

Letter of response to reviewer comments:

Dear Editor-in-Chief,

We are pleased to submit our revised manuscript entitled “Glucose control in critically ill patients”. We appreciate the comments of the reviewers and the proofs of the editors. We have addressed all reviewer comments as detailed below.

Reviewer #1 (02640461):

Report review: In this study, the authors attempt to show that glycemic control has been shown to have an important impact on outcome, especially in critically ill patients, so to discuss the evidence behind current practices of glucose control with emphasis on glucose considerations in special populations, such as trauma and postoperative patients. It was commented the different trials which discuss the better prognostic on glycemic control showing the effects on patients that survived an intensive insulin therapy as compared to conventional glucose therapy. The study is relevant to the area. Only two points must be set for publication:

Thank you for these comments.

1. On page 5, third paragraph, line 6 the statement: “The results were opposite to the Leuven studies. There is no information in the previous text to this statement about Leuven studies. Please comment in the text prior to this statement about the study Leuven, quoting the reference.

We have made corrections in the text to clarify the comparison between the initial Leuven study (which is the first glucose study by Van den Berghe and colleagues) and the NICE-SUGAR trial. Thank you for catching the missing reference in the text.

2. On page 5, third paragraph, line 11 the statement: “When these 886 patients were analyzed separately, there was a trend for decreased likelihood of death with IIT.” Who are these 886 patients? The prior statement was commented that 6,104 patients were included in the study. These 886 patients were that had hypoglycemia event? Please to better the statement in the text.

We have made corrections in the text to clarify that the 886 patients were the trauma subgroup of patients within the NICE-SUGAR trial.

Reviewer #2 (02639698):

This manuscript is concise and well written. Only minor suggestions:

We suggest to add a Table summarizing the results of the main investigations cited and discussed. The Authors should report their suggestions for the management of critically patients, according to available evidence and their own experience.

Table 1: Summary of recommendations for glycemic management

| Recommendations | Evidence |
|--|------------------------|
| In operative patients including trauma, cardiac, and elective surgical patients, it is advised to start a fast acting insulin regimen in the emergency room and perioperatively whenever applicable. | [11], [32], [55] |
| In trauma patients, glucose control with a target of 100-150 mg/dL is reasonable and most important through the first week of hospitalization. | [61],[57],[62] |
| In elective surgical patients, glucose control with a target of less than 130mg/dL is advised perioperatively. | [32], [53] |
| In patient who will receive parenteral nutrition, intensive insulin therapy is recommended in anticipation of feeding and especially within the first 24 hours of initiation. | [34], [37], [42], [45] |
| In patients receiving hypocaloric feeding or with interruption of enteral feeding, less strict glucose control is recommended. | [1], [11], [45] |
| The rate of hypoglycemia should be a widely adopted quality control parameter. Elevated rates of hypoglycemia should prompt corrective action and changes in policy as needed. | [1],[8], [9],[63] |
| It is important to avoid excursions in glucose levels by titrating insulin treatment conscientiously, especially in diabetic patients, in trauma, and in surgical patients. | [61], [66], [68], [69] |
| Frequent glucose monitoring is advised. To prevent increasing clinician workload, continuous glucose monitoring may be indicated. | [64], [65], [71], [72] |
| Unexplained rises or falls in glucose levels may be a sign of worsening clinical status or infection. | [56], [60] |

Reviewer #3 (00502762):

This review reads well, but I have some concerns:

1. I am not sure what is novel? Why did the authors conduct this review and where is it special or novel?

We conducted this review because we were invited to review the current status quo of the overall research in the field. The manuscript aims to synthesize the results of sentinel trials in glucose control in critically ill patient populations so the data can be available to clinicians. Therefore, we review the current evidence and highlight how it applies to different populations. We provide

guidance to clinicians regarding glucose control in different patient populations by relying on this evidence.

2. Some important work on hypoglycemia missing

The data on hypoglycemia is extensive. In this mini-review, we focus on how the increased rate of hypoglycemia offsets the benefits of maintaining glucose at normal levels. We highlight the clinical importance of avoiding hypoglycemia. We describe how glucose control protocols, glucose measurement devices, and patient characteristics may alter the risk of hypoglycemia. We mention that the risk of hypoglycemia may be more severe in postoperative patients and that enteral feeding may alter the rate of hypoglycemia. We therefore have addressed some of the major modifiers of the rates of hypoglycemia that may highlight at risk patients and contribute to the avoidance of hypoglycemia in clinical practice.

3. Some important work on cellular mechanisms in trauma and burns missing. Also clinical trials are not mentioned.

Although we delve into detail about recommendations for glucose control in different populations, we focus on the pathophysiology of hyperglycemia in the overall condition of critical illness. This is meant to provide an overall understanding of the pathophysiology of hyperglycemia, the metabolic response to stress, insulin resistance, inflammatory, immune, and vascular effects of hyperglycemia. We do not offer detailed pathophysiology in each patient subpopulation. We mention many clinical trials that examine overall glucose control in critically ill populations as well as many in different subpopulations.

4. What is the take home message?

We have summarized the recommendations about glucose control in critically ill patients in a Table. This is meant to highlight salient points and inform clinicians about practical considerations for glucose control in different populations of critically ill patients.