Reviewer's report

Title: Metformin associated lactic acidosis: a case series of 28 patients treated with sustained low-efficiency dialysis (SLED) and long-term follow-up

Version: 0 Date: 17 Jul 2017

Reviewer: Darren Roberts

Reviewer's report:

Thank you for the opportunity to review this manuscript which describes clinical outcomes in 28 patients with a clinical diagnosis of MALA, and temporal changes in the incidence of MALA in a region. I have the following comments to make.

Major comments

1. Abstract, conclusion: mortality of 21.4% does not sound particularly "acceptable" to me. Upon what criteria was this assessment made? It may not be reasonable to compare to some of the other studies listed in the paper because these may reflect a different patient group to those presented here (based in ICUs or drug company which are highly selective/biased).

2. Inclusion criteria state AKI stage 3, but Table 1 states that 3.6% had AKI stage 2. I note that metformin levels were not measured - how did the authors exclude alternative diagnoses of lactic acidosis?

3. Please clarify that the key indications for inclusion in this study were the same as the indications for dialysis (given that 100% of patients received dialysis, as per Table 1). These criteria indicate minor illness based on markers of acidemia. Further, they are conservative indications for dialysis, particularly when compared to those criteria proposed by others previously, notably by the EXTRIP group (Crit Care Med. 2015 Aug;43(8):1716-30). I note that the EXTRIP guidelines were published after the patients reported here were treated, but it may be interesting to compare the indications in this study to those in the EXTRIP document.

4. The findings of a change in incidence of MALA following the educational campaign, which is currently in the discussion, is very interesting. I suggest that this be incorporated into the
methods and results and not the appendix. Was there a change in the number of prescriptions of metformin during this period, too?

5. Table 1
   a. Suggest ordering the content into demographics, status on admission, treatment received. At present it seems a bit haphazard. For example, % hemodialysis (which I assume to be "post-admission" and this should be stated) is listed prior to mean baseline creatinine. Also, I don't know why it is necessary to list status which were not present (eg "0")
   b. "before the event" should be clarified - before admission? Before the 6 day prodrome?
   c. What proportion were treated in ICU? This is important to understand severity. At present, based on the BP listed, can we assume that vasopressors/inotropes were not required?

6. Table 2
   a. Some laboratory results are here and in Table 1. Suggest turning Table 1 into demographics and baseline characteristics, and Table 2 into admission and followup clinical and laboratory status

Minor comments
1. Please include both SI and conventional units (notably for creatinine)
2. Page 5, line 48: The endpoints for dialysis treatment would allow a patient to be more medically unwell than when they started on the basis of bicarbonate.
3. Page 7, line 12-14: at present, it looks like the results provided are from admission, but they are actually from a later time point?
4. Further discussion of the causes of death would be of interest to help the reader understand if this applies similarly to their own hospital.
5. Page 8, line 23: add "despite ongoing dosing" to the end of the sentence after "metformin excretion".
6. Page 8, lines 40+: I don't follow these comments about Salpeter's work
7. Page 9, line 43: is this talking about incidence of fatal cases? Also, "to be explained" can be "to explain". 
8. Page 9, line 56-58: it is stated that renal function returned to normal in 3 days. Please confirm that this was the case in 85% of patients (given that in 15% of patients did not return to baseline)?

9. English review would be useful. For example:
   a. Abstract, "clinical restoration" could be "clinical recovery"
   b. Page 4, line 16: "finest" could be "detailed". Does "mechanisms" refer to "mechanisms of action"?
   c. Page 6, line 4: "discharged" could be simply "discharge"
   d. Page 8, line 17: "profound interactions" could be "detailed mechanisms of toxicity"

10. Page 4, line 50: Lalau 2015 (ref 14) was not the first to describe MILA vs MALA. For example, this was discussed in Duong 2011 (Drug Saf. 2013 Sep;36(9):733-46.)

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.
Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.
Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.
Yes

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My non-financial declaration of interests are that I am a co-author of the EXTRIP and Duong papers mentioned in my review.

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