event and occurrence of PP has not been linked with early CRC^[30]. Therefore, screening for CRC in all patients with PP is not recommended before 8-10 years after onset of symptoms^[54-56].*” about the

need and frequency of endoscopic follow-up of patients with PP and adding also the relevant references for justification.

Baars JE, Kuipers EJ, van Haastert M, Nicolai JJ, Poen AC, van der Woude CJ. Age at diagnosis of inflammatory bowel disease influences early development of colorectal cancer in inflammatory bowel disease patients: a nationwide, long-term survey. Journal of gastroenterology. 2012 Dec;47(12):1308-22.[PMID:22627504 DOI:10.1007/s00535-012-0603-2]

Cairns SR, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJ, Evans GD, Eaden JA, Rutter MD, Atkin WP, Saunders BP, Lucassen A, Jenkins P, Fairclough PD, Woodhouse CR; British Society of Gastroenterology; Association of Coloproctology for Great Britain and Ireland. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut. 2010 May;59(5):666-89. [PMID:20427401 DOI:10.1136/gut.2009.179804]

Annese V, Daperno M, Rutter MD, Amiot A, Bossuyt P, East J, Ferrante M, Gätz M, Katsanos KH, Kießlich R, Ordás I, Repici A, Rosa B, Sebastian S, Kucharzik T, Eliakim R; European Crohn's and Colitis Organisation. European evidence based consensus for endoscopy in inflammatory bowel disease. Journal of Crohn's & colitis. 2013 Dec;7(12):982-1018.[PMID:24184171 DOI:10.1016/j.crohns.2013.09.016]

American Society for Gastrointestinal Endoscopy Standards of Practice Committee, Shergill AK, Lightdale JR, Bruining DH, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, Early DS, Evans JA, Fanelli RD, Fisher DA, Fonkalsrud L, Foley K, Hwang JH, Jue TL, Khashab MA, Muthusamy VR, Pasha SF, Saltzman JR, Sharaf R, Cash BD, DeWitt JM. The role of endoscopy in inflammatory bowel disease. Gastrointestinal endoscopy. 2015 May;81(5):1101-21 e1-13.[PMID: 25800660 DOI:10.1016/j.gie.2014.10.030]

2) We have removed the phrase “*There is no*” at the beginning of the section **Long term management** and have replaced it with the phrase “*Questions remain about*” page 12 line 296 of the revised manuscript for avoiding absolutism

3) We have removed the sentence “*There are different approaches, including referral to endoscopists specialized in IBD, segmental colon removal, routine surveillance of mucosa and finally removal of all suspicious lesions*” from the first paragraph of the section **Long term management** in the original manuscript in order to avoid creating confusion in the readers about the way of monitoring patients with PP and removed the relevant reference “*Itzkowitz SH, Present DH, Crohn's, Colitis Foundation of America Colon Cancer in IBD SG. Consensus conference: Colorectal cancer screening and surveillance in inflammatory bowel disease. Inflammatory bowel diseases. 2005 Mar;11(3):314-21.[PMID:15735438 DOI:10.1097/01.MIB.0000160811.76729.d5]*” was also removed

4) We have added the phrase “*or presence of multiple PP wherein endoscopic surveillance is compromised*” at the fourth paragraph of the section of **Long term management** page 13 line 331 of the revised manuscript in order to distinguish the group of patients with multiple pseudopolyps, where diagnostic endoscopy could be challenging and demand different approach for monitoring and we added the following reference for enhance justification at the end of the phrase “*multiple biopsies should be obtained in repeated examinations*” in the same paragraph page 13 line 333 “*American Society for Gastrointestinal Endoscopy Standards of Practice Committee, Shergill AK, Lightdale JR, Bruining DH, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, Early DS, Evans JA, Fanelli RD, Fisher DA, Fonkalsrud L, Foley K, Hwang JH, Jue TL, Khashab MA, Muthusamy VR, Pasha SF, Saltzman JR, Sharaf R, Cash BD, DeWitt JM. The role of endoscopy in inflammatory bowel disease. Gastrointestinal endoscopy. 2015 May;81(5):1101-21 e1-13.[PMID: 25800660 DOI:10.1016/j.gie.2014.10.030*”

5) Following your suggestion we have polished the language of the manuscript

Reviewer 02529197:

Thank you very much for your so valuable comments that have helped to substantially improve our manuscript.

Please see below our point-by-point answers to your suggestions:

- 1) Following your suggestion we have removed the following in order to decrease the number of references without changing the critical content of the manuscript
 - From the first paragraph of the section **Definitions and mechanisms of formation** we have removed the sentence “*The term PP has prevailed although is regarded a misnomer because they are true polyps*” and the relevant reference “*Ferguson CJ, Balfour TW, Padfield CJ. Localized giant pseudopolyposis of the colon in ulcerative colitis: Report of a case. Diseases of the Colon & Rectum. 1987;30(10):802-4.[PMID:3652893 DOI:10.1007/BF02554631]*” was also removed for not adding significant academic content to the manuscript
 - From the first paragraph of the section **Definitions and mechanisms of formation** we have removed from the end of the sentence “*taking their shape from the elongation of mucosal tags from the bowel’s peristalsis and the stream of feces*” page 7 line 159 of the revised manuscript the following reference “*Yada S, Matsumoto T, Kudo T, et al. Colonic obstruction due to*

giant inflammatory polyposis in a patient with ulcerative colitis. Journal of gastroenterology. 2005 May;40(5):536-9.[PMID:15942721 DOI:10.1007/s00535-004-1580-x]” and we have replace it with the reference “*Kelly JK, Langevin JM, Price LM, Hershfield NB, Share S, Blustein P. Giant and symptomatic inflammatory polyps of the colon in idiopathic inflammatory bowel disease. The American journal of surgical pathology. 1986 Jun;10(6):420-8.[PMID:3717497 DOI:10.1097/00000478-198606000-00007]*” as both contain similar context

- From the second paragraph of the section **Histology** we have removed the sentence “*As Balazs et al [11] pointed out, mast cells play significant role for maintaining and extending the inflammation, influencing vascular flow and promoting fibroblast growth*” and we have corrected the mismatch in the references section at the original manuscript. We added at the end of the first paragraph of the same section page 7 line 168 of the revised document the reference “*Jalan KN, Walker RJ, Sircus W, McManus JP, Prescott RJ, Card WL. Pseudopolyposis in ulcerative colitis. Lancet. 1969 Sep 13;2(7620):555-9.[PMID:4185531 DOI:10.1016/S0140-6736(69)90260-8]*” and we added at the end of the second paragraph of the same section page 8 line 179 of the revised document the reference “*Buck JL, Dachman AH, Sobin LH. Polypoid and pseudopolypoid manifestations of inflammatory bowel disease. Radiographics : a review publication of the Radiological Society of North America, Inc. 1991 Mar;11(2):293-304.[PMID: 2028064 DOI:10.1148/radiographics.11.2.2028064]*” for proper justification
- From the first paragraph of the section **Prevalence of PP in IBD** in the original manuscript at the end of phrase “*They are found more often in UC than in CD*” page 9 line 219 of the revised document, we have removed the reference “*Chew MH, Goh MH, Ooi BS, Eu KW. Giant pseudopolyposis in Crohn's disease mimicking malignancy. International journal of colorectal disease. 2008 Aug;23(8):823-4. [PMID:18461338 DOI:10.1007/s00384-008-0475-3]*”, as it was considered pleonasm.
- From the first paragraph of the section **Long term management** in the original manuscript we have removed the sentence “*There are different approaches, including referral to endoscopists specialized in IBD, segmental colon removal, routine surveillance of mucosa and finally removal of all suspicious lesions*” in order to avoid creating confusion in the readers about the way of monitoring patients with PP and we have removed the relevant reference “*Itzkowitz SH, Present DH, Crohn's, Colitis Foundation of America Colon Cancer in IBD SG. Consensus conference: Colorectal cancer screening and surveillance in inflammatory bowel disease. Inflammatory bowel diseases. 2005 Mar;11(3):314-21.[PMID:15735438 DOI:10.1097/01.MIB.0000160811.76729.d5]*”

- From the second paragraph of the section **Long term management** we have removed the sentence “*This fact also applies to GPP*” from the original manuscript as it were considered pleonasm and the following relevant reference “*Jones B, Abbruzzese AA. Obstructing giant pseudopolyps in granulomatous colitis. Gastrointest Radiol. 1978 Oct 1;3(4):437-8.[PMID:729994 DOI:10.1007/BF01887109]*” was also removed
- From the third paragraph of the section **Treatment** we have removed the phrase “*or total colectomy*” as it was considered pleonasm and the relevant reference “*Bryan RL, Newman J, Alexander-Williams J. Giant inflammatory polyposis in ulcerative colitis presenting with protein losing enteropathy. Journal of clinical pathology. 1990;43(4):346-7.[PMID:2341571 DOI:10.1136/jcp.43.4.346-b]*” was also removed

We have removed 6 references from the original manuscript and the total number of references was reduced to 83 from 89.

- 2) Following your suggestion we have polished the language of the manuscript