

Reply to reviewers

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Title: Inflammatory bowel disease and airway diseases

Reviewer 1 comment

I have read with interest the paper by Vutcovici et al. which is focused on a rather unknown but yet important and stimulating topic in IBD. The review is complete and updated. Since the association of NOD2 with Crohn's disease is the most relevant genetic observation in IBD, I think that the observation that similar mutations are observed in COPD would deserve more comments, also focused on the role that this mutation may have in bacterial recognition.

Reply

The authors thank the reviewer for the appreciative comments regarding the manuscript and for suggesting a more detailed discussion of the role of NOD2 mutations. We have expanded the discussion of genetic factors to include the role of NOD2 mutations in bacterial recognition.

Reviewer 2 comment 1

This is a nicely written manuscript that reviews the literature for epidemiologic and etiopathogenesis association between IBD and airway diseases. The authors attempt to find similarities between IBD and airway diseases and state that they focus on "IBD occurrence in patients with airway diseases". Major comments: 1. The review should begin with the last section that actually describes the epidemiological occurrence of IBD in patients with airway diseases and only after this section the authors should discuss the similarities between the diseases.

Reply

We understand the reviewer's point of view regarding the order of the manuscript sections; however, since the possibility of a two-way association between IBD and airway diseases is a new concept, we believe the paper is easier to follow if the biologic plausibility is addressed before the evidence from epidemiologic studies. Furthermore, we included only a brief discussion of the similarities in risk factors and pathogenesis, to provide the context for the epidemiologic findings.

Reviewer 2 comment 2

As the authors state- this is the actual topic of the review and therefore it should be more detailed and findings that are nicely put in the table should be thoroughly discussed and referred to in the rest of the manuscript. For instance, in the two largest studies that evaluated the occurrence of asthma in IBD, one of the studies demonstrated an association with UC while the other did not.

Reply

We thank the reviewer for pointing out that some of the results in the Table were not addressed in the discussion. We have expanded the manuscript to address the omitted results.

Reviewer 2 comment 3

2. Despite the comprehensive review of the literature, the message of the review is not entirely clear and in some sections, statements are too general and more details are required. It would be more convincing to try and discuss common pathways that may drive both diseases rather than looking at general similarities that may be true also other disease such as skin and rheumatic diseases. Is there a common pathogenesis between airways diseases and IBD? This should be discussed with regard to each of the airway diseases that have been associated with IBD (asthma, COPD and bronchiectasis) and not mentioned in a general manner. For instance, are there common dysbiotic bacteria? Are there common immunological pathways? Can these support the greater association of asthma with CD as opposed to UC?

Reply

Unfortunately, no common pathways in the pathogenesis of IBD and airway diseases have been demonstrated yet. We agree with the reviewer that this is an important aspect, one that would strengthen the discussion regarding the airway disease-IBD association. Further studies are needed for the identification of common pathways.

Reviewer 2 comment 4

Minor comments: 1. The hygiene theory should be mentioned as a model that tries to explain the surge in asthma and IBD.

Reply

We have expanded the discussion to include the hygiene hypothesis.

Reviewer 2 comment 5

2. Page 4- Pathogenesis- "Autoimmunity is yet another characteristic that IBD..."- IBD is not considered an autoimmune disease, but a disease that is characterized by immune dysregulation.

Reply

We thank the reviewer for the comment. We have removed the statement from the manuscript.

Reviewer 2 comment 6

3. Page- 6- Airways disease in IBD- "It is estimated that 40-60% of IBD patients have some degree of subclinical lung involvement". This is based on references from more than 10 years ago. Are there more recent data? What is the degree of subclinical lung involvement in the general population? And most important- what is the clinical significance of these associations?

Reply

We have updated the references to include two more recent studies addressing the prevalence of subclinical pulmonary injury in IBD patients. To our knowledge the degree of subclinical involvement in the general population has not been assessed, but the clinical significance of airway injury in IBD patients has been discussed in the works of Yilmaz et al. (Pulmonary involvement in inflammatory bowel disease. World J Gastroent. 2010;16(39):4952-7), Spira et al. (Large airway disease

associated with inflammatory bowel disease. Chest. 1998;113(6):1723-6), Mahadeva et al. (Clinical and radiological characteristics of lung disease in inflammatory bowel disease. Eur Respir J. 2000;15(1):41-8) or Mohamed-Hussein et al. (Changes in pulmonary function in patients with ulcerative colitis. Respir Med. 2007;101(5):977-82). It is recommended that respiratory manifestations in IBD should be treated early, before irreversible damages to the airway wall occur. Likewise, the early detection of IBD may improve the treatment management and prognosis of airway disease patients, as mentioned in the Conclusions section of the manuscript.

Reviewer 2 comment 7

4. Page- 7- Airways disease in IBD- The authors should at least mention the IBD medications that are associated with lung diseases (e.g. sulfasalazine, methotrexate, etc) and what is their clinical manifestations.

Reply

We thank the reviewer for his suggestion. We have included the information related to IBD medication in the manuscript.

Reviewer 2 comment 8

5. The authors mention that exposure of animals to air pollutants may be associated with increased intestinal permeability, but are there animal models of airway diseases that support increased tendency to develop actual enteritis and vice versa- has there been shown that in animal models of colitis there is an airway injury?

Reply

To date there have been few studies addressing the association between exposure to air pollutants and digestive diseases, however, the relationship between colitis and airway injury, both overt and subclinical, has been described in clinical studies. We have summarized the evidence in our manuscript section entitled "Airway diseases in IBD".

Reviewer 2 comment 9

6. Are there any recommendations to the clinician- in terms of screening for IBD in patients with airways diseases or vice versa?

Reply

This is a very important question. If the airway disease-IBD association, described so far in population-based studies, will be confirmed in clinical settings as well, we strongly believe that a recommendation for IBD screening in airway disease patients who present with digestive symptoms indicative of IBD should be issued. As for the reverse association, between IBD and subsequent airway involvement, the diagnosis and treatment of airway injury in IBD patients could prevent irreversible damages to the airway wall, as discussed in the works of Yilmaz et al. (Pulmonary involvement in inflammatory bowel disease. World J Gastroent. 2010;16(39):4952-7), Spira et al. (Large airway disease associated with inflammatory bowel disease. Chest. 1998;113(6):1723-6), Mahadeva et al. (Clinical and radiological characteristics of lung disease in inflammatory bowel disease. Eur Respir J. 2000;15(1):41-8) or Mohamed-Hussein et al. (Changes in pulmonary function in

patients with ulcerative colitis. *Respir Med.* 2007;101(5):977-82).

Reviewer 2 comment 10

7. Should IBD patients who are about to be treated with medications that may compromise the airways, undergo pulmonologic evaluation?

Reply

To date, in Canada pulmonology evaluations/lung function tests are not included in the IBD clinical management guidelines. We agree that this is an issue that should be taken under consideration.

Reviewer 2 comment 11

8. Are there specific recommendations to patients who are about to be treated with anti-TNF agents, especially in the setting of cigarette smoking and Crohn's disease. It has been demonstrated that anti-TNF may be harmful for patients with COPD.

Reply

There are guidelines related to anti-TNF treatment and lung conditions but they address the screening for latent tuberculosis infection and its treatment prior to initiation of anti-TNF therapy. However, smoking cessation counselling is one of the recommendations included in the guidelines for the management of both CD and UC (where the risks associated with tobacco smoking outweigh the benefits of a less severe UC course in active smokers).

Reviewer 3 comment

The article is a concise and practical review and introduces innovative concepts to gastroenterological clinic, arousing the interest in the research of the interaction between the respiratory and digestive immune mucosal systems and its possible clinical consequences. I would suggest that the authors could include a discussion about this mucosal interrelation observed and published by our research group in patients with IBS. This subject is a future challenge for clinical science: Soares, R. L., Figueiredo, H. N., Santos, J. M., Oliveira, R. F., Godoy, R. L., & Mendonça, F. A. (2008). Discrepancies between the responses to skin prick test to food and respiratory antigens in two subtypes of patients with irritable bowel syndrome. *World Journal of Gastroenterology*: WJG, 14(19), 3044–3048. <http://doi.org/10.3748/wjg.14.3044> Soares RL, Figueiredo HN, Maneschy CP, Rocha VR, Santos JM. Correlation between symptoms of the irritable bowel syndrome and the response to the food extract skin prick test. *Braz J Med Biol Res.* 2004;37:659–662. Soares RL, Figueiredo HN, Moreira Filho PF, Oliveira RF, Gonçalves CD, Micuci AJQR, Parada BA, Brandão IB, Rodrigues CC. The prevalence and clinical characteristics of atopic manifestations in patients with irritable bowel syndrome in a Brazilian urban community. *Gastroenterol Ins.* 2010;2:p. e11.

Reply

The authors thank the reviewer for the appreciative comments regarding the manuscript and for the suggested references. However, as our manuscript targets the IBD-airway disease association, we believe that expanding the discussion to include IBS and atopic conditions might confuse the readership and dilute the message of the paper.