Author's response to reviews

Title: Should colloid boluses be prioritized over crystalloid boluses for the management of dengue shock syndrome in the presence of ascites and pleural effusions?

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Author's response to reviews: see over
Dear Madam

Re. Paper entitled “Should colloid boluses be prioritized over crystalloid boluses for the management of dengue shock syndrome in the presence of ascites and pleural effusions?”

I have now revised our manuscript paying attention to all the comments raised by the two reviewers. The changes are highlighted in blue in the text. The details of revisions that were carried out are given at the bottom of this letter with references to the main manuscript. I hope that our manuscript is in order for your kind consideration for publication in the BMC Infectious Diseases.

Many thanks

Yours faithfully

Prof. Ranjan Premaratna
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Responses to Reviewer’s report

Title: Should colloid boluses be prioritized over crystalloid boluses for the management of dengue shock syndrome in the presence of ascites and pleural effusions?

Reviewer: Siripen Kalayanarooj

- Abstract
  - Case presentation
  # Add the following sentences at the end of 3rd line and delete the later sentences. Ascites and pleural effusion were detected in all 3 patients at the time of shock no matter IV fluid were given or not. All 3 adults patients had documented liver involvement at the time of shock by elevation of AST (4,800; 5,000 and 1,960 U). One patient who had profound shock died 6 hours after admission with evidence of acute pulmonary edema while 2 patients who survived developed acute pulmonary edema in convalescence phase. All of them needed ventilator support with potent diuretics.

These changes were done in the abstract
o Conclusion: change to the following sentences.

# DSS patients whom ascites and pleural effusion were detected at the time of shock mostly had received quite a significant amount of IV or oral fluid before. Emphasize on fluid contains electrolyte or oral electrolyte solution is important for plain water can lead to massive plasma leakage because of its hypotonicity. In cases of profound shock, corrections of acidosis, hypoglycemia and hypocalcemia are very important for the patients will not response to only conventional IV fluid resuscitation. Concealed internal bleeding especially those cases with rapid dropping in hematocrit (HCT) without clinical improvement in spite of a large amount of IV fluid resuscitation. Colloidal solution in bolus dose is indicated in those cases while waiting for blood transfusion.

The amounts of fluids given were revised in detail under each case and the facts on the importance of correction of other contributory factors for prolonged shock were included under conclusions.

• Background
  o Last paragraph: The recent outbreak of DF. Change to the recent outbreak of dengue

Done

o Line 6 – delete the sentences begin with Although… and replace with the following sentences. IV fluid resuscitation of shock was done according to the WHO guidelines without follow up hematocrit and investigations/ corrections of the commonly found laboratory abnormalities when the patients did not response to the conventional IV therapy.

A separate paragraph was added at the end of the third case in order to highlight how these three patients were managed. Further details on fluid resuscitation were included under each case.

• Case 1

Following questions on fluid management and the amount of fluids that were given were clarified in detail in order to avoid further confusions and the reasons why they were given have now been included under each case and in conclusions.

o Question about the total volume of fluid resuscitation. Three boluses (each lasting for 15-20 min) of 10-20 ml/kg/hr in a 48-kg-woman = 1,500-3,000 ml in 1 hour, not 1,000 ml in 2 hrs as in the text?

o Question about colloid (4 unit of FFP = 800 ml?) in how many hours? Why?
What is the BP and pulse and HCT? If the patient responded to the treatment, then IV fluid can be reduced further.

- This patient developed respiratory distress at 8 hrs after shock. Total IV fluid she had received = 4,300 ml? (First hour = 1,500; 2nd hour = 1,500 ml, FFP 800 ml between 3-4th hour and 250 ml in 5-6th hour). She deserved acute pulmonary edema if she really received this amount. WHO guideline to repeat frequent vital signs monitoring, HCT, blood gas, electrolyte, blood sugar if not respond to conventional treatment. If stable vital signs, further reduce IV rate.

- **Case 2**
  - This patient presented with profound shock and hypotension so concealed internal bleeding should be suspected although HCT on admission 58%. The text is confused? Two intermittent boluses over 20 mins: 20 ml/kg/hr basis and BW 60 kgs, the total volume should be 2,400 ml in 40 mins? And colloid (6 units of FFP = 750 ml) in one hour. Total IV fluid resuscitation 3,150 ml in 2 hours? She also deserved acute pulmonary edema with CVP = 22-26 cm H2O. Blood gas 2 hours after admission revealed metabolic acidosis – mean that no correction. No HCT follow up. Not mentioned about giving VitaminK1 for liver failure, Ca gluconate for commonly found hypocalcemia.

  - Details on hepatic failure management were added.

- **Case 3**
  - The first 24 hours after shock, she had more than adequate urine output (0.7-0.8 ml/kg/hr). She developed shock again after 24 hours and about 2,050 ml of IV fluid was given. This second shock, the patient was likely to have shock because of respiratory failure due to too much fluid. Colloid solution should be given here together with furosemide immediately.

- **Discussion**
  - The authors followed WHO guidelines only with IV fluid resuscitation but not follow other important recommendation: No follow up HCT, No close monitoring vital signs, no lab investigations and corrections especially in cases with profound shock or cases with not responded to conventional IV fluid therapy. Integrated management for DSS patients is important to reduce case fatality rate and complications. Not only IV fluid resuscitation!

  - This question was answered in the text

- If in febrile or critical phase, patients drink plain water, not electrolyte solution, this will cause more plasma leakage, more ascites, more pleural effusion and probably hyponatremia that can lead to convulsion.

- **Conclusion** – as in abstract

  - Conclusion was changed considering the comments raised by the other reviewer as well.
Responses to Reviewer: Po-Liang Lu

The authors revised this manuscript, described these cases more detailed, and made more reasonable conclusions. The authors' main points are: In DSS with third space fluid “accumulation”, the beneficial of colloid bolus should be evaluated carefully in the future. Because the colloid effect was immediate and transient, reasonable use of colloid (such as FFP) and mention the possible transfusion reaction is important.

Comments were highly appreciated and necessary revisions were carried out.

Minor Essential Revisions
1. In the article, the authors may consider to use the term “third space fluid accumulation” to replace "third space fluid loss”?

Changed to third space fluid accumulation

2. The author hypothesize that resuscitation of patients who already have third space fluid loss at the time of development of severe DSS giving priority to colloids rather than to crystalloids would prevent development of recovery phase pulmonary oedema. However, the three patients had received both crystalloids and colloids resuscitation while DDS with third space fluid accumulation had developed. It is difficult to differentiate the pulmonary edema in recovery phase is related to crystalloids or colloids. The above may be addressed in the discussion part.

We agree with the comment and this fact was added in the conclusion.

3. Regarding to the double blinded RCT, NEJM, 2005, 353:877–889. In the 2nd paragraph of discussion part, the authors stated that “in this study there is no mention about the presence of third space fluid loss at the time of recruitment. They have analysed only the occurrence of them following resuscitation. Therefore, it is difficult to interpret which fluid would be beneficial in patients who already have third space fluid loss at the time of severe DSS.” However, that study analyzed the possible Adverse Effects of Fluid Treatment (in the table 3 of that article); no difference between crystalloids and colloids resuscitation in clinical fluid overload, right pleural effusion, ascites and even the dosage of diuretic agent usage. The article conclude that the effects of colloids are transient; and despite the early rebound in the hematocrit seen in the children receiving colloids but no difference between the different fluids in the overall severity of fluid overload when it was assessed 48 to 72 hours after the study infusion. Besides, the adverse of colloids should be noticed. The comments on the previous articles may be revised to reveal the true situation.
We have now included facts highlighted in this study under conclusions and revised the manuscript accordingly and this paper was referenced.