Reviewer’s report

Title: Anaemia and blood transfusion in African children presenting to hospital with severe febrile illness

Version: 1 Date: 22 September 2014

Reviewer: Walter Dzik

Reviewer’s report:

General comments:

This is a well-written paper from a prestigious clinical research group and presents analysis of a sub-group of patients from the FEAST trial. The study focuses on those FEAST patients who presented with anemia and required blood transfusion. The report provides data on approximately 2,300 children who presented with anemia and among these ~1000 had severe anemia (Hb < 5 g/dL)—a level of anemia rarely seen in developed nations. Thus, this paper presents data on a huge cohort of severely anemic children requiring urgent blood transfusion and adds substantially to the description of this condition.

The authors present data on the relative proportion of mild, moderate, and severe anemia and on the clinical features and basic laboratory tests which accompany each category. They provide data on the number of children transfused, the number of transfusions given, and the timing of the transfusions. There is critically important outcome data provided on the rate of short-term (<48 hrs) survival among those with mild, moderate, and severe anemia. The authors note regional variation in not only the severity of anemia, but also in the need for re-transfusion, as well as in compliance with commonly-accepted WHO guidelines.

This is an important paper with a wealth of information.

Major compulsory revisions:

1. Need to emphasize more strongly the fatal consequences of delay in transfusion.

   The single most striking finding of this paper—both clinically and statistically—is the following: delay in blood transfusion, even for a few hours, for children who present with severe anemia is a fatal delay. The authors data demonstrate that, among children with severe anemia, those who receive transfusion >8 hours after presentation have a 12-fold higher death rate than those transfused more promptly. This is the most important “take away” message because it means there is strong justification for having all pediatric acute care centers stocked at all times with a supply of group O “emergency release” blood available. The actual data from the paper are:

   .....Among those with Hb < 5 g/dL:
This corresponds to unbelievably high chi-square of 250 with a p<< 0.00001. Stated another way, only 4% of children with severe anemia who were transfused within 8 hours died. This value (4%) is little different from the “background” fatality rate among the entire group. In striking contrast, 52% of children with severe anemia who had delays in transfusion died.

I would recommend that the authors make this very important part of their analysis a centerpiece statement in their Results, Conclusion, and Discussion because this data has direct policy implications for blood availability and childhood mortality in sub-Saharan Africa.

While the importance of prompt transfusion is clearly of greatest value in the severely anemic subset of children, it is notable that even in the overall dataset, there remains a fatal price for delay, as shown by the data:

All transfused patients:
Transfused < 8 hours > 8 hours

Dead 57 95
Alive 1061 1133
P< 0.0116

2. Need to report the interaction effect of bolus volume loading on top of transfusion.

A concern in this data (and in the FEAST trial) is that it seems possible that some children presented with severe anemia (Hb < 5) without hypovolemia, and that these children might have been randomized to receive 40 mL/kg of 5% albumin and THEN also transfused with an additional 20 mL/kg of whole blood. Since both 5% albumin and whole blood are fluids confined to the intravascular space, these children may have received 60 mL/kg of intravascular volume in short order. This represents a volume nearly equal to the child’s entire blood volume, or ...a sudden doubling of intravascular volume. The question is whether or not excessive fluid overload may have contributed to mortality. Although the authors present data (in Figure 2) that bolus vs non-bolus did not vary when stratified by presenting Hb, Readers would like to know whether bolus therapy on top of transfusion therapy was deleterious. So, please present an analysis of the following:

…Among the sub-set of transfused individuals…..

Bolus arm No bolus arm
Among the subset of transfused children presenting with Hb < 5 who also received transfusion…

40 mL/kg 5% albumin No bolus arm

3. Factors contributing to a fatal outcome:

In addition, it would be very instructive to do a simple logistic regression analysis restricted to the TRANSFUSED children using death as an outcome to determine the factors significantly contributing to a fatal outcome. Input variables would certainly need to include:

* presenting Hb
* <8 hours vs >8 hours before transfusion
* 5% albumin, saline, no bolus
* presenting lactate <5 or >5
* received whole blood or received packed cells
* other data as you will see fit.

This analysis would help us to understand which co-factors were most significantly related to adverse outcomes among the transfused cohort.

(You might consider the same approach restricted to the subset of children who presented with Hb <5 since most of the death is clustered in this category.)

4. Need to de-emphasize certain features of the current conclusions:

The current manuscript should undertake, in this reviewer’s opinion, some adjustments to the stated conclusions of the paper.

Looking at the abstract, one reads:

a) “Severe anemia is a leading cause of death in children presenting to hospitals in East Africa with a febrile illness.” However the data presented in this paper do NOT tabulate all the causes of death and so one cannot conclude (from the data given) that severe anemia is a leading cause. You CAN say: “Death occurs in 13% of children who present with severe anemia and a febrile illness in East Africa.”

b) “The high rates of re-transfusion…”.

Actually the rates of re-transfusion are low. In the Kenya data, 98% of children
did NOT need re-transfusion. Overall, more than 90% received only one transfusion. I suspect that with a good look at the data you will be able to conclude: “Overall, the great majority of children required one transfusion. However, the lower the presenting hemoglobin concentration, the more likely that a child received a second transfusion. Re-transfusion was given to x% of children presenting with a hemoglobin < 5 g/dL.”

c) The conclusion about “under treatment of a significant proportion of anemic children” is not supported by the overall data. Indeed, it is a small minority. Better just to report the number and not an adjective.

d) “A clinical trial to evaluate the impact of larger volume…” This statement should be removed as a conclusion from the abstract and from the final paragraph. It is not a “conclusion” of the presented data. The manuscript should stand on its own as an analysis of what you found and should not be presented as a “justification” for a planned study. The announcement of the study can certainly be presented in the Discussion, but it simply isn’t an analytic conclusion.

These same concerns (regarding conclusions) arise at the end of the manuscript.

Minor essential revisions:

5) Results, end of prevalence section: The authors report that the prevalence of severe anemia was lowest in Kilifi (13%) and highest in eastern Uganda (39-43%). A few sentences later, they report that the proportion of children receiving 2 or more transfusions was lowest in Kilifi (<5%) and highest in eastern Uganda (23-38%). I expect you will find that these two observations are tightly related. When a child presents with a Hb= 2 g/dL and is treated properly, his post-transfusion Hb is still likely to be low and so a second transfusion is likely to occur. When a child presents with an Hb=4.5 g/dL and is treated properly, a second transfusion is not likely to be needed. This is simply a matter of the “dose-response balance sheet of red cell mass”. So, while you are quite correct to acknowledge that the higher rate of re-transfusion in eastern Uganda (and esp at Mulago) might be (in part) related to greater access to transfusion (your comment in the Discussion), you are likely to find a statistically significant association between presenting Hb and need for re-transfusion. I recommend you undertake demonstrating this association because it would clarify the importance of this “driver” for re-transfusion for the Reader.

6) Results: Number and Type of Transfusions: Given the high rate of death that was attributed by the independent adjudicators to “cardiovascular causes” and the very low rate of treatment with furosemide (only 5 children out of >1000), do you think that there may have been tremendous “under-recognition” of cardiac strain in this cohort? I think so. While you present the information (Results) that only 5 children received furosemide, you may want to comment on this in light of the high rate of cardiovascular death.

7) Discussion, paragraph #3: “…though more recent work suggests that metabolic acidosis[14] and hypovolemia [15-17] may be central to the pathophysiology.” This statement is correct as written, but reference 14 is nearly
20 years old and so the phrase “more recent” is not really very accurate. You could improve this sentence by referring to the work of cited below which is indeed more recent (2013), which covers far more data than that provided in the cited references, and which supports your finding that respiratory distress is highly correlated with lactic acidosis. Reference is: Cserti-Gazdewich CM, Dhabangi A, Musoke C, et al. Inter-relationships of cardinal features and outcomes of symptomatic pediatric Plasmodium falciparum malaria in 1,933 children in Kampala, Uganda. Am J Trop Med Hyg. 2013 Apr;88(4):747-56. doi: 10.4269/ajtmh.12-0668.

8) Discussion, Paragraph #3: With the growing access to point-of-care lactic acid measurements, there is the important question of whether an elevated LA helps to further identify those at high risk of death. If it does, then this would be a good argument to further invest in LA measurement for risk stratification. With this in mind, Readers might be very interested to see:

<table>
<thead>
<tr>
<th></th>
<th>LA &lt; 5 mM</th>
<th>LA &gt; 5 mM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Alive</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

On the other hand, rather than doing this univariate chi-square, you might prefer simply to report the odds-ratio of elevated lactate in the logistic regression. See point # 3 above.

9) Discussion, paragraph 6: “As far as we are aware...”. You may want to adjust the text here if the analysis demonstrates (as I suspect that it will) that re-transfusion is highly associated with the presenting level of Hb.

10) Discussion: “The highest proportion of repeat transfusions occurred in Mulago Hospital...” This paragraph is weak, not fully supported by the data, and I urge you to reconsider the message. You do NOT present data demonstrating superiority of whole blood over packed cells. The suggested logistic regression (see above) could include that variable to demonstrate whether or not there is a statistically meaningful association between survival and whole blood vs packed RBCs...as well as demonstrate the magnitude of the effect. Unless you are armed with such data, I would recommend AGAINST speculation in this section that whole blood brings advantages. In fact, from a strictly transfusion medicine perspective, the opposite can be argued. Consider the following points:

* Making packed cells does NOT add much cost at all. Most regional blood suppliers have a centrifuge and, even without a centrifuge, one can make packed RBCs by simple gravity sedimentation overnight by placing the bags in a vertical posture.

* Your data demonstrates that for ANY level of Hb worthy of transfusion, that the bolus group did less well. Thus excess volume is NOT an advantage to these children and so it may not be wise to promote whole blood without better data to support it.
Your data very strongly demonstrates that “time” is of the essence for saving lives among the severely anemic. This is a very strong a powerful data point. Seeing this fact, as a Transfusion Medicine professional, I would want to have Group O Red Cells available at all times in my pediatric urgent care area because the child who arrives at 6 pm may not make it until morning without transfusion. However, whereas group O packed RBCs can really be given to nearly every child without much risk, group O whole blood carries anti-A and anti-B antibodies in the plasma. These antibodies can “add” to the hemolysis if the recipient is group A or group B or group AB. This is especially a greater risk in children (compared with adults) where the relative volume of donor blood is high. Hemolysis contributed to by passive transfer of anti-A and anti-B from the group O whole blood bag is often hard to observe in patients who present with hemolytic conditions (like malaria) and so you could miss it. As a result, in regions where whole blood is used, blood bank professionals prefer to provide “ABO matched whole blood” rather than “emergency group O”. In contrast, when working with packed RBCs, facilities provide “group O packed RBCs for all”. It is, of course, far easier to maintain an “emergency inventory” of just one blood group. Emergency inventories of group O packed RBCs do not require ABO typing the recipient or crossmatching and so delay in therapy “after hours” is less likely to occur. For all these reasons, if I were setting up an “emergency transfusion” scheme in sub-Saharan Africa, it would be far easier to defend the use of “Group O packed RBCs” as the initial management product.

11) Discussion, end of the paragraph referred to in #10 above: “the paucity of serious adverse events…” I would first check the chi-square analysis referred to above in item # 2.

12) Discussion: “The high proportion of repeat transfusions also…” I think this is a bit self-serving and not fully supported by the data. See discussion above. You can refine this for Readers, I think, by pointing out that re-transfusion is really a topic for those who present with extreme anemia. You might want to be a bit more conservative in your comments here. I do not think that we have good clinical outcomes data on children who present with Hb’s of 1-3 g/dL (really severe anemia). These children, who often have systemic acidosis and thus a cardio-depressant effect of low pH, are fragile recipients. We do not have sufficient clinical research data to know that 30 mL/kg is safe for this sub-set. It may be that they are better treated with repeated lower dose transfusions. If I were writing this section, I would rephrase this to make the following points:

* Repeat transfusions are more likely in those who present with extreme anemia.

* The ideal volume and rate of red cell replacement for patients with extreme anemia is unknown and deserves further study.

Minor issues not for publication:

Results: Furosemide is mis-spelled.

Summary

Finally, I would like to congratulate the authors of this paper on this fine work.
Anemia in children is an extremely important topic in sub-Saharan Africa. This group has distinguished itself as leaders in the effort to do pragmatic clinical research that will benefit millions of children worldwide. I hope that each and every author of this work is proud of this effort and that you know how grateful are Readers for the insight gained from these important results.

I would like to also thank the Editors for the privilege of being allowed to review this important manuscript.

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.