Author’s response to reviews

Title: High frequencies of elevated alkaline phosphatase activity and rickets exist in extremely low birth weight infants despite current nutritional support

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Version: 2 Date: 8 May 2009

Author’s response to reviews: see over
May 8, 2009

Dear Editors,

We have read the Reviewer’s Report of our manuscript (Manuscript #2017773422254943, “High frequencies of elevated alkaline phosphatase activity and rickets exist in extremely low birth weight infants despite current nutritional support”) and have incorporated the recommended changes. Beneath this letter, we provide responses for each comment made by the reviewer. Our manuscript incorporating the suggested revisions is submitted as a separate file.

In addition, our revised manuscript now includes an “Acknowledgements” section which provides funding information. We also provide a revised “Figure 2.” This revised figure has been reformatted with some additional information included for clarity.

Please submit future correspondence to Steven Abrams (sabrams@bcm.edu).

Thank you,
Shannon Mitchell

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**Reviewer's report**

**Title:** High frequencies of elevated alkaline phosphatase activity and rickets exist in extremely low birth weight infants despite current nutritional support

**Version:** 1  **Date:** 31 March 2009

**Reviewer:** Reginald Tsang

**Reviewer's report:**
This is an important study in view of the survival of extremely low birth rate infants, and the lack of data on estimates of rickets and fractures in this population. The original study (of Koo et al, which should be referenced) set the stage for the detection and highlighting of these problems in very low birth rate infants, but since then there has been no clarification of the existence of these problems using current modes of nutritional support.
- The study by Koo et al is now referenced in the “Background” section.
Page 5, First paragraph, The descriptions are imprecise in many regards. What do the authors mean about infants who have “persistently high APA”: what is persistent?
- We clinically define persistently high APA values as > 800 IU/L for two measurements taken at least one week apart. The manuscript has been edited to reflect this.

What is the definition of “evidence of persistent or long term inadequate mineral intake”?
- This refers to intake below 150 mg/kg/d of calcium and 75 mg/kg/d of phosphorus for at least 3-4 weeks. These specifications have been added to the manuscript.

What is the definition of “inability to tolerate a full volume”?
- “Inability to tolerate a full volume of fortified human milk or preterm formula” refers to necessary use of parenteral nutrition in conjunction with the tolerated volume of enteral feeds to meet necessary caloric requirements of the infant. Reference to inability to tolerate full volume of enteral feeds has been taken out, as prior reference to infants on long-term TPN also applies to this group.

What is “a few infants with lower APA…”?
- “A few” refers to 8 infants with APA <800 IU/L who were evaluated for rickets. “A few” has been deleted from this statement. Table 2 reports the number of infants evaluated for rickets with P-APA <800 IU/L.

The authors need to give a better definition or better series of definitions in order for the reader to understand the clinical modus operandi in this particular nursery.
- Definitions have been added as indicated above.

Page 6, Paragraph 4, The authors need to stress that radiographic evaluation was not done on a broad comprehensive basis, but only for those who had high APA, so this is a biased population.
- The basis for which the 32 patients received radiographs has been restated, and the total number of patients in our study has been repeated to add clarification.

What is the definition of osteopenia?
- Osteopenia refers to radiographic evidence of low mineral density of the bones. This definition is now included in the “Methods” section.

Page 7, Paragraph 1, the details of these subjects are clearly seen on the table, and probably need not be elaborated in the text, which actually does not help.
- This paragraph has been deleted and replaced with a sentence referencing Table 2.

Page 7, Paragraph 2, Presumably when the authors say “when the infants were not evaluated for rickets,” in this paragraph they mean that no x-rays were done
– is that correct?

• Yes, this is correct. The text has been modified to clarify this point.

Page 8, Last Paragraph, comments of “diagnosis of rickets and how physical examination is not useful etc, unless evidence of the fracture is present”, needs to be referenced – what exactly do the authors mean about that sentence anyway? That physical examination is not useful in predicting osteopenia or rickets, unless evidence of a fracture is present?

• This sentence has been rephrased as follows, with the appropriate reference included: “Physical examination may reveal signs of osteopenia or rickets, including pathologic fractures or bony prominences at the costochondral junctions [4].”

Page 9, Paragraph 2, the authors need to clarify why they say that the biochemical data were 60% specific, since the data were retrospective, without a comprehensive evaluation of all clinically relevant measures etc.

• This statement has been deleted.

Furthermore, the authors indicate that “it is likely that these parameters will identify most infants with radiologic rickets” – how do they justify this comment?

• This statement has been deleted.

Paragraph 3, the authors indicate that “preterm formulas, fortified human milk, and TPN typically provide about 60 to 100 mg/kg/d of retained calcium”….the question would be what about this particular population? What was the actual intake?

• In general, US preterm formulas and human milk fortifiers provide 180-220 mg/kg/d of calcium. We did not attempt to quantify actual mineral intake in our cohort. The manuscript has been clarified accordingly.

The sentence, “the large difference in APA within a narrow range of birth weights indicates ....”is not justified, nor proven, by the study. In fact it is unclear what the sentence means.

• The word “indicates” has been removed and replaced with “may be caused by” to imply speculation. The sentence has been rephrased for clarification as follows: “The large differences in P-APA and percentage of infants diagnosed with rickets within a narrow range of birth weights may be caused by other factors in addition to differences between in utero Ca retention among these infants.”

Furthermore, the authors state that “it is likely that there is a unique and extremely elevated short term demand for minerals in these smallest infants that is not met....” This is an unusual statement, with no proof, as is the comment that it is “often apparent to clinicians, but has not been documented”, whatever that means.

• The words “It is likely” has been replaced with “It is possible.” The anecdotal reference to what is “apparent to clinicians” has been deleted.
Page 10, the first paragraph is very speculative and unproven, and with no references. The comment that “bone growth may be rapid at some phase in these infants leading to very high APA etc” is not proven, nor referenced.
- Wording in this paragraph has been changed to emphasize that these comments are based upon our speculation rather than any existing proof.

The comment “we did not attempt to document the feeding or TPN course of these infants as it would not be feasible to categorize these” is an unusual statement – why is it not feasible?
- Sorting through and the feeding schedules of these infants would have been extremely arduous, and we chose not to for the purpose of this investigation. The reference to feasibility has been removed.

And what is the relationship with the last sentence of the paragraph, about the acute events being not increased? “However, ....”. “However” implies a connection that escapes the reader.
- The occurrence of acute events listed (necrotizing enterocolitis, gastrointestinal perforation) generally requires reduction of enteral feeds and concomitant increase in TPN. Thus, the lack of correlation between acute GI events and rickets may imply a lack of correlation between TPN use and rickets. (However, this cannot be clearly demonstrated because we did not record the feeding schedules of these infants.) The link between GI events and TPN use has been clarified.

Last paragraph, the sentence that “our data generally support the use of APA as a useful parameter in this screening of rickets” is a loose statement with no real data provided in the study.
- Statement has been revised to emphasize that rickets may be present even at levels of APA <600 IU/L, as shown in our study.

Page 11, First paragraph, Paragraph 2, the authors say that “further indications for radiographs would be any infant with an extremely prolonged course of parenteral nutrition. Do the authors have any data on this? And what do they mean by extremely prolonged?
- We do not have specific data related to the effects of prolonged parenteral nutrition. In general, this would be parenteral nutrition in a premature infant for more than 3-4 weeks. The time frame has been added to our text.

The authors’ recommendations, while interesting, are not really based on their data, but on a clinical suggestion. Specifically, the last sentence should be rephrased “we suggest” rather than “our data suggest;”
- Wording has been changed accordingly.

in any case the authors paper do not give any indication that early nutritional intervention has a direct effect on the APA rise or the development of rickets. This
comment as expressed in the conclusion is also incorrect, and it should be expressed as a speculation if the authors so wish.

- The concluding sentence has been reworded to express further nutritional intervention / screening as our recommendation to be considered.

Page 16 might be something that could be available on the website or something similar, or “available on request.”

- Tables and figure references have been included in the manuscript as requested in the manuscript formatting guidelines.

The last figure while interesting is not what this study proves, and at most is a suggestion/ speculation that these authors wish to make.

- The manuscript has been edited to emphasize that we offer this figure as a recommendation.

**Level of interest:** An article of importance in its field  
**Quality of written English:** Acceptable  
**Statistical review:** No, the manuscript does not need to be seen by a statistician.  
**Declaration of competing interests:**  
i have no competing interests