Author's response to reviews

Title: Undercorrection of hypernatremia is frequent and associated to mortality.

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Author's response to reviews: see over
Dear Editor-in-Chief,

We thank you for having considered our original article entitled "Undercorrection of hypernatremia is frequent and associated to mortality." for publication in *BMC Nephrology*. Please find below the answers to reviewers' concerns and the modified manuscript. As many reviewers discussed our statistical analysis and results, all statistical analysis were reworked and improved. An additional table has also been provided as required by reviewer 2. We hope that the changes made will fulfill the editorial board and the reviewer's questions.

Sincerely,

Stanislas Bataille, MD
Answers to Editorial Requests:

1) Format Abstract

Done as recommended in instructions for authors.

2) Tables should be removed from figure files and included in manuscript document to appear after References section.

Done.

3) Please can you include a statement to acknowledge that retrospective studies do not require formal ethical approval in France. Please include name or relevant laws that confirm this.

The following statement was included in the methods section:
"Research was conducted with regards to standard recommendations of local ethics committee (Comité de Protection des Personnes Sud-Méditerranée II - www.cpp-sudmed2.fr) and followed the ethical standards of the Helsinki Declaration. As defined by French Public Health Code (Articles L1121-1 and R1121-2), no institutional review board and no written informed consent is required for "research in which all practices and products are used in the usual way, without any additional or unusual procedure for diagnosis or monitoring"."
Answers to the reviewers:

Reviewer 1:

- Introduction: “In most cases, treatment of hypernatremia is started at ED, but so far only one publication has studied characteristics, symptoms, treatments, and outcomes of severe hypernatremic patients at ED (1).” – This is not correct. The study by Arampatzis and coworkers (Am J Med 2012) included patients presenting to the ED solely.

This second study which was already present in reference list has been added in the text.

- Introduction: “Unless shock or hypotension is present, isotonic or hypertonic solutes are not recommended.” – Indeed experts recommend to first replace fluid losses in dehydrated/hypovolemic patients by use of isotonic or slightly hypotonic fluids (e.g. lactated Ringer’s). See the review by Lindner and Funk in J Crit Care. 2013 Apr;28(2):216.e11-20

We agree with the reviewer and completed manuscript.

- Introduction: “To avoid over- or under-treatment, at risk for neurological complications (cerebral edema, seizing, or coma), management of intravenous fluid must be rationalized. Mathematic calculation of water deficit based on sodium and water distribution in the intra- and extracellular spaces have been proposed. They require two clinical data: measured natremia and patient’s weight. For example, Adrogue and Madias’s formula enables to calculate natremia variation after perfusion of one liter of solute according to the type of solute, initial natremia and total body water volume: Attended natremia = ([Na] of solute – initial natremia) / (Total body water volume - 1) (3, 8, 9). Most formulas consider human body as a closed system and do not integrate undergoing losses of water. Furthermore, total body water volume required for calculation is extrapolated from weight regardless of percentage body fat variability. For authors, their inappropriate use is at risk of hypernatremia under-correction or worsening (10).” – These formulae have been studied in the past and were found to be too imprecise in the individual patients with deviations > 10 mmol/L (Lindner et al. NDT 2008) – you should include these findings when making this statement due to the potential danger of the formulae.

We completed this paragraph as advised.
- Introduction: “While hypernatremia acquired during the hospitalization is a mortality risk factor (14), it is not clear if hypernatremia at admission evaluation increases mortality (2, 15).” – In fact the large study by Funk and coworkers on about 150,000 patients clearly showed that even mild hypernatremia is an independent predictor of mortality (see your own citation No 13)

The sentence has been modified.

- Methods: Why were only patients with Na > 150 mmol/L included? – In order to bring more light into the chimera of hypernatremia it would be helpful to study the group with Na 145-150 mmol/L too since only little data is available.

In this study, our aim was to evaluate every day practices and their impact on mortality. Unfortunately, in the emergency room, many patients with hypernatremia did not receive an appropriate treatment, even when natremia was >150! Patients with Na 145-150 mmol/L were not included because we wanted to show that even with SEVERE hypernatremia, practices are sometimes inappropriate. Secondly, we wanted to know if these inappropriate practices increased mortality. To increase sensibility, we kept the group with the highest expected mortality group: patients with Na>150. Nevertheless, we agree that studying this group could be helpful.

- Methods: “Optimal correction rate of hypernatremia was defined in accordance with the literature as a decreasing rate between 0.5 to 1 mmol/L/h (3-6).” – It should be added: …with a maximum of 12 mmol/L/day. – Although many experts feel more comfortable with a daily maximum of 10 mmol/L.

Thank you for this contribution which is more precise than our initial sentence.

- General: The manuscript should undergo language editing by a native speaker.

Since last version, the manuscript has been corrected by a native English speaker.
- Abstract: “…an associated extracellular dehydration were associated to death.” – Should be …associated WITH death.

Done.

- Abstract: “…22% of patients without hypotension who received an isotonic solutes or weren’t perfused.” – The sentence is not clear – please clarify.

We clarified the sentence as required.

- Discussion: Header for discussion section is missing

BMC Nephrology Instructions for authors allows a unique results and discussion paragraph. To facilitate reading, paragraphs have been separated.

- Table 1: There is a fault in the number of patients (Total 85; died 19; survived 59) – 10 patients are missing...

In fact, there is no fault in Table 1, but for 7 patients who were lost of follow-up after the emergency room, no data on death was available and they were not included in the comparison. This data was already explained in the Table legend. To clarify our statistical analysis, p were given in a separate Table.

- Table 4: “Arampatzis et al. published two studies in the same year. Patients of the second study with hypernatremia definition _ 150 mmol/L were a subgroup of the former larger study with an unclassical hypernatremia definition.“ – The definition of hypernatremia in the second study (> or equaling 150 mmol/L is a common definition for hypernatremia in many studies on hypernatremia). The first study used the reference range of serum sodium in the local laboratory. Thus, I would not call it unconventional.

We agree normal values of natremia are hard to precisely define and that the local laboratory reference range is the best definition. The sentence was improved.

Reviewer 2:
1. The study sample is relatively small (for any meaningful outcome analysis) and is limited only to patients with Na > 150 mmol/L (N=85), and therefore we do not have an effective reference group for comparisons of survival times.

We agree with reviewer 2 that our sample is relatively small. Severe hypernatremia, as shown in our paper, isn't a frequent comorbidity found in emergency rooms. Nevertheless, the question we tried to answer in our study is whether inappropriate treatment of hypernatremia was associated to death and even in this small sample. Whatever it be, of course, our results need to be confirmed in larger independent cohorts.

2. The small sample size also effectively limits the ability of the authors to evaluate the impact of mild, moderate and severe hypernatremia (as well as hyponatraemia) on mortality. Why for example were patients excluded (n=141) with sodium levels of 141 to 149?

As also answered to Reviewer 1, our aim was to evaluate every day practices and their impact on mortality. Unfortunately, in the emergency room, many patients with hypernatremia did not receive an appropriate treatment, even when natremia was >150! Patients with Na 145-150 mmol/L were not included because we wanted to show that even with severe hypernatremia, practices are sometimes inappropriate. Secondly, we wanted to know if these inappropriate practices increased mortality. To increase sensibility, we kept the group with the highest expected mortality group: patients with Na >150. Nevertheless, we agree that studying this group could be helpful.

3. A better approach might have been to include all patients with measured serum sodium in the ER, and compare mortality risks across the strata of serum sodium concentrations in a graded fashion. This would help explore the risks across the spectrum of sodium concentrations. The authors might consider repeating their analysis but with inclusion of the entire cohort admitted to the ER at their centre and explore the association of serum sodium with mortality across all range (low, normal and high). This is important, as prior studies have described a u-shaped mortality risk association.

We thank reviewer 2 for their considerations, but again, the aim of our study wasn't to make the link between hypernatremia severity and mortality. This link has been already shown. Our aim was to focus on hypernatremia inappropriate treatment which leads to a long
hypernatremia lasting. In this study, we show for the first time that hypernatremia, which is theoretically easy to treat, is often under-treated, lasts for too many days and that this undertreatment increases risk for death.

4. It appears that although the speed of sodium correction to normal levels was associated with mortality, elevated serum sodium levels were not associated with death. This appears to be the inference although the models are not well described in the manuscript. This may again reflect the limitations of the small sample size.

We agree very much with this point. Our sample size is probably too small to prove a relationship between serum sodium level at emergency room and death. However, this argument doesn't modify our original results on hypernatremia treatment, correction speed and inappropriate treatment.

5. This reviewer would like to have seen a table displaying the univariable and multivariable models, along with respective Hazard Ratios and 95% CI. I would also like clarity on the list of covariates that were included in the final model. Was serum sodium accounted for in the final model? It is a bit concerning that a variable, not significant in the univariable model, suddenly becomes very significant in the multivariable analysis. As a result, the authors may be mis-interpreting the relationship between speed of sodium correction and death.

We acknowledge the reviewer's concern about multivariable model. To clarify our results, all statistical analysis were redone and improve. The table displaying univariate and multivariate analysis results for data included in the multivariable model has been provided. Regarding serum sodium, it hasn't accounted for the final model, but calculated osmolarity, which had p<0.1 in univariate analysis and is of course linked to natremia, was included as defined in methods section. Calculated osmolarity did not reach statistical significance in the multivariate model.

6. A greater discussion on the limitations of this study is warranted appears to be the inference although the models are not well described in the manuscript. This may again reflect the limitations of the small sample size.

We also agree with this statement and the following sentence in the discussion: "This small
size explains probably that the relationship between hypernatremia and death did not reach statistic significance."

7. The observations found in this study may not be readily generalizable to the wider population. Similar the management practices described here may well represent a centre effect.

This point was not clearly described in the original manuscript. We raised this question in the discussion part of revised article.

8. The manuscript was difficult to read as
1) The authors did not follow the standard guidelines of BMC nephrology
2) The abstract was not formatted correctly
3) The manuscript lacked a separate results and discussion section (both were intertwined)
4) The narrative description provided on page 8 appears excessive and appears to duplicate the findings presented in Table 1. The authors should consider either a brief text description where the Table itself is self-explanatory. A more focused narrative on the results and subsequent discussion would be beneficial.
5) The text used to describe the hazard ratios and the actual estimates appear to be inconsistent.
6) Please correct typographical errors

Paper has been corrected by a native English speaker and was carefully read to fulfill standard guidelines of BMC nephrology. Narrative description has also been shortened.

9. Prior studies have demonstrated that hypernatremia is an independent risk factor for death when measured either at admission or during the hospitalisation (reference 2, 14), and thus the current study is not particularly new in this regard.

This point has already been discussed in other questions/remarks. The original result provided in this study isn't the link between hypernatremia and mortality, but between treatment practices, correction rate, and mortality.