

Peer Review File

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Reviewer A

Comments to the authors

Summary

This review summarizes in a very brief fashion results of recent research regarding the treatment of DKA in children. The authors conclude that dehydration is typically at 6-7%, that normal saline should be used primarily along with low dose insulin 0.05 units/kg/hour.

1. Critique

Overall the literature is covered well and this is an appropriate format.

Reply: *We thank the reviewer for encouraging comments*

2. The authors discuss the PECARN study regarding cerebral edema but it should also be discussed under fluid volume and choice because it studied and reported on the effects of both on DKA recovery and hyperchloremic acidosis.

Reply: *As suggested, we have added the PECARN study under fluid volume estimation. We have not added this study under the fluid choice as in that we have mainly discussed about acute kidney injury.*

3. The fluid section should address differences in rates and type of early fluid boluses in the first hour and later fluid treatment.

Reply: Thank you for this suggestion. *We have added this point.*

Reviewer B

Comments to the authors

1. A well-conducted review of the research being the basis for the current consensus guidelines on DKA management. I suggest the revision of some spelling and punctuation mistakes.

Reply: *Thank you for pointing out these mistakes. We have rectified this to the best of our knowledge.*

Reviewer C

Comments to the authors

1. Overall: Nice review of important clinical topics related to pediatric DKA.

Reply: *We thank the reviewer for positive comments*

2. Division of topics is well organized and easy to follow.

Reply: *We again thank the reviewer for encouragement*

3. Authors use appropriate contemporary and historical references, but do not adequately address the limitations (small n and retrospective in majority of papers)

Reply: *Thank a lot for highlighting this. We have addressed these issue in the manuscript.*

SPECIFIC FEEDBACK AREAS:

4. -Page 3 line 68, the authors state that "The presence of hyperchloremia at 24 hours of admission was a predictor for AKI suggesting causal association", reference 11 by Baalaji et al. The term "causal association" is confusing here, and in fact, the authors themselves state that they were unable to separate association from causation.

Reply: *Thank you for pointing out this error. We have rectified this and modified the statement to "The presence of hyperchloremia at 24 hours of admission was an independent predictor for AKI however, further studies are needed to establish cause-effect relationship"*

5. -Page 4 line 85-86, the authors state that "The trajectories of glucose-corrected sodium and effective osmolarity are helpful in predicting the onset of cerebral edema", reference 15 by Durward et al. The authors then seem to suggest, based on the location of this in the manuscript and the subsequent language, that a slower insulin infusion rate is therefore recommended. It would be important to point out that the study was retrospective, and that the patients in that study who developed cerebral edema received significantly more fluid and had significantly less urine output than those who did not develop cerebral edema. Additionally, the patients were in severe DKA and all received 0.1 unit/kg/hr of insulin infusion. Nothing this will help guide the reader to better understand how to make decisions

"at the bedside". The current explanation, in my opinion, oversimplifies the connection between excessive insulin dosing, decreased glucose corrected serum sodium, and potential risk of cerebral edema.

Reply: *Thank you for this suggestion. We have highlighted the limitations of study by Durward et al but as this study does not discuss regarding insulin dosage, we have discussed other studies regarding this.*

6. -Page 6, line 169: Consider breaking up into a separate conclusions section

Reply: *As suggested, we have added the conclusion section.*

7. -Page 6, line 171-172: Authors state that they recommend that: "Initiate low dose insulin at 0.05 units/kg/hour with further hiking if recovery is not as expected". This line is too vague and, in my opinion, not supported by the evidence presented. As the authors claim earlier in the manuscript, the ISPAD recommends 0.05-0.1 unit/kg/hr of insulin with clinical determinations to be individualized.

Reply: *We have modified this statement as suggested.*

8. -Page 6, line 174, authors state "Cerebral edema is pre-existing in majority of cases rather than therapy related". Again, in my opinion, it is important to note that cerebral edema likely exists prior to onset of treatment in many children, but the statement that this is the case in the "majority of cases" is not supported by evidence presented.

Reply: *We have modified this statement.*

Reviewer D

Comments to the authors

Very interesting topic, but I am sorry the quality of the review is poor, needs to be far more detailed and with grading of evidence from papers.

It reads poorly and especially the introduction.

I made some comments and have attached but then it is too many to outline.

Reply: *Thank you for critically analyzing the paper and helping us improve the quality of the review. We are sorry that the Reviewer D did not like the quality of our paper. We have tried to improve the manuscript as per the suggestions given by the reviewers.*

Comments:

Abstract

1. This sentence needs rewording

Trying to set right a deranged physiology is more than just attaining normal numbers and need careful understanding of the pathogenesis and bench studies have come to the rescue.

Reply: *This has been modified, as suggested.*

Ditto for rewording

2. With newer studies, guidelines are revised every few years moving towards a more conservative therapy with continuous and advanced monitoring.

Reply: *This has been modified.*

Intro

3. Sentence one defining DKA needs a reference (suggest IDPAD 2018)

Ditto for reference sentence 2

Reply: *References have been added.*

4. **This is too vague and needs more attention**

The greatest breakthrough came with discovery of Insulin therapy which has decreased the DKA related mortality. The dosage range has undergone modifications through the years based on new evidence. Likewise, a lot of debate regarding choice and volume of fluid has led to changing of protocols with still no consensus among the various societies publishing these guidelines (1–3).

Reply: *We have modified these lines with more specifics and reference.*

5. **Sentence below on challenges ignores all aspects of the metabolic wasting in diabetes including intra and extravascular volume reduction**

Challenges: Clinical estimation of degree of dehydration is unreliable due to the preservation of intravascular volume till the end stages secondary to hyperosmolarity. Metabolic acidosis leads to drying of mucosa and hampers assessment.

Reply: *We are trying to say in this statement is that in the clinical assessment of the dehydration in DKA, as compared to other types of dehydration, assessment of skin turgor, sunken eyes etc. may not be useful. Mucosal drying secondary to acidotic breathing may not correlate with degree of dehydration is what we want to emphasise.*

Reviewer E

Comments to the authors

1. A table/tables if possible would be helpful

Reply: *We have added the table summarising the contents.*