



5 December, 2022

Editor-in-Chief

World Journal of Gastroenterology

Manuscript No: 81184

Manuscript title: Functional constipation in children: Optimizing treatment

Authors: Duc Long Tran and Palittiya Sintusek

Dear Editor,

Thank you for your letter dated 14 November 2022. We are pleased to know that our manuscript has been rated as potentially acceptable for publication in *World Journal of Gastroenterology*, subject to major revisions and response to the Reviewer comments.

We would like to submit a revised manuscript that has been modified according to the instructions provided in the decision letter and reviewer comments. All changes made during the revision process are appropriately marked and highlighted in red. Also appended to this letter are point-by-point responses to the comments raised by the reviewers.

We would like to take this opportunity to express our sincere thanks to the reviewers who have identified areas of the manuscript that needed corrections or modifications. Their suggestions have indeed improved the

quality of our manuscript. We would also like to thank you for allowing us to submit a revised copy of the manuscript.

We hope that the revised manuscript is in order and that it can be accepted for publication in the World Journal of Gastroenterology.

Sincerely Yours,

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Point-by-point responses to Reviewer comments

Response to reviewer 1

Reviewer #1: This review regarding functional constipation is of extreme importance for guiding clinicians in decision making, this prevalent dysfunction can be challenging and demands special efforts for assertive treatment. The review is updated and the discussion is convince. Congratulations for the authors.

Answer: We would like to thank the Reviewer for the positive comments and hope that our study will indeed help physicians gain knowledge, and ultimately, benefit patient-care.

Response to reviewer 2

We would like to thank the Reviewer for the in-depth critique of our manuscript and for the constructive comments.

Reviewer #2: 1. Matter of whole article must be revised and written with the headings i.e., Background, Objectives, Method of searching, Observations and discussion and Conclusion. However, many narrative reviews were available online without this type of format but it is more reliable for high quality publications. 2. Abstract is poorly written. It must be a nutshell of your article and must contains important outcomes of your review matter with concluded statement. 3. Mention full form of Abbreviation at the first time. Abbreviation without full form is not acceptable at the beginning of the article. 4. Linguistic correction is required. Some sentences are corrected in the word file as examples. 5. Go through all the comments and suggestions highlighted in the word file of manuscript and revised whole article accordingly. 6. In no. 1, definition of functional constipation, the matter is more than the requirement. Many sentences are not relevant. Clear definition of functional constipation in children didn't identified even from these 508 words of literature. One paragraph related to Functional incontinence (FI) were found which are irrelevant with the topic. 7. Algorithms especially for differential diagnosis and treatment (according to various etiology or symptomatology) make this article more valuable. Hence, try to make algorithms if possible. 8. Discussion is missing. However, some matter of point no. 4 and 5 can be considered as discussion. One matter in point no 4, was highlighted in word file as an example. Write this type of

matter in discussion portion along with your personal opinion and comments. 9. Limitation and importance of this article must have to be discussed in discussion. 10. Assistance of the article for further research should have to be mentioned. 11. Expert comment related to the aim (optimizing treatment for functional constipation in children) must be mentioned as conclusion after the discussion of reviewed matter.

Comment: 1. 1. Matter of whole article must be revised and written with the headings i.e. Background, Objectives, Method of searching, Observations and discussion and Conclusion. However, many narrative reviews were available online without this type of format but it is more reliable for high quality publications.

Answer: We sincerely appreciate the reviewer's comments. This review is based on knowledge derived from our experience and a database search. All images are of our patients. Hence, we would like to retain the existing format and request the reviewer to understand this matter.

Comment: 2. Abstract is poorly written. It must be a nutshell of your article and must contain important outcomes of your review matter with concluded statement.

Response: Thank you for pointing this out. The abstract has been rewritten and a definition of FC has been added, as follows.

"Functional constipation (FC) is considered the most common functional gastrointestinal disorder in children with a pooled global prevalence of 14.4%

(95% CI: 11.2–17.6) when diagnosed based on the Rome IV criteria. Its pathophysiological mechanisms are thought to be multifactorial and complicated, resulting in difficult management. Currently, the most effective medication, when used in parallel with toilet training, is osmotic laxatives. Children's adherence to medication and parental concern regarding long-term laxative use are the main contributors to treatment failure. Recently, novel therapies with a high safety profile have been developed, such as probiotics, synbiotics, serotonin 5-hydroxytryptamine 4 receptor agonists, chloride channel activators, and herbal and transitional medicines; nonetheless, well-designed research to support the use of these therapies is needed. This review aims to focus on multiple aspects of FC in children, including global prevalence, pathogenesis, diagnostic criteria, tools, as well as conventional and novel treatment options, such as non-pharmacological management, including adequate fiber and fluid intake, physiotherapy, or neuromodulators. We also report that in very difficult cases, surgical intervention may be required."

Comment: 3. Mention full form of Abbreviation at the first time.

Abbreviation without full form is not acceptable at the beginning of the article.

Answer: We have expanded all abbreviations at first use, as follows:

Functional constipation (FC), functional gastrointestinal disorders (FGIDs) (page 2), Hirschsprung's disease (HD) (page 6), the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and

North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) (page 9), radiopaque marker (ROM), colonic transit time (CTT) (page 10), milk of magnesium hydroxide (MOM) (page 14), the National Institute for Health and Care Excellence (NICE) (page 20).

Comment: 4. Linguistic correction is required. Some sentences are corrected in the word file as examples.

Answer: We have carefully read the manuscript and have corrected typographical and linguistic errors. We have also utilized the services of professional language editors at Enago to polish our revised manuscript.

Comment: 5. Go through all the comments and suggestions highlighted in the word file of manuscript and revised whole article accordingly.

Answer: Thank you for your insightful comments, we concur and have accordingly revised the manuscript accordingly. Nonetheless, we would like to retain the sections on normal bowel habits of healthy and exclusively breastfed infants who usually have infrequent stool passage during the first 1-2 months of life (page 3) because parents usually visit our clinic with this complaint and misunderstand it to be constipation. We hope that physicians learn to recognize this as a normal finding, reassure parents, and do not subject infants to unnecessary investigations or treatment.

Comment: 6. In no. 1, definition of functional constipation, the matter is more than the requirement. Many sentences are not relevant. Clear

definition of functional constipation in children didn't identified even from these 508 words of literature. One paragraph related to Functional incontinence (FI) were found which are irrelevant with the topic.

Answer: We concur and have changed the subheading of “definition of constipation” to “normal defecation and functional constipation.”

Likewise, we have removed the section on non-retentive functional incontinence (NRFI) as it is not relevant and have deleted Table 2, i.e., Rome IV Criteria for Pediatric Functional Nonretentive Fecal Incontinence (FNRFI).

Comment: 7. Algorithms especially for differential diagnosis and treatment (according to various etiology or symptomatology) make this article more valuable. Hence, try to make algorithms if possible.

Answer: Thank you for the suggestion, we have provided an algorithm that summarizes the management of constipation in children in the manuscript (figure 12).

Comment: 8. Discussion is missing. However, some matter of point no. 4 and 5 can be considered as discussion. One matter in point no 4, was highlighted in word file as an example. Write this type of matter in discussion portion along with your personal opinion and comments.

Answer: We have added a conclusion and have provided an algorithm to summarize the review, instead of providing a discussion section.

Comment: 9. Limitation and important of this article must have to be discussed in discussion.

Answer: Limitations of each topic are present in the original manuscript, especially in the sections on investigation and management.

Comment: 10. Assistance of the article for further research should have to be mentioned.

Answer: The need for well-designed studies has been highlighted for each part and in the conclusion in the original manuscript.

Comment: 11. Expert comment related to the aim (optimizing treatment for function constipation in children) must be mentioned as conclusion after the discussion of reviewed matter.

Answer: The conclusion section provides this information.

Response to reviewer 3

We would like to thank the Reviewer for the in-depth comments and critique of our manuscript as it has helped to improve it.

Reviewer #3: This is a well-written review paper on the large and interesting field of functional constipation in childhood. The pathophysiology and diagnostic criteria are correct and well presented. Different treatment assessments are thoroughly presented (with references). Tables and figures are excellent. My main objection is that I

miss very much a conclusion in this review paper. What is the authors' opinion on optimizing treatment for FC? The title is "Functional constipation in children: Optimizing treatment" but in the abstract is stated that "this review will focus on the pathogenesis of FC, as well as its diagnostic criteria and tools and conventional and novel treatment options". If a conclusion could be added at the end of the main manuscript, to summarize the field, the review would be very much improved. Should the title of the manuscript be rephrased? My minor objections are: About abdominal ultrasound (part 4.3.3): There is a need to add references that are more recent, for example: Pop D et al. Rectum sizes: Assessment by ultrasonography in children with functional constipation. *Journal of Paediatrics and Child Health* 57 (2021) 1244–1249 (doi:10.1111/jpc.15435) Matsumoto D et al. Consensus Document: Diagnosis for Chronic Constipation with Faecal Retention in the Rectum Using Ultrasonography. *Diagnostics* 2022, 12, 300. (doi.org/10.3390/diagnostics12020300) About education (part 5,1): Other specialized staff (pediatric RN or urotherapeut) could be mentioned as an important complement to physicians to work with the families creating a thorough plan for treatment and follow-up.

Comment: 1. If a conclusion could be added at the end of the main manuscript, to summarize the field, the review would be very much improved.

Answer: The conclusion section, summarizing the review, is present in the original manuscript at page 24.

Comment: 2. Should the title of the manuscript be rephrased?

Answer: We were invited to write this review article and as this title was provided by us initially, we continued with the same title for the first submission. However, as the content far exceeded the scope indicated by that title, we agree with your opinion and have changed the title from “Functional constipation in children: Optimizing treatment” to “Functional constipation in children: What physicians should know” (page 1).

Comment: 3. About abdominal ultrasound (part 4.3.3): There is a need to add references that are more recent, for example: Pop D et al. Rectum sizes: Assessment by ultrasonography in children with functional constipation. Journal of Paediatrics and Child Health 57 (2021) 1244–1249 (doi:10.1111/jpc.15435) Matsumoto D et al. Consensus Document: Diagnosis for Chronic Constipation with Faecal Retention in the Rectum Using Ultrasonography. Diagnostics 2022, 12, 300. (doi.org/10.3390/diagnostics12020300)

Answer: We agree and have cited two recent references. The conclusions of these studies have also been included as part of the investigation (abdominal ultrasonography; page 9-10).

Comment: 1. About education (part 5,1): Other specialized staff (pediatric RN or urotherapeut) could be mentioned as an important complement to physicians to work with the families creating a thorough plan for treatment and follow-up

Answer: We agree and have added the following text at page 13

“In some complex cases, such as in children with intractable constipation or in those suffering from other comorbidities such as urinary problems, it is necessary to involve a multidisciplinary team that includes pediatric specialist nurses, pediatric research nurses, psychiatrists, urotherapists, and urologists for long-term follow-ups. Hence, such children require customized care.”

Revision reviewer

SPECIFIC COMMENTS TO AUTHORS

Whole article is written under the heading of Introduction. This is not fair for good publication. Introduction should be written first which must be separated from the main contents and it should highlight or introduce the background of the topic and main objectives of the review. All others are ok.

Answer: We would like to thank the Reviewer for the comments.

Introduction part was added in the beginning following with the main contents and conclusion. I also reordered the heading 1 and 2 to the epidemiology and then followed by Normal defecation and functional constipation instead.

Response to Editor-in-Chief

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-

published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. *World J Gastroenterol* 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at:

<https://www.referencecitationanalysis.com/>.

Answer: We sincerely appreciate the editor's helpful comments. We revised all tables and figures to conform to Journal requirements and have incorporated editable figures into a ppt file. Some of the original figures have been taken from a Thai medical book and we have requested the Editors of these books for permission. Please find enclosed the relevant permissions, as supplementary material.

Others: We have also edited out some sections in the manuscript as per comments from reviewers and have utilized the services of professional English language editors at Enago. Additionally, table 2 has been deleted and figure 12 has been added.

Sincerely,

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