

October 18, 2018

Fang-Fang Ji

Science Editor, Editorial Office

Baishideng Publishing Group Inc

Re: **Manuscript NO.:** 41729

Title: "Prevention of Necrotizing Enterocolitis in Premature Infants – an Updated Review"

Dear Dr. Ji:

Thank you for the careful review of our manuscript. We fully appreciated the constructive comments raised by your expert reviewers and the editor. Changes in the manuscript have been made accordingly. We hope the carefully revised manuscript will meet the standard of the Journal and satisfy reviewers and editors for publication.

The point-by-point response to the comments of the reviewers is enclosed. Please let me know if you need other information.

Sincerely yours,

Jing Lin M.D.
Associate Professor of Pediatrics
Icahn School of Medicine at Mount Sinai
New York, NY10029

The point-by-point response to the comments of the reviewers

Reviewer 1: Some English editing is needed. Is this meant to be a review article? If so, how were the various papers identified? Please clarify research method. After the Introduction section, the purpose of the research should be written. A discussion is needed summarizing what research still needs to be done -- what are the gaps in knowledge and what further studies are needed? What are the limitations to the identified studies?

We made detailed English editing as suggested. The method of identifying various papers is presented. The purpose of the review is added in the introduction section. A summary of the review is added. Since we included many studies, the limitation to the identified individual study is too variable to be summarized in a simple paragraph.

Reviewer 2: I think the comment that enteral feedings are among risk factors for NEC is misleading. I would rewrite this to say lack of enteral feedings. I would include p values when discussing results of prior studies. I like the section that discusses pasteurized donor human milk and agree that the statement about poor growth should be included. There should probably be a bit more information about how to combat the poor growth since it is considered more ideal than preterm formula in terms of preventing NEC but is associated with lower growth rates. I am glad to see the research on this topic compiled. I wrote a review on it but it was close to 10 years ago now.

We change the enteral feeding to formula feeding which is the risk factor for NEC. All p values are included in the tables that summarize the results of identified studies. A standardized feeding

protocol may be used to combat the poor growth associated with donor milk feeding. A section of standardized feeding protocol was added into the manuscript.

Reviewer 3: This is an excellent review that is well written, up to date and has well balanced recommendations.

Thanks for the encouraging comment.

Reviewer 4: Dr. Jin and colleagues aimed at summarizing the results of recent clinical trials and meta-analyses that support some of the existing clinical practices for reducing the risk of NEC in premature infants. Only three interventions have been studied by the authors: human milk feeding, probiotics and antibiotic prophylaxis. The main flaw of this study is the fact that the authors did not report on other potentially important measures, for example: the use of fortifiers and the type of fortifier to be used/avoided; the utility (or not) of minimal enteral feeding; the speed of feeding advancement; the early or late initiation of feeds; the identification of infants at increased risk for NEC and the application of preventive measures in this subgroup vs all newborns. Several RCTs have been published on these themes, and a review of these would be very useful for the clinician. The authors state that “the costs of probiotics is so low”. They should specify what product are they referring to and the actual cost. Are they referring to probiotics with clear benefits or to home-made probiotics from yoghurt? Some words (i.e. mystery) are out of context and not applicable to present knowledge. The authors should rather briefly discuss the main pathophysiologic factors so far documented or proposed, and show

potential controversies between them. Mystery is maybe applicable to some humanistic disciplines. There are some typos and grammatical errors in the manuscript.

Standardized feeding protocol usually dresses the questions about the use of fortifiers and the type of fortifier to be used/avoided; the utility (or not) of minimal enteral feeding; the speed of feeding advancement; the early or late initiation of feeds. Therefore, a section of standardized feeding protocol was added. Similar to the point raised by the reviewer 1, we have changed the wording and have made further detailed English editing.