

Peer Review File

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This is a nice review idea, on a topic for which there are no official guidelines/policies. However, it needs major revision prior to publication.

General thoughts:

1. What guidelines there are now should be listed. Does the ELSO have guidelines? If so, they should be listed. Any others?

Reply: There is a lack of studies for building evidence-based guidelines.

2. What are the general differences between liberal and restrictive transfusion strategies?

Reply: generally, a restrictive transfusion strategy is a series of clinical actions aimed at sparing blood products by using clearly defined threshold, targets and protocols as opposed to a liberal approach in which the choice to transfuse is driven by the sole clinical judice or local practices. A transfusion strategy is conventionally defined “restrictive” if is it aimed at maintaining an hemoglobin levels above 7 g/dL.

3. For the summary, it needs to be fleshed out and preliminary conclusions may be reached.

Reply: The final summary has been changed (lines 225-239).

4. Based on the studies reviewed, are there differences in transfusion and outcomes based on the ECMO indication? If so, why?

Reply: Dear reviewer, we understand your point but probably we would go too far away from the focus of our narrative review.

5. Based on the studies reviewed, survival seems to be based partially on transfusion strategies. Discuss why this might be the case.

Reply: We discuss the need for more defined homogeneous samples to investigate future

indications for transfusions during ECMO support.

6. Based on the studies reviewed, higher haemoglobins lead to increased mortality, why?

Reply: a study (Abbasiano et al. 2021) demonstrated the higher haemoglobin transfusion threshold the higher mortality rate.

7. Based on the studies reviewed, higher transfusion rates lead to increased mortality, why?

Reply: as mentioned in the text, higher transfusion rate leads to more complications and transfusion-related adverse events that can worsen clinical outcomes.

8. Suggest topics/hypotheses for broader observational studies.

Reply: First of all, we need to understand and define the standard practice of major ECMO centers.

In particular:

1) The paper could use editing by an English language editor. As it is currently written, it is stilted and has no flow. There are also grammar idiosyncrasies that need to be addressed.

Changes in the text: We had revised the text by an English language editor as you advised.

2) Line 34: define ELSO

Changes in the text (new line: 44): “*Extracorporeal Life Support Organization (ELSO) recommends Hb within normal limits (12-14 g/dL) and platelet counts at > 75,000/mm³ but these data are not yet supported by solid scientific evidence*”.

3) Lines 42-45: It does make sense that VV ECMO results in less transfusions than VA, but there is no explanation of why. The following sentence is in fact a new statement, but it reads like an explanation of the previous one.

Changes in the text (new lines: 53-56): *“For example, both adult and paediatric venovenous (VV) ECMO patients with respiratory failure are shown to be less needful of transfusions than venoarterial (VA) ECMO patients mainly because hemolysis and haemorrhagic complications often occurs during VA ECMO configuration”.*

4) Line 46: This paragraph belongs with the last sentence of the previous paragraph. Hemolysis is introduced here for the first time, if it is important, it should have been mentioned earlier.

Changes in the text (new line: 49): *“There are several reasons why clinicians may decide to transfuse a patient with ECMO support: to counteract the haemodilution resulting from circuit priming, to improve oxygen delivery, to restore the haemostatic balance and to compensate for blood losses due to hemolysis and ultimately haemorrhagic complications”.*

5) Line 49: New indications for ECMO should be in a new paragraph.

Changes in the text (new line 125): we created a dedicated paragraph as you advised

6) Line 82: For ease of reading, the paragraphs should be clearly broken into, with headings, conventional vs unconventional uses of ECMO.

Changes in the text (new lines: 103 and 125): we created dedicated paragraphs as you advised

7) Line 84: What was the restrictive strategy used in this study?

Changes in the text (new lines: 110-111): *“In one of them¹³, 402 patients were treated with VV ECMO between 2011 and 2017. In 2014, after switching from liberal to a restrictive transfusion protocol (with hemoglobin transfusion threshold below 8 g/dL), investigators described the outcomes, complications related to transfusions and costs of patients treated with a liberal vs restrictive strategy”.*

8) Line 85: What change was made? Liberal guidelines used --> restrictive guidelines used.

Changes in the text (new line: 110): *“In one of them¹³, 402 patients were treated with VV ECMO between 2011 and 2017. In 2014, after switching from liberal to a restrictive transfusion protocol (with hemoglobin transfusion threshold below 8 g/dL), investigators described the outcomes, complications related to transfusions and costs of patients treated with a liberal vs restrictive strategy”.*

9) Lines 93-95: It is not clear that these patients were not on ECMO initially. This needs to be re-written to make it clear that these were intubated/ventilated patients with ARDS, some of whom went on to require ECMO support.

Changes in the text (new lines: 184-188): *“In a multicentre historical cohort study¹⁸ of 234 infants needed ECMO support, the cut-off for platelet administration was between 110,000/mm³ (centre A) and 100,000/mm³ (centres B and C). For patients with pulmonary hypertension, the mean daily platelet transfusion requirement was 1.4 +/- 0.6 units with a mean duration of ECMO therapy of 6.9 +/- 4.2 days”.*

10) Line 100: introduction of transplantation. Move transplantation too early in the paragraph.

Changes in the text: we moved transplantations as you advised (new lines:)

11) Line 103: Discussion of lung transplantation, but the term is not introduced until the second sentence. Move to early in the paragraph.

Changes in the text: we move it as you advised (new line: 126)

12) Line 111: Define Berlin heart support. Quick summary.

Changes in the text (new lines: 142-143): *In a retrospective single-centre observational study¹⁵ that included 64 children undergoing mechanical circulatory support for at least two days, over a period of approximately 12 years (January 1990 to July 2002), the authors compared outcomes of interest among those on ECMO support (34 patients) and those who were on a pulsatile flow (paracorporeal and pneumatically driven) mechanical support device called Berlin Heart (30 patients).*

13) Line 119: what do these results mean in terms of outcomes?

Changes in the text (new lines: 150-152): *“These results suggest that the decision-making process to transfuse the patients should take into account not only the levels of haemoglobin but also the circuit management and the configuration of ECMO”.*

14) Line 123: this paragraph, although about liver transplantation, mentions nothing about transfusions. Expand or delete.

Changes in the text (new lines: 153-154): *“Regarding ECMO support during liver transplantation, applying restrictive strategy to transfusion become imperative because of the higher risk of bleeding”.*

15) Line 128: Statement that the lung is the most common source of sepsis requires a reference.

Changes in the text: we inserted the citation (Mayr et al. 2014) as you advised (new line: 160)

16) Line 138: The p-values mentioned would seem to be significant, but the authors state that they are not, explain.

Changes in the text (new line: 170): there were statistical significances in amount of transfusion but not in mortality rate: *“Although there was no statistically significant difference in mortality between the two groups, the ECMO group received significantly more transfusions of red blood cells [6 (0-14) vs 0 (0-4), $p < 0.001$], fresh frozen plasma [0 (0-4) 0 (0-10), $p 0.019$] and platelets [10 (0-30) vs 0 (0-15), $p 0.001$] than the control group”.*

17) Line 142-143: Confusing. Please rework this sentence. "Determine" is a confusing word here. Consider "looked at" instead.

Changes in the text: We changed the text (new lines: 184-188)

18) Line 147: Is the other disease pulmonary hypertension? Not clear. Paragraph is

about pulmonary hypertension, so another disease seems to refer to that, but maybe its any other disease.

Changes in the text: We changed the text (new lines: 184-188)

19) Line 153: This is the only time in the entire paper that the type of oxygenator is mentioned. Why? Is there something special about it, if yes, explain. If no, delete.

Changes in the text: We delete it

20) Line 160: This seems to be an excessively liberal transfusion strategy. Why? What does that mean for the results?

Changes in the text: “*The targeted values of the restrictive protocol were haemoglobin 8-9.5 g/dL, fibrinogen > 250 mg/dL and platelet count > 50,000/mm³*” As mentioned in the summary, there is a lack of standard practice about transfusion strategy reported in literature. As we suggested in the summary section, more observational and preliminary studies is advocated in order to establish the best threshold values to transfuse.

21) Tables

Table 1) These are emerging indications, most of which are touched on in the paper, however, burns and hepatic transplantation do not have much discussion in the paper. Would consider eliminating them from the table.

Reply: We decided to delete burns; we extended the discussion about liver transplantation

Table 2) This is an excellent summary of the studies included in this paper. I would used the results of these studies to flesh out the discussion section. Similarities, differences, etc.

Reply: We extend the discussion section (new lines: 216-224)