Peer Review File

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Reviewer 1

Comments to the authors:

This review of initial neonatal management of the CDH is an excellent summary of current controversies & available options. It nicely accentuates the best science and clinical research available. Really quite an impressive and concise distillation of the available literature without obvious bias regarding the discussed therapies. I have just a few comments.

Thank you for your review. Please see our response below to your comments:

-ll 40-41: "These issues are most often addressed through medical management in a neonatal intensive care unit (NICU)." Should state "or pediatric intensive care unit (PICU)" which is the case at many centers.

"or pediatric intensive care unit (PICU)." was added to the manuscript.

-ll 51-70: The data supporting lower FiO2's is not substantial and such a practice may lead to underresucitation in severe patients. I think it is potentially missing the point to imply lower FiO2 is better. Rather, it is more appriopriate to recommend targeting an O2 saturation of >80-85% with whatever FiO2 is necessary. A good FiO2 is not the target, but rather adequate oxygen delivery. 100% FiO2 for all CDH patients with a rapid wean may be a safer recommendation for most centers & patients.

The following was added to the end of the section: "However, the data supporting this are lacking, therefore, it is more appropriate to target a pre-ductal O_2 saturation level of 80 – 85% using the FiO_2 as necessary to do so. If an FiO2 level of 1.0 is initiated, it should be weaned as able to maintain the appropriate level of oxygen support."

-Surfactant section: too much detail; can cut this to two sentences. (It doesn't help.)

The section was changed to the following: "Animal studies suggested that surfactant deficiency may contribute to CDH pathophysiology with a decrease in lung compliance, decreased concentration of alveolar phospholipids (especially phosphatidylcholine), and higher lung concentrations of total DNA and glycogen{Glick, 1992 #41;Suen, 1993

#1}. Although a limited number of case reports observed possible benefit with surfactant therapy in CDH infants{Bae, 1996 #570;Finer, 1998 #39}, this was not supported in studies reviewing its use in CDH neonates using the CDH study group (CDHSG) registry{Van Meurs, 2004 #55;Lally, 2004 #44}. Currently, routine surfactant administration is not recommended in children born with CDH{Snoek, 2016 #13}."

-I love the gentle ventilation section. Very nice.

Thank you

-Nitric oxide section: nicely done; I would also add that the response to NO may be transient (hours) which sorely limits its utility.

"Given the transient nature of response to iNO, it's utility may actually be significantly limited in even these infants." was added to the final paragraph of the section.

-ECMO section: This is quite well done also. However: "the use of extracorporeal membrane oxygenation can be used as rescue therapy". This should be reworded; use of ECMO as salvage therapy when the patient is critically ill is precisely the kind of use that leads to poor outcomes; rather, anticipated ECMO with early cannulation before severe lung injury has occurred probably will lead to better outcomes with ECMO. Experienced ECMO centers have better outcomes with ECMO. It is important to describe ECMO as an anticipated part of care in severely affected infants, rather than as a hail mary when everything else has failed. (This is David Kays philosophy.)

The introductory paragraph to this section was changed as follows: "When a newborn with CDH remains critically ill from pulmonary hypoplasia, the use of extracorporeal membrane oxygenation should be used before severe lung injury has occurred. It is important that the utilization of ECMO be anticipated in these infants with early cannulation prior to levels of ventilator support that can permanently damage the fragile lung tissue."

- l. 369: they don't "require" ECMO; use of ECMO is a clinical decision. Would say "only the most severe cases are treated with ECMO".

The sentence was changed to: "Therefore, there may be benefit in using the VV approach in infants who are placed on ECMO prior to CDH repair and the VA approach

in only the most severe cases treated with ECMO."

-Timing of surgical repair: I would emphasize reference 114 over reference 115 and especially 116 as the methodology and N in 114 (using CDHSG) is superior to 115 (using ELSO) and far superior to 116 (single center study). Dao et al. included unrepaired patients in their analysis to perform a true mortality comparison.

"Another recent study concluded that survival was improved if babies were repaired on ECMO compared to after ECMO and also that early repair on ECMO was superior to late repair(114). Dao et al. performed a retrospective study of the CDHSG database using propensity score matching to evaluate 2 individual aims: 1) compare repair on versus after ECMO and 2) compare early versus late repair on ECMO. A total of 1,423 patients were available for analysis spanning a 10 year period. Following propensity score matching, 136 patients were analyzed in each arm of aim 1 (n = 272). The analysis showed that those repaired on ECMO had an overall lower mortality with a hazard ratio of 0.54 (CI 0.38, 0.77, $p<0.001$) and odds ratio of 0.52 (CI 0.32, 0.85, $p=0.01$). Additionally, they were more likely to undergo repair (94.1% v 66.2%, $p<0.001$). In their analysis of aim 2, a total of 154 patients were available for analysis following propensity score matching, 77 per arm. Those infants repaired early demonstrated an overall lower mortality rate with a hazard ratio of 0.51 (CI 0.33, 0.77, $p=0.002$) and odds ratio of 0.19 (CI 0.09, 0.39, $p<0.001$). Again, more were able to be repaired (90.9% v. 55.8%, $p<0.001$) with an overall lower duration of ECMO support (median 13 days v. 15 days, $p=0.02$) and overall hospitalization in survivors (median 54 days v. 95 days, $p=0.004$). They concluded that early repair may be key to higher repair rates and improved mortality at higher volume centers." was added to the timing of repair section.

Reviewer 2

Comments to the authors:

This is an excellent comprehensive review of CDH in neonates. This review covers an extensive amount of information regarding treatment modalities and surgery. Attention is focused on some of the more controversial areas such as ECMO criteria and timing of surgery. There is a reference near the end regarding some of the more recent controversies from Dr. Kayes at All Children's regarding timing of surgery for severe cases. The outcomes reported from his center certainly are controversial compared to other large registry data. There is no mention of neonates presenting after fetal therapy. This may beyond the scope of this review article. I commend the authors for the great work.

Thank you for your comments. The following addition was made to the manuscript following Dr. Kays cited paper.

“However, these outcomes reported are contrary compared to other large registry data previously described.”

We specifically did not address neonates with CDH who underwent fetal therapy since a separate section of this volume will address fetal therapy for CDH.