Author's response to reviews

Title: Are diagnostic criteria for acute malnutrition affected by hydration status in hospitalized children? A repeated measures study

Authors:

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Version: 2 Date: 15 August 2011

Author's response to reviews: see over
Dear Dr Nehme Gabriel,

Re: Revised manuscript MS: 8904383655729599

I would like to resubmit the revised manuscript now titled: ‘Are diagnostic criteria for acute malnutrition affected by hydration status in hospitalized children? A repeated measures study’, for publication in the Nutrition Journal. We would like to confirm that all reviewers’ comments have been carefully addressed. We have provided a point-by-point response (in bold letters) beneath each reviewers concern to be found within this cover letter as follows:

1. Reviewer 1: Please see pages 2 & 3 of this cover letter
2. Reviewer 2: Please see pages 4 to 6 of this cover letter
3. Reviewer 3: Please see pages 7 to 9 of this cover letter

We have also highlighted (yellow highlighter) all changes referred to herein in the revised manuscript accompanying this letter.

15th August 2011
Reviewer 1: Nicholas Connor

Minor Essential Revisions

1. Abstract: Results paragraph, last sentence, double spacing between “admission” and “by” - delete.
   Double space deleted – See page 2

2. Body: Introduction, last sentence – add space between “circumference” your parenthesis.
   Space added – see page 3 paragraph 1

3. Please use “F-75” or “Formula 75” instead of “F75” to be consistent with literature
   Text revised to read milk formula (F-75) – See page 8 paragraph 2

Discretionary Revisions

4. I would like to see some gesture towards the programmatic implications of these findings, if close to 1/5 of children are wrongly classified at a district hospital level. Some researchers will note that correcting this will lower admission numbers (at least into the SAM category) and thus marshall less resources, other researchers will argue that the children who need treatment can be better cared for with properly allocated resources. Etc.

This has been addressed on page 13 last paragraph. We are of the opinion that dehydrated children who are classified as severely malnutrition should be managed according to malnutrition protocol and their anthropometry be re-assessed after rehydration. Those who are then found to be only moderately malnourished may then enter a supplementary feeding programme in order to focus inpatient therapeutic resources on those most at risk.

5. I would also like to see something which acknowledges your context, a hospital, in contrast to the community/villages. Sometimes during the conducting of nutrition clinics in African villages mothers will walk with their children in heat for hours and the children become dehydrated by virtue of their travel distance alone to some extent, not (only) gastroenteritis or other illnesses. This is my observation and it has been echoed by others in the field. The thing here is the synergistic nature of malnutrition and illnesses (Scrimshaw, 1970, 1997, 2003), so if the poor nutrition caused or exacerbated the gastroenteritis/illnesses which in turn caused the dehydration… which got him into the treatment program then perhaps the measure is sound as-is.

Our study focused on ill hospitalized children and therefore our findings reflect the hospital setting and may not be representative of a village or community setting. This has been acknowledged on page 12, paragraph 1, last sentence. We have included a comment on dehydration in relation to travel distance in a hot climate.

6. Body, Introduction 3rd paragraph: First sentence: MUAC actually “directly” measures the circumference of the upper arm which is comprised of mostly lean
muscle and some adipose tissue, as well as a considerable cross section of bone
and blood vessels. It is a proxy measure of protein and lipid reserves/storage,
and as such, a proxy measure of nutrition status. The use of the word directly
struck me as inaccurate.

This has been revised to reflect reviewers suggestions – see page 3, paragraph 3

7. F-75 is not “aimed” at growth, but it does contain high levels of macronutrients
which tissues are craving even in early stages of therapy, you might want to spell
that out a little more.

This has been revised – see page 7 paragraph 2

8. Discussion paragraph 5: Children who lose weight even on treatment are
sometimes suspected of having HIV this is not mentioned here. I imagine you
would have some of this disease burden in your region. Likely not a quarter
though. Interesting. Were these numbers omitted from analysis?

The prevalence of HIV in our study sample was very low (2.8%). That of those who lost weight
was too small to look at specifically. We have added some information on the burden of HIV,
Malaria and Pneumonia in our cohort. See page 8 paragraph 3
Reviewer 2: Andre Briend

Discretionary comment

1- General comment

The title and the introduction suggest that the paper is about assessment of wasting. This is not totally true, as most of the discussion is based on measure of mid-upper arm circumference (MUAC), which is not really an indicator of wasting. Wasting by definition is related to low weight for height, not to MUAC, and the two indicators are not interchangeable, as they identify different children. On the other hand, since 2007, both MUAC and low weight for height are accepted independent diagnostic criteria for severe acute malnutrition (SAM) (see 2009 WHO UNICEF statement available at: http://www.who.int/nutrition/publications/severemalnutrition/9789241598163_eng.pdf ). And currently, many NGOs use MUAC based definition of moderate acute malnutrition. I think the paper would avoid this problem by using a different title, namely: “Are current diagnostic criteria for severe acute malnutrition affected by hydration status in hospitalized children? A repeated measures study”. And by replacing the term “wasting” by “SAM diagnostic criteria” or “malnutrition” whenever it refers both to low weight for height and low MUAC. The 2009 WHO UNICEF Joint statement could be quoted.

We agree with the reviewer on both his comments. First, we have amended the title of the manuscript as suggested but because within the scope of this manuscript we have also included analysis on children who were not severely malnourished, we have omitted the word “severe” so that the title reads “Are diagnostic criteria for acute malnutrition affected by hydration status in hospitalized children? A repeated measures study”- see page 1

Secondly, we have replaced the word wasting with SAM diagnostic criteria or malnutrition whenever it refers to both WFLz and low MUAC. These are numerous changes within the manuscript and have been highlighted.

Minor points

Abstract:
mid-upper arm circumference
weight-for-length z-score

These have been revised- see page 2

In the result section, the authors say:
"Each 1% change in hydration was associated with a 0.40mm (95% CI: 0.30 to 0.44mm, p<0.001) change in MUAC, 0.035z (95% CI: 0.027 to 0.043z, P<0.001) change in MUACz score and 0.115z (95% CI: 0.114 to 0.116 z, p<0.001) change in WFLz.” It would be more correct to say: “Each 1% change in weight…” (not hydration which was not directly measured).
The statement has been revised- see page 2

Line 5 of the results section: correct: aged 6 m

This has been corrected to read aged and not age – see page 2

Conclusion: nutritional assessment (not general assessment)

This has been revised to read nutritional assessment – see page 2

Introduction
p 4 introduction: content, not “contents”

This has been revised – see page 4 paragraph 2

p 4 The authors could mention to support their statement that hydration has an effect on weight that in most clinical guidelines, severity of dehydration is assessed by % weight loss, which can go up to 10% and beyond. WHO and other clinical guidelines could be quoted to support this statement, in addition to ref 3 (not directly related to this topic).

We agree with the suggested amendments in reference and statement. This statement has been revised- see page 3 paragraph 2 and also the revised reference 9 (WHO clinical guidelines for management of illnesses with limited resources)


Study design has been restated-see page 4
“MUAC, weight and height were measured and recorded, and were repeated after 48 hours.” Reword. Measures were repeated, not MUAC weight and height.

Statement has been revised – see page 4

p6 The authors say children were treated according to the WHO protocol but quote an USAID document as reference. Not consistent.

Reference has been revised – see page 5

“Measures were taken within 30 minutes of each other and readings were blinded from each other.” readings ? Or readers ? Or observers.

Statement revised – see page 5 paragraph 3

p 8 : “Neither rehydration therapy, nor the starter milk formula (F75) used for stabilization of severely malnourished children are aimed at growth.” Not explicit enough. Suggested rewording: The
composition of rehydration solution providing hardly any energy and that of the low protein starter milk formula (F-75) make deposition of lean or fat tissue unlikely or if present, negligible and unlikely to influence measures. Two lines further: change “growth” with “tissue deposition”.

This statement has been revised in agreement with the reviewer’s suggestions-see page 7 paragraph 2

p 9. No way to compare the ICC for different nutritional indices?

The inter-observer section of this study is not powered enough to compare the different ICCs from nutritional indices. However, related to this question, we have submitted another manuscript that has attempted to compare ICCs of different nutritional indices in a much larger population.

p 10. “In linear regression models, adjusted for age and sex, a one percent (1%) change in hydration,...” weight ?? See above.

Table 2 and figure: replace change in hydration by weight change

This has been revised – see table 2 page 22 and figure 1 page 24

p 11 cut-off

Revised – see page 10

p 12 The authors say: Similar to our findings, the authors concluded that the anthropometric changes observed were explained by dehydration and not malnutrition. Replace “malnutrition” by “change in nutritional status”. Malnutrition hopefully unlikely to occur after treatment.

This has been revised to read “change in nutritional status” – see page 11 paragraph 2

p 13:
“There is a controversy over the use of oral versus intravenous fluids among severely malnourished children.” Delete. No need to mention this controversy here. This study does not contribute to it, just about SAM diagnostic criteria. This paragraph makes perfect sense without this sentence. “Many of the children would not then have fulfilled the WHO criteria for severe wasting in many of these children.”

Rephrase. Not clear.

This statement has been rephrased, deleting this controversy, and considering the reviewers comments – see page 12 paragraph 1

p 15 list of abbreviations
Weight-for-height
Weight-for-age
World Health Organization.
ICC Intra Class Correlation Coefficient

These have been revised – see page 14
References:

Reference 1 has been revised to reflect reviewer’s suggestion – see reference 1

Reviewer 3: Steve Allen

Major Compulsory Revisions

1. An important issue that is not fully addressed in this study is that the clinical signs of dehydration and malnutrition overlap – so a critical issue is the reliability of the diagnosis of dehydration in malnourished children. In this study, 81 children had lost weight by 48 hours suggesting that they were not in fact dehydrated at baseline (assuming that they were assessed as no longer dehydrated at 48 hours). It would be important to know how many of these 81 children were classified at baseline as malnourished. In these children, it would be reasonable to conclude that dehydration was diagnosed incorrectly. This is directly relevant to clinical management as rehydration may then be deleterious.

In addressing this important comment, we have gone back to re-analyze the data and looked closely at the 81 children who had lost weight after 48 hours. There were fewer children with SAM: 24% in the study overall and only 10% among those who lost weight. On page 9, paragraph 2, we have added that about 10% of the 81 children were severely malnourished at baseline by WFLz and by MUAC.

2. As well as the overall effect of dehydration on the reliability of the 3 parameters of wasting in the whole cohort of children, it would be useful to also present this information in just those children in whom dehydration was confirmed – i.e. excluding the 81 that had lost weight at 48 hours. Although this information would have limited relevance to clinical practice, it would give a more accurate estimate of the effect of rehydration on nutritional parameters in confirmed dehydration cases.

We agree with the reviewer’s comments and had originally considered including this. We have added the findings excluding the 81 children who had lost weight after 48 hours of rehydration. Interestingly, we found that the results did not differ when repeated excluding the 81 children and therefore did not see the need to alter table 2, however, we have added a statement on page 9 paragraph 3 to this effect.

Additionally, for the benefit of the reviewer, we have added in this letter a summary table indicating the statistics leading to our conclusion of no difference explained above.

<table>
<thead>
<tr>
<th>Predictors of change in MUAC</th>
<th>ALL PATIENTS</th>
<th>EXCLUDING 81 WHO LOST WEIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=325)</td>
<td></td>
<td>(N=244)</td>
</tr>
<tr>
<td>Coefficient</td>
<td>P value</td>
<td>Coefficient</td>
</tr>
<tr>
<td>1% change in weight</td>
<td>0.359</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>0.892</td>
<td>0.020</td>
</tr>
<tr>
<td>Age in months</td>
<td>-0.019</td>
<td>0.330</td>
</tr>
</tbody>
</table>
Predictors of change in MUACz

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>P value</th>
<th>Coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% change in weight</td>
<td>0.035</td>
<td>0.001</td>
<td>0.037</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>0.079</td>
<td>0.033</td>
<td>0.096</td>
<td>0.022</td>
</tr>
<tr>
<td>Age in months</td>
<td>-0.002</td>
<td>0.203</td>
<td>-0.003</td>
<td>0.123</td>
</tr>
</tbody>
</table>

Predictors of change in WFLz

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>P value</th>
<th>Coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% change in weight</td>
<td>0.115</td>
<td>0.001</td>
<td>0.112</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>-0.024</td>
<td>0.001</td>
<td>-0.041</td>
<td>0.001</td>
</tr>
<tr>
<td>Age in months</td>
<td>-0.001</td>
<td>0.721</td>
<td>0.00004</td>
<td>0.89</td>
</tr>
</tbody>
</table>

3. The misclassification of wasting according to index used is presented in table 3. Related to the above, removing the children whose weight fell would help to clarify how children moved between nutrition classifications following rehydration.

We have the analysis including only those who gained weight added to table 3. Because this analysis excludes infants below 6 months, the total number included was 218 children. We found that the proportion misclassified as moderate or severe malnutrition was markedly increased. These results have been illustrated in text on page 11 paragraph 2 and have also been presented alongside those including all the patients on table 3 page 23.

4. In the discussion (top of page 13), the authors state that their findings contribute to the debate on appropriate treatment for dehydrated malnourished children regarding oral versus IV fluids. However, no data are presented on the route of rehydration. Also, the value of the findings of this study to this debate seems limited because data regarding the reliability of individual clinical signs at baseline (table 1) according to “true” hydration and nutritional status as assessed at 48 hours are not presented.

**Minor Essential Revisions**

1. Children with kwashiorkor were excluded. What were the criteria for kwashiorkor? Was this the presence of nutritional oedema alone or were other clinical signs of kwashiorkor required? If signs additional to oedema were required, could the weight loss in some children be due to loss of oedema?

Admission diagnosis for inclusion into this study was done by a trained clinician. In order to distinguish children with Kwashiokor from other ailments, they were assessed mainly for change in skin pigment, large protruding stomach and presence of swelling (oedema) among other signs. This has been indicated on page 5 paragraph 1

2. The potential clinical importance of the findings could be explored more in the discussion. How might clinical management be adversely affected in the 1 in 5 dehydrated children misclassified as severely malnourished on admission? Also, as above, the possibility of the incorrect diagnosis of dehydration in malnutrition could be discussed.

In our conclusion on page 13, we discuss the potential effects of our findings to clinical management of children misclassified as malnourished at admission.
3. It would be useful to add the denominators in the “change” column for WFLz in table 3. Denominators on column 3 of table 3 have been added – see table 3 page 23

4. Correct “including” to “included” in 5th sentence of “Study participants” section. This has been corrected – see page 4

5. Check syntax in last sentence of 4th paragraph, Discussion. This has been revised – see page 12

Discretionary Revisions
6. In the discussion, some mention of the apparent importance of sex as an independent predictor of change in nutritional index (table 2) would be useful. Does this have a reasonable explanation? If not, why might it have occurred in the analysis?

Our findings suggest a positive gender coefficient for MUAC and a negative one for WFLz. We investigated this deeper by looking at the proportion of boys and girls that lost weight or MUAC over the observation period. We found that a larger proportion of girls lost weight and this was reversed for MUAC. Further upon restricting the analysis to those who gained weight or MUAC (gained MUAC n=152 & gained weight n=243) and excluding those with no change in MUAC or in weight, we found that the effect of gender on MUAC is no longer statistical significant although this was not the case for WFLz. We therefore think that the slight differences with regards to WFLz and MUAC by gender are because we included all patients in our final analysis (which is more practical to do). Thus we are simply adjusting for gender to make a more precise estimate of the effect of the percent weight changes, and would not wish to overplay it’s importance.

I confirm that all authors have read and approved the final submitted manuscript, that we have not submitted this manuscript to any other journal and that we still have no competing interests to declare.

Yours sincerely,

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