To the Editorial Office of *Annals of Gastroenterology,*

Ioannina, 25 April 2012

Dear Prof Koutroubakis,

Please find attached our manuscript entitled “**ELECTROLYTE AND ACID-BASE DISORDERS IN INFLAMMATORY BOWEL DISEASE**” revised according to the Reviewers’ and Section Editor’s comments. All changes are highlighted in yellow in the revised text. At this point we would like to thank the Reviewers for their constructive comments.

Specifically,

**According to Reviewer A:**

**1)** *This review article although thorough is not well written and it is very
difficult for the reader to follow it and understand it. Given the
difficulty of the subject itself and the limited knowledge that most
gastroenterologists have on these issues, I believe that the article should
be written in a more simple and comprehensive way. Apart from this the
bibliography is not uptodated as should be the case in an invited review
article.*

We now divide the chapter 'Electrolytic disorders in inflammatory bowel disease' into 2 sections: (a) Electrolytic disorders in ulcerative colitis(page 6; line 5 - page 10; line 2) and (b) Electrolytic disorders in Crohn's disease (page 10; line 3 - page 11; line 8). We now believe that it is easier for the reader to follow.

Unfortunately, there are few new references on this topic. This is why the bibliography seems outdated.

**According to Reviewer B:**

We would like to thank the Referee for his/her kind comments.

**1)** *Page 4, line 4 to page 5 line 8: section “Electrolyte transport in the
mammalian colon (or probably more appropriately… in the normal gut)”
 General issues. The physiological mechanisms of electrolyte absorption and secretion and the specific transporters (? Where exactly are they located) should be mentioned and categorized / enumerated more clearly what is the case with a. sodium, b. potassium, c. chloride, d. bicarbonate, e. calcium and magnesium transport.*

*The same care should be taken to clarify the meaning and significance of PD
and electrochemical transport, especially in the light of the fact that
active Na+ resorption is an electrogenic process and a principal
contributor of mucosal PD, practically directing Cl- and HCO3- transport
along a favourable PD gradient (Sandle et al, Gut 1986). The authors should
briefly elaborate on these issues instead of alluding to them
telegraphically as is the case in the phrase: “This can be electrogenic
….Cl-/HCO3-exchange”.
The authors should always keep in mind that they are
addressing an audience that may not be, or at least no longer is, quite
familiar with these issues.*

We have corrected the title into ‘Electrolyte transport in the normal gut’ (page 4; line 4). In addition, we further analyze the physiology, location and biochemical mechanisms of each electrolyte transport in the colon [page 4; line 12 - page 6; line 3 and new references [9]-[18)]

**2)** *Page 5, line 9 to page 8, line 19: section “Electrolyte (or better
electrolytic) disorders (…in Inflammatory Bowel Disease)”*

We corrected the title ‘electrolyte disorders’ into ‘electrolytic disorders’ (page 6 line; 4)

**3)** *General issues. This section of the manuscript is quite long without
any clearly discernible sub-division of entities in terms of separate
electrolyte disorders in terms of a. UC and b. CD and as result it can be
quite an effort to go through.*

*There appears to be some backwards and forwards
movement in the discussion of specific electrolytic disorders (…first
sodium then potassium and then again a study on sodium…) that might get
the reader a bit confused.*

Indeed this section seems somewhat long. However, we aimed to quote all studies and come to a conclusion basing on their results.

We now divide the chapter 'Electrolytic disorders in inflammatory bowel disease' into 2 sections: (a) Electrolytic disorders in ulcerative colitis(page 6; line 5 - page 10; line 2) and (b) Electrolytic disorders in Crohn's disease (page 10; line 3 - page 11; line 8). We now believe that it is easier for the reader to follow.

Of note, each study investigated all electrolyte disorders. This is the reason why there appears to be some backwards and forwards in the discussion of specific electrolytic disorders.

**4)** *Point-by-point comments. Page 5, line 18 – line 20: “Thus, …UC features” : apparently the authors allude to malabsorption of Na+ with the subsequent same-directional water efflux that is not quite obvious the way it is stated here. On the other hand no relevant literature is mentioned in such a key issue of the review.*

The referee is right; we have added more data from the Edmonds et al study (page 6; lines 12-17) to make underlying mechanisms more obvious. The respective bibliography has been added (ref. [29]).

**4)** *Page 5, line 20 – line 22: “In contrast …normal”: again a very important issue not supported by any bibliographic quotations.*

The relevant reference has been added. (Ref [29], page 7; line 1)

**5)** *Page 5, line 22 – page 6, line 2: “On the other hand … excessive” : not clear, should be explained better.Bibliographic quotation missing here as well.*

It is now explained more clearly (page 6; line 19 - page 7; line 1). The relevant bibliography has been added (Ref [29], page 7; line 1)

**6)** *Page 6, lines 11 – 14: “Of note …inflammation”: should be phrased in a different manner as its meaning is quite elusive as it is (is electrolyte malabsorption inflammation-related or not?).*

It has been rephrased so as to better explain the positive effect of glucocorticoids on the electrolyte disorders in ulcerative colitis (page 11; lines 10-17)

**7)** *Page 7, lines 8-14:”Increased … in UC.”: it is not clear what the effect of IBD is on PGE2 and how that translates into electrolyte malabsorption.*

An earlier study of the same group has been added, in which the inhibition of large intestinal salt and water absorption by enhanced local mucosal prostaglandin (PG) synthesis was tested (page 8; lines 14-16). They concluded that despite rectal PGE2 being increased in ulcerative colitis, it was not the reason of electrolyte malabsorption. Changes have been made in order this to be clearer (page 8; lines 20-24).

**8)** *Page 7, line 20 to page 8 line 6: “In another study … healthy subjects”: it is not quite clear how the osmolality data translate into clinical outcome in the setting of IBD (more diarrhea? more electrolytic malbsorption?). Also the data on the effect of CS and or sulfasalazine treatment on electrolytes should probably be better discussed in the same paragraph instead of being dispersed into different parts of the manuscript.*

Vernia et al used osmolarity measurements to test if organic anions, such as lactic acid, lactate and short-chain fatty acids, contributed to the diarrhea of inflammatory bowel disease. As this is not relevant to our topic we decided not to report on osmolality measurements (page 9; line 9 and lines 18-19).

We now add a separate section on the effect of IBD treatment on electrolyte homeostasis (page 11; line 9 - page 12; line 18).

**9)** *Page 8, line 15: “In addition, calcium and magnesium…”: in this part that concludes the “electrolytic imbalance” section magnesium is being mentioned without any previous discussion of that particular electrolyte apart from a quite general reference in the first paragraph of the section on generalized electrolytic malabsorption that includes Mg2+.*

Unfortunately, no further articles on the homoeostasis of Mg2+ in IBD could be found.

**10)** *Page 8, line 21 to page 10, line 14: section on “IBD and acid-basis homeostasis (not homoeostasis)*

Done (page 13; line 5)

**11)** *Page 8, line 24: “…the amount of intestinal gas”: how is that measured / quantitated in the relevant studies?*

We decided to delete ‘the intestinal gas’ as it seems to have no relevance with our topic (page 13; line 9).

**12)** *Page 9, line 1: “..fecal water…”: better fecal fluid.*

The term ‘fecal water’ has been replaced with ‘fecal fluid’ (page13; line 10).

**13)** *Page 9, line 8 to line 10: “On the other hand … colitis”: why do we go back to potassium concentrations in the acid-base balance section? How does that sentence fit in the corresponding paragraph and what exactly is the point it alludes to?*

The referee is right. This sentence has been mistakenly added in this section. Therefore, it has been deleted (page 13; lines 14-19) and a rephrase has been added (page 13; lines 19-21)

**14)** *Page 9, line 14: “… luminal (mucosa) pH values were higher in (the) CD group..’*

The respective changes have been made (page 13; lines 22, 23 and page 14; line 2)

**15)** *Page 9, lines 17 to 19: “In other studies … volunteers”: which part of the bowel do these studies refer to?*

We now discuss the part of the colon which these studies refer to (page14; line 6).

**16)** *Page 9, lines 19 to 21: “Moreover … luminal pH”: this sentence is probably contradictory to what has been stated so far on IBD and luminal pH. Is that actually shown in the same studies (ref. numbers 52-54) that were quoted in the previous sentence that states an opposing observation?*

The referee is right. Ewe et al study has been misplaced with the other studies of which the findings were opposite. We now present these findings in a different paragraph (page 14; lines 8-10, ref. [62]).

**17)** *Page 11, line 4: “… bicarbonate secretion of the colon when it is not affected.”: or is it of the affected colon?*

The referee is right: it is actually of the affected colon (page 15; line 18).

**According to Section Editor:**

**1)** *CD and UC despite being considered as part of a single spectrum of diseases are fundamentally different diseases regarding their distribution in the gastrointestinal system, the nature of the inflammatory infiltrate, and the depth of the inflammation in the intestinal wall. This is at least in part due to different nature of luminal triggering factors and their varying handling by the intestinal neuroimmune system under the control of different genetic factors. Therefore, electrolytes and acid-base disorders should be presented separately for small bowel (and/or right colonic) CD and colonic CD/UC. In each part, the reader should have a clear view of how these pathogenetic mechanisms affect homeostasis both in the active state and during remission of disease.*

We now divide the chapter 'Electrolytic disorders in inflammatory bowel disease' into 2 sections: (a) Electrolytic disorders in ulcerative colitis(page 6; line 5 - page 10; line 2) and (b) Electrolytic disorders in Crohn's disease (page 10; line 3 - page 11; line 8). We now believe that it is easier for the reader to follow.

Of note, not all of the studies present available data of electrolytic disorders during remission of disease.

**2)** *The influence of treatment (5-ASA, corticosteroids, traditional immunomodulators, and anti-TNF alpha biologicals) should be presented.*

We now add a separate section on the effect of IBD treatment on electrolyte homeostasis (page 11; line 9 - page 12; line 18).

**3)** *Smoking is a dominant environmental factor in CD and UC and is known to exert many effects on the elements that consist the intestinal barrier. Are there any data regarding the effect of smoking on electrolyte and acid-base disorders in IBD?*

No bibliography could be found on the effect of smoking on electrolyte and acid-base disorders in IBD except for one reference on the effect of smoking on hypocalcaemia. (page 11; line 8)

**4)** *References should be updated*

Unfortunately, there are few new references on this topic. This is why the bibliography seems outdated.

We do hope that the revised manuscript now meets your requirements.

Yours sincerely,

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