Author's response to reviews

Title: Nutrition of preterm Infants who develop Bronchopulmonary Dysplasia

Authors:

Andreas Wemhöner (andreas.wemhoener@uniklinikum-dresden.de)
Daniel Ortner (daniel.ordner@gmx.com)
Edda Tschirch (etschirch@hotmail.com)
Alexander Strasak (alexander.strasak@i-med.ac.at)
Mario Rüdiger (mario.ruediger@uniklinikum-dresden.de)

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Author's response to reviews: see over
Dear Editor and reviewers,

Thank you very much for reviewing the manuscript. We do acknowledge the valuable suggestions concerning the manuscript. We thoroughly revised the manuscript and suggestions of reviewers have been thoughtfully considered. The major questions are answered below.

**Specific comments to Reviewer Vineet Bhandari:**

According to the suggestions of the reviewer changes were made to improve the quality of the manuscript as follows:

**Major criticism**

1. Abstract. Page 2, line 9: We are sorry for this mistake. According to the criticism of the reviewer corrections have been made in the manuscript (Table 1: number 69).

2. According to the suggestion of the reviewer changes were made (background. Page 3, lines 8 and 25).

3. We agree with the reviewer, that the study by Braz et al (Med Biol Res. 2009 Jul;42(7):606-13) should be added in this paragraph. Changes were made accordingly (background. Page 3, line 16.)

4. According to the suggestion of the reviewer the term “prenatal lung maturation” was changed to “use of antenatal steroids” (Page 4, line 14./Table 1). Data refers to complete courses given.

5. We kindly confirm to the reviewer, that the diagnosis of BPD used in the manuscript was defined correctly and added “treatment with oxygen >21% for
at least 28 days on 36 weeks post menstrual age or discharge to home, whichever comes first....” (page 4)

6. We kindly confirm to the reviewer and added data for NEC, ROP and IVH into results on page 8. We do agree with the reviewer, that other aspects of morbidity would be of interest. However, we did not collect more data for the following two (prospectively defined) reasons: (I) the incidence of most of the morbidities is too low to obtain data that allow a useful interpretation in our study, (II) it was the primary aim to detect an association between nutritional intake and BPD development. We are aware that BPD is a multifactorial disease that is associated with different causes (differences in surfactant composition, in inflammatory mediators, in genetic predisposition etc.) and it would be impossible to determine the impact of each single aspect in such a small study population.

7. Whereas previous studies have found an association between amount of fluid intake and subsequent development of BPD, the present study did not find a difference in median fluid intake between both groups. However, all infants who developed BPD had a higher fluid intake than recommended. These data are new and of interest for subsequent studies (not median of groups should be compared, but a certain threshold)

8. Whereas previous studies have found an association between less calories intake and less weight gain of infants developing BPD our results showed not this association. We discussed that in the discussion and included references.

9. We agree with the reviewer, that it would be interesting to know the status of chorioamnionitis. However, in our clinic the data were not obtained in a reproducible manner, thus, data were not collected.
10. We kindly apologize for the inadequate quality of figure 3. The correction has been made.

11. According to the reviewers suggestion the minor revisions in background, page 3, line 17 and page 8, line 2 changes have been made in the manuscript.

**Specific comments to Reviewer Namasivayam Ambalavanan:**
According to the suggestions of the reviewer changes were made to improve the quality of the manuscript as follows:

**Major criticism**

1. We do agree with the reviewer concerning the small sample size. The problem has been discussed in the discussion. However, the study was planned as a pilot study to obtain data for calculating sample size for a sufficient large prospective study. Nevertheless, sample size could have been increased by prolonging the collecting period. However, our NICU has a very strict evidence based approach of therapy. Thus, changes in therapy are very likely within a longer time period. To minimize potential disturbing effects that could limit data interpretation, we restricted the time interval of the study.

2. The reviewer argued, that it would be of interest to know whether the results we observed regarding enteral and parenteral intake may be due to differences in patient characteristics as birth weight, gestation, gender etc. We certainly agree with the reviewer and we did perform a multivariate regression analysis to evaluate the nutritional variables, but we did not find a significant result.
3. We kindly confirm to the reviewer, that the diagnosis of BPD used in the manuscript was made at 36 weeks corrected gestational age, as per ref. #9. For clarification we deleted the sentence “In short, .....28 days.” (page 4, line 29.)

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4. We certainly agree with the reviewer, that it would be very interesting to determine if there is any threshold or “minimal nutritional requirement” in relation to BPD. However, it was our intention to test a recommended threshold and to define the cut-off prospectively. Nevertheless, we tried to analyze the data as suggested, however, did not find a threshold level for protein intake (it might be due to the small sample size).

5. According to the criticism of the reviewer more detailed description of the NICU were added in the manuscript.

6. We agree with the suggestion of the reviewer. It seems to be very likely that medical conditions, or other reasons can explain the discrepancy between the suggested amount of feeding (according to protocol) and the achieved amount of feeding. However, the study was not designed to detect the reasons for differences. It was only the aim of the pilot trial to test whether there are differences between both groups. A subsequent study with a sufficient sample size could have addressed that question.

7. We kindly apologize for the inadequate quality of figure 3. The correction have been made.