Peer Review File

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Reviewer A

Comment #1: The main problem is the plan of the manuscript. Indeed, for each organ system, the authors describe the management in ALF Children then ACLF children. It makes the manuscript a bit confusing. ALF and ACLF are two different diseases. I invite the authors to rework the manuscript by separating the work into 2 parts: first part: in ALF children and describe the set of organ systems (respiratory, cardiovascular…) and in a second part: in ACLF children.

Reply #1: We appreciate the reviewer's point that ALF and ACLF are two different disease processes. Our original intent was to show that ALF and ACLF are more alike than different, and that there is much overlap in the ICU management of each organ system in both ALF and ACLF. This is why we elected to outline the manuscript by organ system, addressing the differences in management between them. Given these reasons, we prefer to present the manuscript in its current format. However, recognizing the importance of highlighting the difference between ALF and ACLF, we have made additional efforts to ensure that we are clear when we are talking about each of the disease processes.

Comment #2: In patients with porto-pulmonary hypertension, HPS and hydrothorax, please describe the ICU management (ECMO in porto-pulmonary hypertension; NO in HPS patients…). Do you have data about high PEEP and the impact on ICP and hepatic venous pressure ? What is meant by "ammonia scavenging therapies" ?

Reply #2: Thank you for the recommendations to add data on these ICU strategies for porto-pulmonary hypertension, HPS and hydrothorax. We have now described a report of VV-ECMO use in porto-pulmonary hypertension (lines 153-157) and three reports on the use of iNO in HPS immediately post-transplant (lines 140-142). We have clarified how high PEEP impacts ICP and hepatic venous pressure (lines 171-173). Finally, we have added additional information about the use of ammonia-scavenging therapies in hyperammonemia associated hepatic encephalopathy (lines 250-252).

Comment #3: Line 191: the effect of NAC on cardiovascular system is anecdotal. The most important is the impact on transplant-free survival. Please, move this paragraph to the corresponding chapter.

Reply #3: We agree with the reviewer that the cardiovascular effects of NAC were anecdotal. Thus, given these reports, we thought it was important to discuss the later prospective, placebo-control study by Squires et al. (2012) that evaluated the outcomes of both survival and transplant-free survival in patients who received NAC for non-APAP associated PALF. We explained that NAC did not show benefit on long-term transplant-free survival, and in fact showed significantly lower 1 year transplant-survival especially for children less than 2 years of age (lines 195-202). We have provided further information in order to clarify the lack of benefit for the use of NAC for non-APAP PALF. Given the proposed hypothesis in this study that NAC impacts oxygen delivery and cardiovascular dynamics, we thought it was appropriate to have this

information in the cardiovascular section. We appreciate further recommendations from the reviewer if there would be another location in the flow of the review that would be better for the reader.

Comment #4: Do you have data about increased ICP in ACLF patients? Line 230-231, what is the place of liver supports systems on reducing the ammonia load in children ? In neuroprotective strategies, seizure prevention is not a usual practice.
Reply #4: Thank you for highlighting the need for these clarifications. We have highlighted that the presence of elevated ICP in ACLF is less frequent than ALF (line 238). In addition, we further clarified that monitoring for the presence of seizures and if there are clinical concerns for seizures, seizure treatment and prevention are an important part of neuroprotection in order to decrease the metabolic demand of the brain tissue and prevent propagation of injury (lines 252-254).

Comment #5: This chapter concerns mainly ACLF children. Hematologic / coagulation systems and renal systems are more important and should be placed before in the text.
Reply #5: Thank you for the recommendation on how to better prioritize our systems presentations, we have made this re-organization. The manuscript is now ordered as follows: Respiratory, Cardiovascular, Neurologic, Hematologic, Renal, Gastrointestinal, Infectious Diseases, Endocrine, Fluid/Electrolytes/Nutrition, and Extracorporeal Liver Support systems. Please note that track changes were not used for the re-organization of these sections in order to easier facilitate demonstration of other changes made in response to the reviewers.

Comment #6: Line 380 The sentence “prophylactic antibiotics… “ must be removed
Reply #6: We have removed the comment about use of prophylactic antibiotics for potential infectious causes of AKI per the reviewer’s request.

Comment #7: A chapter on liver transplantation in ALF and ACLF children could be interesting (criteria, results…)

Reply #7: We agree that the information specific to liver transplant indications and outcomes for both ALF and ACLF are interesting. However, we were concerned that might be a separate document needed as post-liver transplant ICU care has many important intricacies that should be not be overlooked.

Reviewer B

Comment #1: Cirrhosis is not really an etiology but the common final-stage of all chronic liver disease (page 3 line 33).
Reply #1: Thank you for highlighting this distinction regarding cirrhosis for CLD. We have deleted the word cirrhosis per reviewer recommendation on line 24.

Comment #2: Are the authors referring to neonatal ALF when reporting that HSV is the most common infectious etiology? (Page 4 line 54) Suggest to qualify that causes of ALF in children vary depending on geographic location. For example in Asian populations, viral hepatitis A/B are the most common infections leading to ALF.

Reply #2: We appreciate the confusion our statement on infectious etiologies presents to the reviewer given the differences based on age. We have further clarified our statement on HSV to ensure the reader understands that when we refer to HSV as the most common infectious etiology, we are referring to all cases of pediatric ALF, including neonatal (line 69). We also appreciate the recommendation to highlight how geographic differences will impact the infectious etiologies – we have added the following statement: *"Etiologies also vary by geographic location: for example, viral hepatidities are more common in Asian populations."* (line 72-73).

Comment #3: Suggest using the term "agitated saline contrast echocardiography" instead of "bubble echo"(page 7 line 118)
Reply #3: We appreciate this recommendation. We have made the change as suggested (line 136).

Comment #4: HE: may be useful to show the distinction between standard adult scoring versus adapted infant/young children (<3 years) HE scoring
Reply #4: We thank the reviewer for highlighting the importance of distinguishing how HE scoring is unique for the pediatric patient. In Table 3, we included qualifiers for each HE grade that would be applicable for infants to young adults. We have included a footnote in this table to highlight the subtilties of this presentation.

Comment #5: Non-selective beta blockers for prophylaxis against variceal haemorrhage is not routinely recommended as first-line in children because of relatively greater reliance on tachycardia to compensate for hypovolaemic shock during major bleeding. (Schneider BL et al. Portal hypertension in Children: Expert pediatric opinion on the report of the Baveno V consensus workshop on methology of diagnosis and therapy in portal hypertension. Pediatric Transplantation 2012;16:426-437) –(page 12, line 251)
Reply #5: We appreciate the reviewer providing us this reference to include without this document. We have included this reference and highlighted this point as requested (lines 369-372).

Comment #6: I am not certain how hyperaldosteronism causes hyponatraemia which the authors are implying (page 19)
Reply #6: Thank you for highlighting the need for further clarification. We have edited the mechanism for hyponatremia for clarity as the following *"The mechanism is secondary to release of arginine vasopressin and anti-diuretic hormone, as well as renin-angiotensin axis activation leading to increased water intake that can potentiate the hyponatremia."* (lines 441-443).