Author's response to reviews

Title: Deficiency of ADAMTS-13 in Pediatric Patients with Severe Sepsis and the impact on in-hospital mortality

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Version: 2 Date: 21 February 2013

Author's response to reviews: see over
In response to the concerns raised by the reviewers and the editor. The response is given one by one to each concern.

1. Please include the name of the ethics committee that approved the study in the ethics statement in your manuscript. Please also state whether consent from parents/guardians was written.

The Ethics committee that approved was the study was the ethics committee of Aga Khan University Hospital. The approval number has been mentioned in the materials and methods section.

2. Consent: Please state in the Methods section whether written informed consent for participation in the study was obtained from participants or, where participants are children, a parent or guardian.

Written informed consent was obtained from parents/guardians. It has been added in the materials and methods section.

3. Copyediting: After reading through your manuscript, we feel that the quality of written English needs to be improved before the manuscript can be considered further. We advise you to seek the assistance of a fluent English speaking colleague, or to have a professional editing service correct your language. Please ensure that particular attention is paid to the abstract.

Quality of written English has been improved.

4. Competing interests: Manuscripts should include a Competing interests section. This should be placed after the Conclusions/Abbreviations. Please consider the following questions and include a declaration of competing interests in your manuscript:

Declaration of competing interests have been included in the manuscript keeping in mind financial and non-financial interests.

5. Structure: Please check the instructions for authors on the journal website to ensure that your manuscript follows the correct structure for this journal and article type.
The structure of the journal and article type has been followed.

6. **Figure titles:** All figures must have a figure title listed after the references in the manuscript file. The figure file should not include the title or number (e.g. Figure 1... etc.). The figures are numbered automatically in the order in which they are uploaded. Done. Separate figure file uploaded in PDF format.

7. **Figure cropping:** It is important for the final layout of the manuscript that the figures are cropped as closely as possible to minimize white space around the image. For more information, see the instructions for authors:
   
   [http://www.biomedcentral.com/info/ifora/figures](http://www.biomedcentral.com/info/ifora/figures).

   Cropped.

8. **Copyediting:** After reading through your manuscript, we feel that the quality of written English needs to be improved before the manuscript can be considered further.

   Changes made.
Reviewer's report (1)

Title: Deficiency of ADAMTS-13 in Pediatric Patients with Severe Sepsis and the impact on outcome.

Reviewer: MOREL Nathalie

Reviewer's report:

Please, could you answer to the following questions or correct mistakes, before a decision on publication can be reached (major compulsory revisions).

1/On the content:

- In materials and methods:

  o Is it possible to briefly recall severe sepsis criteria?

  Yes, additions have been done in materials and methods section.

  o Are you sure that this type of study is descriptive, cross-sectional? Outcome data necessites a longitudinal study. Otherwise, retrospective character must be indicated.

  A cross-sectional study examines the relationship between disease and other variables of interest as they exist in a defined population at a single point in time or over a short period of time (e.g. calendar year). Cross-sectional can be both descriptive or analytical. In practice, cross-sectional studies will include an element of both types of design. (Reference: Hennekens CH, Buring JE. Epidemiology in Medicine, Lippincott Williams & Wilkins, 1987.)

  It is a cross-sectional study. The condition (ADAMTS-13 deficiency) and related factors (thrombocytopenia, clinical characteristics) were measured at a specific point in time for a defined population (pediatric patients with sepsis). We also investigated the association between a putative risk factor and a health outcome (in-hospital mortality) for a short period of time. I have omitted the term descriptive because it contains both elements (descriptive and analytical).

  o ADAMTS 13 analysis: What type of test was used to describe decrease of ADAMTS-13 levels? Activity? Antigen?

  It was ADAMTS-13 antigen levels. It has been added in ADAMTS-13 analysis section. (Materials and methods)
Precise what is assayed in outcome: mortality? Could you give average time of follow up in your study, and, time of follow up for the last patient included in the study.

It was in-hospital mortality that was assayed. I have replaced the terminology of outcome by in-hospital mortality where ever it was used. The patients were not followed up after being discharged from hospital. The average time of hospital stay was 12.4 days in patients with ADAMTS-13 deficiency, while it was 8.8 days in the non-deficient group.

- In results:
  o At second line: sum of the two percentages (56.3% and 43.8%) is not equal to 100: could you verify the rounding of percentages.

It has been corrected.

o “Clinical characteristics were compared and were not statistically significant”.

You can’t use “statistically” because statistical tests were not performed for all characteristics compared. In fact, statistical tests are not necessary in this case but you can’t write “statistically”: Clinical characteristics were compared and don’t seem to be different between two groups.

Changes made as suggested.

o Precise time of follow up in this part too; otherwise it’s difficult to understand proportion of alive patients, dead patients, and patients lost to follow-up.

As answered above, we only looked at in-hospital mortality and compared it between two groups. I have changed the term lost-to-follow up. These patients were diagnosed as having severe sepsis in our hospital but were shifted to other hospitals due to various reasons, so they were not included in the mortality analysis. The alive patients were those who became well and were discharged from hospital in stable condition. Dead patients are those who expired within the hospital.

- In discussion:
  o “our results revealed that pediatric patients with severe sepsis seem to have a higher incidence of ADAMTS13 deficiency. (in fact, you didn’t give a statistical test to affirm that incidence is really higher.” Furthermore, who is the control group used?

No comparison is made here. There was no control group. It is stated that ‘pediatric patients with severe sepsis have high incidence of ADAMTS-13 deficiency’. This is based on the results that 60% of pediatric patients with severe sepsis were ADAMTS-13 deficient.

o “Septic patients with ADAMTS13 deficiency were more thrombocytopenic”: results allowing to affirm that, and statistical tests must be detailed in results paragraph.
It has already been mentioned in results section that out of total 37 patients with thrombocytopenia, 75.6% were in the ADAMTS-13 deficient group. The sentence has corrected as follows “Our results revealed that majority of the patients having thrombocytopenia were in the ADAMTS-13 deficient group.”

- For figures:
  o Table 1: Give the signification of used abbreviations: PT, APTT. You speak about which type of cultures? (blood cultures?). Give the p-value for negative cultures, if you gave it for positive cultures.

Signification of PT and APTT has been added in the abbreviations section. ‘Culture’ have been replaced with ‘blood culture’. The importance was of positive cultures, therefore p-value of positive cultures was given. I have removed the negative cultures from the table.

  o Figure 1: Length of hospitalisation in place of hospitalisation’s duration. Please give units of two axes. Please, could you give title of Y axe without abbreviation.

Changes made as advised.

2/On the form:

- Some precisions could be done to make easier reading and comprehension:
  o In summary and in full text: “comparison was done with regard to some clinical and biological characteristics and outcome between two groups”

It has been corrected.

  o First paragraph of discussion: could you reformulate the first sentence, because I think we could not class defect in ADAMTS-13 because of acquired antibodies in primary causes.

Sentence was reformulated.

  o Second sentence of discussion: precise that specific treatment must be performed in emergency.

Corrected as advised.

- Some mistakes must be corrected:
  o Please, could you unify abbreviation use for “von Willebrand Factor”: vWF or VWF but not both.

I have now used the term ‘vWF’ throughout.

  o In introduction: “decreased levels of ADMATS-13 are particularly seen in TTP”.
Corrected

- In introduction: “systemic lupus erythematosus”.

Corrected

- In materials and methods: “kept at -80°C temperature until analyses”.

Corrected

- At the fourth paragraph of results: “difference was not statistically significant”.

Corrected

- In discussion: “may have change the results (and not changed).”

This is not clear but I have changed the sentence as follows: “Inclusion of these patients in analysis may have affected the results.”

- Proofreading by an anglophone seems essential.

Done

- In fact, style is perfectible and some sentences are difficult to understand (for example, “thus the burden…until end of introduction”; Prefer “preventive strategies are needed… in place to “there is a need for preventive strategies”;

Agreed, corrected.

- “the outcome these of patients”; “dead” in place to “expired”; “ADAMTS13 supplementation and use of synthetic granulocyte…”).

Changes made to make reading easier.

- Presentation of references must be unify and concordant to instructions to authors of the review: particularly, caution to the presentation “;” or “.” Between names of authors and title of article. Caution to presence or not of month of publication.

References are as per Vancouver style. I have edited all the references according to the journal style.
Reviewer's report (2)

Reviewer: VINCENZO DE FILIPPIS

The results of this study indicate that 65% pediatric patients with sepsis have low levels of ADAMTS13 and that 75% of the latter patients also display lower than normal platelet counts. However, as stated by the Authors, correlation between lower ADMTS13 levels, thrombocytopenia and mortality was not statistically significant, likely because of the problems that occurred during the follow-up of the patients. As recognized by the Authors, these results match those previously reported by others in different studies (refs 13, 26). Nevertheless, the results (albeit confirmatory) may have important implications in understanding the clinical effects of alterations in the ADAMTS13-vWF system.

Finally, the use of ADAMTS13 as a prognostic marker emphasized in the discussion (last phrase) should be downregulated.

Done.

Typing errors should be corrected (es: Introduction, page 5: ....we conducted this study is to detect...)

Corrected.