

Response to reviewers

Reviewer #1:

Authors describe an interesting case of Pulmonary Hypertension Associated with Bronchopulmonary Dysplasia. The case is of interest to the readership and they highlight an important topic through the literature review. However, the case report is poorly written with significant redundancy.

Question 1: They do not even mention how old the infant was when born (have to at least mention gestational age, pre-gestational work up including ultrasound screening etc).

Response: We appreciate the reviewer's suggestion. We have mentioned how old the infant was when born and the gestational age in the History of present illness of manuscript (please see line 100). We have provided the information of pre-gestational work up in the revised manuscript (please see line 112-113).

Question 2: It is entirely unclear how they made the diagnosis of PH solely based on echocardiographic features and without the diagnostic right heart catheterization (RHC) with vasoreactivity. This is especially important as they also mention the presence of right to left shunt which may complicate treatment with pulmonary vasodilator. While RHC may not be necessary for diagnosis if it can not be done due to critical illness or contraindication, the authors should mention that in their report suggesting that diagnosis was made purely on echo findings without catheterization.

Response: We appreciate the reviewer's suggestion. Right heart catheterization (RHC) is the gold diagnosis standard for PH, however, it is rarely used in preterm infants because it is invasive and difficult to perform in preterm infants. We have discussed this in the "Discussion" of the manuscript (please see line 228-231). The reason for not conducting cardiac catheterization is that the infant was critical illness and the infant's parents refused. We have mentioned this in the manuscript (please see line 357-359). We have also mentioned that the diagnosis of PH was made based on the

echocardiography in the manuscript (please see line 147-150, line 231-232), and discussed this limitation in Discussion (please see line 228-240).

Question 3: Additionally, they have to describe the echo findings including tricuspid regurgitation velocity, RV/LV ratio, Tricuspid annular planar systolic excursion (TAPSE) and RV size and function to suggest severe PH.

Response: We appreciate the reviewer's suggestion. We have provided the echo finding related with PH in the revised manuscript (please see line 147-150, 157-161, 171-174, and 178-181).

Reviewer #2:

The manuscript "Combination of bosentan and tadalafil in the treatment of pulmonary hypertension in an extremely low birth weight infant with bronchopulmonary dysplasia: A case report and literature review" by Jiao Li bring to the readers the possible use of tadalafil and bosentan in infants with pulmonary hypertension due to bronchopulmonary dysplasia. Also, an important issue presented was the role of NT-pro-BNP in analyzing the risk and the prognosis of pulmonary hypertension due to bronchopulmonary dysplasia. The case is interesting and generally well written, following the steps for a case report. The discussion includes a narrative review of the BPD-associated PH, including NT-proBNP's role in monitoring and treatment (including nitric oxide, Sildenafil, Tadalafil and Bosentan).

Question 1: Regarding the use of bosentan in infants, the authors should probably include this reference: Mohamed WA, Ismail M. A randomized, double-blind, placebo-controlled, prospective study of bosentan for the treatment of persistent pulmonary hypertension of the newborn. J Perinatol. 2012 Aug;32(8):608-13. doi: 10.1038/jp.2011.157.

Response: We appreciate the reviewer's suggestion. We have read this reference and cited it in the revised manuscript (please see line 330-331).

Question 2: Also, in Discussions, it would be better to mention the possible side effects, liver injury and teratogenic effects. The liver function should be monitored for the treatment's duration, as demonstrated in adults.

Response: We appreciate the reviewer's suggestion. We have provided the laboratory examination related with liver function during the treatment's duration in the revised manuscript (please see line 185-187, line 195). We have discussed side effects of treatment in the discussion (please see line 352-356).

Question 3: In the Introduction, I suggest that the authors should cite the references read regarding the sentences from line 88 (bosentan), line 90 (European guidelines and tadalafil) and line 91 (reports on using tadalafil in children).

Response: We appreciate the reviewer's suggestion. We have cited the related references in the revised manuscript (please see line 87-91).

Question 4: In the Conclusion section of the manuscript, I would mention the name of tadalafil and bosentan as this was the main idea of the case report, besides the role of NT-proBNP in monitoring the disease (as it is in the Conclusions of the Abstract).

Response: We appreciate the reviewer's suggestion. We have modified the abstract and conclusion in the revised manuscript (please see line 63-65, line 366).

Question 5: Regarding some minor issues: - The images from Figure 1 may be enlarged; - Figure 2 title should include the time when Rx was performed; - All abbreviated words should be explained at the first use and then abbreviated (verify line 77 and line 85); - Specify the diuretic treatment in line 148; - Do not use "can't" but "can not"; - Verify the name of tadalafil in line 298.

Response: We appreciate the reviewer's suggestion. We have enlarged Figure 1 and added the time of Rx in the title of Figure 2. Abbreviated words in line 77 and line 85 have been explained in (please see line 74 and line 77). We have specified the diuretic

treatment (please see line152) and modified the sentence in line 174 and verified the name of tadalafil in line 316.

Reviewer #3:

This manuscript consider combination of bosentan and tadalafil in the treatment of pulmonary hypertension in an infant with an extremely low birth weight and bronchopulmonary dysplasia.

Question 1: Delete " and literature review" in the title.

Response: We appreciate the reviewer's suggestion. The " and literature review" has been deleted in the title.

Question 2: The topic of the manuscript is "Combination of bosentan and tadalafil in the treatment of pulmonary hypertension in an extremely low birth weight infant with bronchopulmonary dysplasia", but the authors didn't mention in background of abstract and in conclusion about the current treatment. Authors should mention the therapeutic effect of combination of bosentan and tadalafil in the treatment the studied disorder.

Response: We appreciate the reviewer's suggestion. We have mentioned the therapeutic effect of combination of bosentan and tadalafil in the treatment in the abstract.

Question 3: The authors have written "The baby was born prematurely for four hours" in "CASE PRESENTATION" part. Is it correct???

Response: We appreciate the reviewer's suggestion. We have modified this in CASE PRESENTATION.

Question 4: Please organize the history of infant, Treatment, and condition of the infant after the current treatment in a chart. It is more easier to understand for readers.

Response: We appreciate the reviewer's suggestion. We have organized the history of

infant, Treatment, and condition of the infant after the current treatment in a chart (please see Figure 3).

Question 5: Discuss more details of the previous research about the therapeutic effect of combination of bosentan and tadalafil in the treatment of BPD.

Response: We appreciate the reviewer's suggestion. We have added more details of the previous research about the therapeutic effect of combination of bosentan and tadalafil in the treatment of BPD in the revised manuscript (please see line 343-351).