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

Authors:

Shannon M Mitchell (ShannonMitch@gmail.com)
Stephanie P Rogers (Stefanie_Rogers@hotmail.com)
Penni D Hicks (pennih@bcm.edu)
Keli M Hawthorne (kelih@bcm.edu)
Bruce R Parker (brucep@bcm.edu)
Steven A Abrams (sabramps@bcm.edu)

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Author’s response to reviews: see over
June 22, 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. We welcome the opportunity to make the manuscript more clear and appreciate the comments of the reviewer.

Thank you,
Shannon Mitchell

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: 2 Date: 4 June 2009

Reviewer: Reginald Tsang

Reviewer’s report:
The authors are to be commended for an excellent point by point revision of the text which answers most of the original questions. However, I feel uncomfortable about being the only reviewer for this paper, as I understand it. No one person can adequately cover all the bases and as I re-review the paper, I now find additional questions that could have been detected possibly by a second reviewer.

Abstract section.
Results: The sentence “32 patients had radiographic…” should be rephrased as “evaluation for evidence of rickets, based on p-APA greater than 800, parenteral nutrition greater than 3 to 4 weeks, and clinical suspicion”. This allows the reader to understand this approach clearly; this is a key feature of the study; otherwise it is quite unclear why radiographic evaluation for rickets occurred. Infants with birth weight less than 600g were more likely to have radiologic rickets. This is to allow the reader an understanding that it is not biochemical or chemical rickets that the authors are talking about, since some authors use those as definitions of rickets.

- These changes have been incorporated into the manuscript.

The sentence “p-APA was significantly higher in infants with rickets compared to those not evaluated for rickets” is a circular argument, since the reason for diagnosis of rickets was based on a high p-APA to begin with. Also the authors should say radiologic rickets.
• This sentence has been removed from the abstract. The abstract and manuscript has also been reworded to differentiate radiologic diagnosis of rickets from biochemical rickets.

Conclusions
Radiologic rickets
• The distinction between radiologic rickets and biochemical rickets has been made.

The authors should be a bit more precise by what they mean with more aggressive mineral supplementation. Do they mean earlier mineral supplementation or actually higher dose?
• Clarification that aggressive mineral supplementation means early mineral supplementation has been made.

Page 3 background
Metabolic bone disease may also theoretically worsen the respiratory problem........ a reference should be given for this concept.
• A reference has been added.

• This original reference now replaces our previous reference for fractures in infants <1500g, and “30%” now replaces “10%” in the manuscript.

Paragraph 2 last line. Medications….also appear to contribute to the development of metabolic bone disease
• Sentence has been rephrased accordingly.

Page 5 First line During this period (delete time)........
• Time has been deleted.

The authors have now defined very clearly the situation for doing a radiograph
Paragraph 2 what happened to the data on “early” rickets vs. “advanced” rickets? If these data are not available or of interest, then maybe they should not mention this. It leaves the reader dangling in suspense.
• Reference to “early” vs. “advanced” rickets has been removed.

Page 6 Results Paragraph 3 Normally we reverse the sequence of comparison, i.e. state that the infants less than 600grams had significantly higher p-APA than the other groups etc. since that is the main point of concern. i.e. we compare the group with “disease” in contrast to the more “control like” groups.
• The sequence of comparison has been reversed.
Last Paragraph
Only infants with elevated p-APA greater than 800, total TPN greater than 3 weeks........
The authors should be consistent in their criteria and I would assume that all three criteria are necessary for the evaluation of radiographic evidence of rickets
- Criteria for radiographic evaluation have been clarified at this point in the manuscript.

Page 7 Paragraph 2
Similarly 17 infants with p-APA greater than 800 units, is fine, but on page 9 the authors use greater than 1,000 units, so which one is correct?
- The same group of infants with P-APA >800 IU/L has now been referenced in both places.

Page 8 the authors present 55 patients with cholestasis and 58 without cholestasis. The main question is how many of the increases in p-APA had cholestasis, etc..
- The manuscript has been revised to include the fraction of infants with both elevated cholestasis and elevated P-APA.

Discussion Line 2 radiographic rickets
- “Radiographic” has been added as a descriptor.

Line 3 mean p-APA exceeded 600 IU/L in all birthweight (delete size) subgroups
- “Size” has been deleted.

Last line of paragraph: “There was no significant difference in p-APA in those in whom rickets was diagnosed compared to those who had osteopenia without rickets.” This is the first time osteopenia without rickets is commented upon. Where are the osteopenia data? Not sure what this means and why it is introduced at this point.
- The 4th paragraph in the “results” section reports that a total of 32 patients received radiographic evaluation for rickets, of which 18 showed rickets and the remaining 14 showed osteopenia without rickets.

Last Paragraph the sentence might read better: The diagnosis of rickets generally remains dependant on clinical suspicion and on biochemical p-APA data with the radiograph verifying the findings.
- Sentence has been reworded accordingly.

Page 9 Paragraph 2 here the authors talk about p-APA greater than 1,000 IU/L which could be confusing; it is best to say “including 5 patients with p-APA greater than 800 units” (is that correct?); in all these 5 infants, p-APA was actually greater than 1,000 units
- Seventeen infants with P-APA >800 IU/L did not receive a radiograph, including 5 infants with P-APA >1000 IU/L. The reference to the 5 infants has now been replaced with a reference to the larger group of 17 to avoid confusion with the information presented on Page 7.

Line 3 radiographic rickets
- “Radiographic” has been added.

Last Paragraph line 3 “preterm formulas, fortified human milk and TPN……..typically should provide about 180 to 220 milligram per kilogram per day.” This is only true if it is given appropriately and successfully, which may not be the case in reality. This is a major consideration which should be emphasized unless the authors have data to the contrary.
- It has been emphasized that these levels of Ca and P delivery are not always achieved.

Another possibility is that p-APA is really non-specific for detection for rickets in any case, and is complicated by the presence of cholestasis?
- This possibility has been added to the discussion.

The authors should say at least one sentence about the case report in reference 13, since it is not clear that a high mineral demand was “documented.”
- A statement has been added which describes the high Ca and P administration to an infant (600 mg/kg/d and 500 mg/kg/d, respectively) which were followed by decrease in APA.

Page 10 since rapid bone growth has not been documented, the authors should say we suggest that very high APA……. may be caused by rapid bone growth, rather than “suspect”; “suspect” implies that there is some evidence
- “Suspect” has been replaced with “suggest”.

Paragraph 2 …..predicted radiographic osteopenia……..(just to be sure that there are no other definitions of osteopenia)
- “Radiographic” has been added.

Other studies have shown……. correlated with APA, with sustained elevated? levels of P-APA correlating with more severe disease. Was there a period of elevation that was significant?
- The source article which made the assertion that sustained levels of elevated APA correlated with more severe disease did not clearly identify a time period. I deleted the reference from the manuscript to avoid confusion.

Elevated APA….. is associated with decreased bone strength. Is this a general statement or is that related to infants? Or are we talking about animals?
- The references made are for preterm infants. This clarification has been added.
Quoting the results of Faerk and their challenge to the utility of AP and serum P is ok, as long as the authors at least state in one sentence what the challenge consists of.

- A sentence has been added which states that Faerk et al found no relationship between bone mineral content and the following: P-APA, mean serum APA, and mean serum P.

Page 11 the statement “birthweight alone may be a more sensitive indicator of rickets of patients with birthweight less than 600 grams” – This sentence is not very clear and should be rephrased to make it more understandable

- This sentence now clarifies that birthweight may be a more sensitive indicator than biochemical markers.

Paragraph 2 the authors again use 1,000 units for the limit of APA, but previously used 800 units; is there some reason for this?

- This sentence has been clarified.

Further indications for radiographs........ are the findings in an incidental Radiograph

- This sentence has been clarified to reflect abnormal bone findings on an incidental radiograph.