The Reply to Reviewer Comments

Dear Professor,

I have made revision one by one in accordance with the reviewer's comments and replied one by one as followings. The revised parts have been marked in red in the manuscript. And the proof of this language embellishment was provided as well. I'm very sorry for the delay. I am deeply grateful for your help. Thank you very much again.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: I read with interest the review by Changzhen Zhu et al. about CIPO. The manuscript is well written and updated. I have just minor comments

1. In the epidemiology section, I suggest to mention data about the prevalence of the idiopathic against the the genetic and secondary cases of CIPO.

Response: Dear Professor, I will give you a more detailed description of the incidence rate according to your suggestion. I hope this revisement will meet your requirements.

2. Regarding the diagnosis, I do disagree about the role of manometry. Intestinal manometry can be useful to define the pathophysiological (neuro-muscular) mechanisms involved in CIPO (e.g. neuropathy or myopathy), although it has a low diagnostic specificity. Intestinal manometry can differentiate mechanical from functional forms of sub-occlusion, provided that the organic cause is at the early stage. (Stanghellini V et al. Gut 1987, Chronic idiopathic intestinal pseudo-obstruction: clinical and intestinal manometric findings. Fell JME et al Gut 1996, Fell J M , Smith V V , Milla P J . Infantile chronic idiopathic intestinal pseudo-obstruction: the role of small intestinal manometry as a diagnostic tool and prognostic indicator.[J]. Gut, 1996, 39(2):306-311. Cucchiara S et al. JPGN 1994. Antroduodenojejunal manometry in the diagnosis of chronic idiopathic intestinal pseudoobstruction in children.)

Response：The expression of "the role of gastrointestinal manometry in diagnosis" is not accurate. In fact, to some extent, gastrointestinal manometry can differentiate the pathological types of CIPO, which were mentioned in the literature you provided, such as "felljme et al gut 1996" and "Cucchiara s et al. Jpgn 1994". This mistake was caused by my careless reading of the literature. I appreciate your advice very much. I have revised it in the manuscript.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

A. General Comments:

1. The article needs English language correction in several places.

Response: In accordance with your suggestion, I have once again asked native speakers of English to polish the language and revise the grammar. Please see the attachment for the proof of language embellishment.

2. A better description of the clinical picture and the mode of presentation of the disease is advised.

Response: According to your suggestion, I described the clinical symptoms in more detail. Hope to meet your requirements.

3. Authors should pay more attention in the differential diagnosis of CIPO.

Response: Dear Professor, thank you very much for your constructive suggestions. I have consulted all the literatures in recent years, but I have not seen any specific diseases that can be differentiated from CIPO. However, I think your suggestion is quite correct. Therefore, I emphasized the difficulty of diagnosis of CIPO at the end of clinical symptoms, in order to arouse the attention of readers.

B. Major Comments:

1. (Page 4, Line 16): Besides mentioning only frequency of symptomatology, authors should describe the actual clinical presentation of a CIPO patient, eg usual mode of presentation, preceding symptoms, quiescent intervals if any, acute symptoms, etc.

Response: According to your second suggestion in "general comments", I described the clinical manifestations of CIPO in more detail. At the same time, it has been modified according to your suggestion. Hope to meet your requirements. Thank you very much for your advice.

2. (Page 4, Line 20): What type of abdominal pain? Colicky? Persistent? Nocturnal? Postprandial? Generalized? Localized?

Response：I'm sorry I didn't describe the nature of the pain in detail. I have made changes in the manuscript according to your requirements. I hope it can meet your requirements.

3.(Page 4, Line 21): This sentence needs further clarification.

Response：Dear professor , according to your second suggestion in "general comments", I described the clinical manifestations of CIPO in more detail. I reread the literature and rewrite this sentence in manuscript. Hope to meet your requirements. Thank you very much for your advice.

4.(Page 4, Line 22): Do the authors imply that a symptom-free interval may last for several months?

Response：Dear Professor, I'm very sorry that I didn't make this sentence clear. I made some changes in the manuscript, " Sub-occlusive episodes can strike in apparently healthy people, but the onset of CIPO is generally insidious, with gastrointestinal symptoms which precede the first acute episode and these symptoms worsened significantly in during acute episodes, which can last only a few hours. In the acute interphase, the patients are very rarely asymptomatic or persistent gastrointestinal obstruction. The frequency and severity of acute and intermittent exacerbations is the unpredictable, no detectable causation and vary widely from patient to patient."

5.(Page 4, Lines 25-26): How often the urinary symptoms precede the GI ones? How common are urinary tract infections in CIPO? Gall bladder dilatation? Cholelithiasis?

Response：Thank you very much for your advice. I reread the literature and clarify the problem: The megacystis can be associated with a microcolon, a phenotype referred to as megacystis-microcolon-intestinal-hypoperistalsis syndrome (MMIHS), which is considered to be the most severe form of CIIP and onset is antenatal period. Namely megacystis and megaureter, often evident at birth, may also be detected prenatally by ultrasound imaging up to 59% of CIPO. Analysis of published studies has shown that most patients of CIIP develop symptoms in the first year of life, often in the neonatal period. Therefore, urinary tract symptoms precede gastrointestinal symptoms for about a year. As for the frequency of urinary tract infection, gallbladder dilatation, cholelithiasis, I have looked up the literature carefully again, and found no relevant data.

6.(Page 5, Line 1): Why the correct diagnosis of CIPO is so much delayed and its misdiagnosis so common? The authors must expend more on that point, either in this or in another section of their review.

Response：Since other reviewers have also made a lot of suggestions on this clinical manifestation, I almost rewrote this part. As I wrote in the manuscript. I hope this modification can meet your requirements. Thank you again for your advice.

7.(Page 5, Line 1-Diagnosis): A note of similarities, differences and possible coexistence between CIPO and Hirschsprung's disease should be made somewhere in the text.

Response：Thank you very much for your constructive comments. These two diseases are easily confused with each other. I mentioned this in CIPO classification and pathology, namely hirschsprung's disease is caused by dysplastic disorders of the enteric nervous system, belongs to intestinal neuropathy, which is one of secondary diseases of CIPO, which I put at the end of pathology of CIPO,

8.(Page 6, Line 4): After mentioning all the pros and cons of the diagnostic methods in CIPO, what is the authors conclusion? How the diagnosis of CIPO can be established without any doubt?

Response：Dear Professor, thank you very much for your advice. I really lack a summary in this part. I've perfected this in the manuscript: “The establishment of CIPO was mainly based on clinical manifestations, as well as extensive intestinal dilatation, multiple gas-liquid levels supported by imaging findings and abnormal intestinal manometry, after exclusion of mechanical obstruction caused by occupying lesions detected by imaging or endoscopy must be excluded. In addition to the above purpose, diagnostic examination should also be as clear as possible the potential pathogenesis of CIPO and pathogeny, such as full-thickness biopsies.”

9.(Page 8, Line 28): Authors should mention the use of prealbumin, as a marker of malnutrition, in the context of evidence described in the article Am J Med 2015;128:1023.e1-22.

Response：Dear Professor, thank you very much for your advice. I have made corrections in the manuscript.

10.(Page 10, Line 1): The authors refer to a “lifetime” or to “annual” morality rate?

Response：This ratio refers to the proportion of deaths related to "PN complications" during the follow-up period of both studies. In one study, after 10 years of follow-up, 13 of 85 patients died of parenteral nutrition complications (15.29%). In another study, the median follow-up time was 85 months. Five out of 105 patients died of parenteral nutrition complications (4.7%). So it shouldn't be " annual ". I didn't make it clear. I am so sorry and I have made corresponding revisement in the manuscript.

C. Minor Comments:

1. (Page 3, Line 6): Do authors mean “1 per 40,000 births?”

Response：This question was also raised by other reviewers, so I rewrote this part after rereading the literature to make the expression clearer. What you said is exactly what I want to express. Thank you for your advice.

2. (Page 3, Line 6): Consider changing the expression to “2.0-2.4 per 1,000,000”.

Response：This question was also raised by other reviewers, so I rewrote this part after Rereading the literature to make the expression clearer. Thank you for your advice.

3. (Page 3, line 21): Please give a reference.

Response：As other reviewers pointed out that "pathology, pathology and differential diagnosis should be in more detail", I rewrite this part, and the relevant contents are supported by references. Hope to meet your requirements. Thank you again for your advice.

4. (Page 5, Line 6): Plain upright abdominal radiography.

Response：Thank you for your suggestion. I have replaced it in the manuscript.

5. (Page 5, Line 12): “cine-MRI”.

Response：Thank you for your suggestion. I have replaced it in the manuscript.

6. (Page 10, Line 13): Please replace the term “uroschesis” by “urinary retention” a term more familiar in western medical terminology.

Response：Thank you for your suggestion. I have replaced it in the manuscript.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The topic of manuscript is good and will be of interest to readers. There are lot of grammatical and formatting mistakes. It should be read and corrected by some one proficient in English. Pathology, pathogenesis and differential diagnosis should be in more detail.

Response: 1) In accordance with your suggestion, I have once again asked native speakers of English to polish the language and revise the grammar. Please see the attachment for the proof of language embellishment. 2) According to your suggestion, the pathogenesis and differential diagnosis are described in more detail, I hope this can meet your requirements. Thank you very much for your constructive suggestions.

Reviewer #4:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

Specific Comments to Authors: The authors review the diagnosis, pathogenesis, and treatment of CIPO with the goal of improving clinicians' understanding of this complex and poorly understood disease. The review is relatively brief, superficial, and lacking in details. My comments are detailed below.

1.The second sentence of the Introduction states that CIPO is caused by the enteric neuromusculature "and/or its autonomic innervation." This sentence needs to be clarified. The autonomic innervation of the gut includes both intrinsic and extrinsic innervation. The intrinsic part is the enteric nervous system, which is already included in the "enteric neuromusculature." Primary CIPO is due to a disorder of the enteric neurons, muscles, or ICCs. Are abnormalities of the extrinsic innervation of the gut known to cause CIPO?

Response：Dear Professor, thank you very much for your advice. The answer to this question is yes. This part is described as " neuropathy(either intrinsic or extrinsic) "or "nerves (either intrinsic, the enteric nervous system [ENS] or extrinsic)" in other literatures. The extrinsic nerve is the autonomic innervation. Intestinal autonomic nervous system dysfunction is more likely to cause acute CIPO. I hope this reply will satisfy you.

2.It would be helpful to explain briefly the difference between primary and secondary CIPO, a distinction that is often made in the literature.

Response：Other reviewers suggested that I should describe the CIPO classification in more detail, so I made a big change, almost rewriting this part. I hope the rewritten part can meet your requirements. Thank you again for your constructive comments, which have benefited me a lot.

3. The "Classification & Etiology" section states that exposure to alcohol can lead to CIPO. Is there any evidence for this? The authors cite Reference #16, but that is an article about POLG mutations.

Response：1) Dear Professor, I'm very sorry that I didn't express it clearly, which made you misunderstood. What I want to express is that fetal alcohol syndrome may cause CIPO. The supporting

literature is " Uc A,Vasiliauskas E,Piccoli D A et al. Chronic intestinal pseudoobstruction associated with fetal alcohol syndrome.[J] .Dig. Dis. Sci., 1997, 42: 1163-7.".

2) Dear Professor, I'm very sorry for such a mistake. In order to avoid the same mistakes in other references, I checked all references carefully and re marked them. Thank you again for your help.

4. In their review of treatment options, the authors should include use of immunosuppressive therapy in carefully selected patients given the identification of an inflammatory or immune-mediated neuropathy or myopathy in some individuals with CIPO.

Response: Dear Professor, thank you very much for your constructive suggestions. I made corrections in the manuscript according to your suggestion. I hope these changes will meet your requirements.

5. The incidence of CIPO in children is much higher than in adults. This is presumably because affected children do not survive to adulthood. If that is the reason, this should be clarified in the text.

Response: Dear Professor, thank you very much for your advice. The reason why the incidence of children is significantly higher than that of adults may be related to the etiology of CIPO. The etiology of children is mostly primary, and adults are mostly caused by secondary factors. It was my fault that I didn't make it clear in the manuscript. According to your suggestion, I have made some corrections in the manuscript.

6. The authors state that "the majority of patients with CIPO are autosomal dominant." This is not correct. They cite two references from the 1980s, one of which is a case report and the other is a case series. Most cases of CIPO do not run in families. Those that do can be inherited in autosomal dominant, autosomal recessive, or x-linked recessive fashion.

Response: Dear Professor, thank you very much for your constructive suggestions. First of all, thank you for your advice. My description in this part is quite wrong. Because other experts have also commented on this, I reread the literature, rewrite this part and summarize the information into a table.

7. In the section on "Classification & Etiology," the text suggests that all cases of congenital CIPO include a history of toxic exposure, which is not true. Autoimmunity is another potential cause, possibly post-infectious etiologies also. The sentence should be changed to "The acquired pathogenesis of CIPO may include a history of…."

Response: Dear Professor, I'm really sorry that I didn't express it clearly in the manuscript, which made you misunderstand. In order to express it more clearly, I rewrite this part, hoping to meet your requirements.

8. Mesenchymopathies refer to ICC abnormalities, but the authors include Reference #30 in this category. That study is about connective tissue development in the gut, desmosis, and intestinal dysmotility. Its relevance to CIPO is unclear.

Response: Dear Professor, thank you very much for your advice. In order to avoid the same mistakes in other references, I checked all references carefully and re marked them. Thank you very much for your guidance. It helped me a lot.

9. The authors state that the age of onset of CIPO is a median of 17 years. That is based on Reference #31, which is a small study of 20 adult patients. The age of onset of the condition is usually much younger.

Response: Dear Professor, thank you very much for your advice. This statement is indeed inaccurate. I have made some corrections in the original.

10. The section on diagnosis does not mention genetic testing at all. There are several genes associated with neuropathic and myopathic causes of CIPO and these should be discussed.

Response: Thank you very much for your advice. This is indeed my negligence and your suggestion is a very useful supplement to my article. As you said, the literatures like "Variants of the ACTG2 gene correlate with degree of severity and presence of megacystis in chronic intestinal pseudo-obstruction" and " Mutations in SGOL1 cause a novel cohesinopathy affecting heart and gut rhythm." belongs to this category. I have added this part in the manuscript.

11. The authors refer to "CIPO patients with Hirschsprung's disease." This needs to be explained. Is this referring to patients with Hirschsprung disease prior to pull-through surgery? After surgery? Those with total intestinal aganglionosis?

Response: Dear Professor, thank you very much for your advice, which has helped me a lot. The Hirschsprung's disease mentioned in the manuscript is patients with aganglionosis. Thank you again for your valuable advice. This is very important for my future research work.

12. The term "uroschesis" is not defined.

Response: Dear Professor, other professors have also raised this question, so I replace the term "uroschesis" by "urinary retention". I hope this correction can meet your requirements.

13. The manuscript cites a 10-16% mortality rate for children with CIPO. In the "Prognosis" section it states that 10-25% of children with CIPO die before adulthood. These numbers should be reconciled.

Response：Dear Professor, 10% - 16% refers to PN related complications mortality, and 10% - 25% refers to overall mortality. I didn't express it clearly. It was my mistake. I have corrected it in the original manuscript.

Reviewer #5:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Thank you for asking me to review this article. It is a summary of published work regarding Chronic Intestinal Pseudo-obstruction. The article is easy to read, a sensible discussion of the main clinical features of Chronic Intestinal Pseudo-obstruction, and provides a lengthy list of references for further reading. Although Chronic Intestinal Pseudo-obstruction is not common, to the interested professional (adult or paediatric surgeon, gastroenterologist), it could be a useful point of reference. I have a question and a comment for the authors.

1. **Question - in the introduction the authors state 'Most congenital cases are sporadic, and patients have no clear family history; however, the majority of patients with CIPO are autosomal dominant [12,13].' I was confused by this, as the 2 parts of the sentence seem to contradict each other. Could the authors clarify this please?**

Response: I'm very sorry, dear professor. It's my improper expression that leads to misunderstanding. What I want to say is, Most CIPO cases are sporadic and have no clear family history. However, some cases with obvious genetic characteristics suggest that CIPO does have autosomal dominant, autosomal recessive and sex chromosome inheritance. I summarize it and present it as a table. I have revised it in the manuscript.

2. **Comment - at the end of the discussion the authors state 'Clinicians should improve their understanding of this disease because it is very important to diagnose and treat patients early, which improves patients' quality of life and their long-term prognosis.' Although I agree that clinicians should keep themselves educated, I could not see any reference in their paper that concluded that early diagnosis improved prognosis. I read reference 92 (Amiot et al, Am J Gastroenterol. 2009;104(5):1262-1270.) and I could not see that the data in this paper came to the conclusion that early diagnosis improves prognosis. However, I could be wrong and I look forward to the authors' comments.**

Response: Dear Professor, thank you very much for your question. In fact, I read the literature carefully again and I found I made a mistake of "taking it for granted" in this place. The message I want to convey is that a greater awareness of CIPO would indeed help to limit surgical procedures to a

minimum and reduce unnecessary damage. I have made revisement in the manuscript. In addition, I carefully searched the literature on the correlation between early diagnosis and prognosis of CIPO, and found no relevant reports. Thank you very much for your constructive suggestions, which helped me a lot.