Peer Review File

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Reviewer A

Overall, I think the manuscript is well written and structured. It is a comprehensive review of PH in patients with structural heart disease covering a broad area with a moderate amount of depth.

Typo in introduction “du” to left-sided heart disease
Accepted
Corrected in the text

Consider changing to - “Prevents advanced pulmonary vascular lesions from developing in the vast majority of cases”
Accepted
Corrected in the text

Would add a reference for “majority of pulmonary vasodilators are used off-label in children” and expand on why.
Accepted
Corrected in the text and reference added.

The whole manuscript would benefit from an English editing service. There are numerous word choice and subject-verb errors that disrupt the flow of the reading.
I don’t agree, and this observation doesn’t seem to be shared by the other reviewers.
No correction made.

This sentence in conclusion is not particularly clear to me: “If the use of specific therapies in PAH-CHD is not debated, upfront combination strategy should be assessed in this setting and treatment goals should be clearly stated.”
Accepted.
Sentence changed in the text.

Reviewer B

The authors have provided a good overview of current knowledge about pulmonary hypertension associated with congenital heart defects in the pediatric population. They provide hemodynamic definitions as well as what is known about treatment options. Given the content of the review, I think the term ‘acquired’ heart disease in the title could be omitted.
Accepted
Correction made

Furthermore, I would prefer somewhat more in depth insight about mechanisms, and perhaps animal models.
Accepted
Sentence added on animal models

Given that many corrective surgeries in CHD result in valvular insufficiency and/or stenosis in the pediatric population, which profoundly affects hemodynamics, this would be a good topic to discuss.
Accepted
Sentence added in the text.

Patients with congenital heart disease and/or pediatric PAH have a reduced exercise capacity. Several studies have addressed exercise testing and/ or exercise training. Please include this in the diagnosis and treatment paragraphs where appropriate
Accepted
Paragraph on exercise testing added

Finally, a tabular overview of guidelines and recommendations for treatment, with level of recommendation would be useful for the reader.
I do not think that such a tabular overview of guidelines, as a copy/paste from published guidelines is useful as reader can refer to them in the source paper.
No change made.

Please provide references for the text in the paragraph between ref 9 and 10.
Accepted
Done.

Reviewer C

The Authors submitted a review of the problems associated with Pulmonary Hypertension.
The manuscript has been well prepared, with adequate analysis of the issues related with PH, as expected based on the worldwide experience of the senior Author, Maurice Beghetti.
The Reviewers made appropriate comments, and I agree with most of them, as they originated from the desire to further improve the quality of the manuscript.
The suggestions to the Authors is to prepare a revised version, taking in account all the suggestions received from the Reviewers, because the quality of the manuscript will substantially benefit.
Accepted
Correction in the text as per other reviewers comment

Reviewer D
I read with great interest the review ‘Pulmonary vascular disease as a complication of

pediatric congenital and acquired heart diseases' submitted by experts in the field of pulmonary hypertension. The review summarizes the current evidence, controversies and knowledge gaps regarding this very important topic. This review adds to the body of literature by including sections on WHO group II PH in children and patients with single ventricle physiology, both topics rarely addressed in similar reviews and overall, under studied.

The review is easy to read and understand with minor grammatical errors and missing references, that I will highlight in the minor comments section. I would have liked to see a few topics addressed in further depth.

1) The review does not address the contribution of chromosomal defects to development of pulmonary vascular disease. The review should specifically address Down syndrome given its prevalence in CHD and multifactorial pathogenesis of PVD. (Hopper et al, J Pediatr, 2023 Jan;252:131-140.e3.)

Accepted

Paragraph added

2) The review does not address the issue of prematurity and congenital heart disease. About 50% of infants with BPD associated PH also have a systemic to pulmonary shunt. The dilemma of what to do with these patients and when to close their defects and should they be evaluated based on the guideline criteria or not should be highlighted.

3) The issue of developmental lung disease in patients with CHD including congenital diaphragmatic hernia should be highlighted. These patient's pulmonary vascular disease is progressive (not diaphragmatic hernia but other developmental lung diseases) regardless of repair of their CHD. Having a high suspicion for these associated lung diseases in CHD is important for proper management and prognostication.

2) and 3) Accepted.

A few sentences on the subject have been added in the diagnostic chapter, and in the treatment chapter. I think that it is however slightly beyond the scope of this review, and we don't have a lot of data on the subject.

4) The scope of pulmonary vascular disease in univentricular palliation in the review is narrowed down to the Fontan circulation. Many of these patients develop PAH prior to Fontan circulation and some secondary to genetic syndromes and developmental lung disease that can be associated with univentricular lesions. It would be prudent to alert the reader to the possibility of PAH in the prior stages of the univentricular palliation and it's presentation, usually lower saturations due to low pulmonary blood flow, and effect, some patients are not candidate to continue down the univentricular pathway. It would also be prudent to highlight that there is no current evidence supporting the best treatment pathway for these patients; treat with pulmonary vasodilators and continue down the univentricular pathway, refer for heart-lung transplantation or addition of aorto-pulmonary shunts.

Accepted.

Title changed. Sentences and ref added in the chapter. Comorbidities already mentioned in the chapter.

Minor comments:

1) In the Abstract, 3rd paragraph, 4th line: in the sentence “with some increase in pulmonary vascular resistance ..” the word “some” is redundant and should be removed.

Accepted

Removed from the text

2) In the introduction, the first sentence, the words “dreadful” and “dismal” are both dramatic and subjective. Can use instead for example “serious” and “poor”.

Accepted

Changed in the text

3) In the Introduction, first paragraph, line 5; please clarify that group 1 is according to the WHO classification of PH, not to be confused with the Panama classification. This should be consistent throughout the review.

Accepted. As most of the published literature on ped PH uses WHO classification, Panama classification not eluded to throughout the manuscript.

WHO classification specified in the text

4) In the Introduction, first paragraph, line 8, the word “due” is missing an ‘e’ at the end.

Accepted

Changed in the text

5) In the Introduction, first paragraph, line 11, please specify WHO classification instead of international classification, since the Panama classification does address univentricular palliation.

Yes but I am referring to guidelines.

Changed “international” for “European” guidelines

6) In the Introduction, second paragraph, the first sentence requires a reference.

Agree

Ref Added

7) In the Introduction, second paragraph, the second sentence requires addition of age (or duration of the shunt) and presence of comorbidities, and removal of the word “possible” since genetic susceptibility is clearly present as highlighted later in the review. (Van der Feen et al. Eur Heart J, 2017)

Agree for the first part. I would like to leave “possible” genetic susceptibility, because a mutation is not found in the majority of the cases.

Modified in the text for age and comorbidities.

8) Overall, the Introduction can be significantly shortened. The third paragraph that addresses the size of the problem in developing countries is important and should be moved to the end of the first paragraph that highlights the size of the problem. However, the 2nd,4th and 5th paragraphs can be summarized into a couple of sentences noting the topics that will be addressed in this review e.g. This review will discuss the pathophysiology, evaluation and management of PH-CHD in systemic to pulmonary shunts, left sided heart disease and univentricular hearts.
I don't agree. The 3rd paragraph talks about Eisenmenger syndrome, a particular population, that deserves a paragraph. The 2nd, 4th and 5th paragraph develop each a different subject.
No changes made.

9) In the Definition and Classification section, it is important to note the presence of the Panama classification as well as the WHO classification.
As mentioned in comment 3, we focus our manuscript on the WHO classification. Panama classification is 12 years old, and is not referred to in PH guidelines.
Sentence added about Panama classification.

10) The section PAH-CHD should probably be renamed PAH – systemic to pulmonary shunts.
I agree. However, in the international guidelines, that is how PAH-systemic to pulmonary shunt is named. For this reason, I think it is important to stick with the accepted nomenclature in the published literature. I however added a sentence in that sense in the definition.

11) In the section PAH-CHD – Pathophysiology, first paragraph, I think replacing delta P with the 'transpulmonary gradient' would be easier for the reader to understand.
Agree
I have added transpulmonary gradient in the sentence.

12) In the section PAH-CHD – Pathophysiology, the second paragraph, third line, states that PA pressure rise secondary to increase pulmonary blood flow will progressively increase PVR. I think it is important to state the in the beginning, increase in PBF leads to flow mediated pulmonary vascular dilation and a decrease in PVR. It is only after pulmonary vascular injury from increase PBF and transmission of the systemic pressure to the pulmonary circulation that PVR starts to increase. I think it is also important to point out that the increase in PVR is not an early sign and that it is estimated that 50% of the pulmonary vascular cross-sectional area is lost prior to an increase in PVR is detectable.
Agree
Sentence added

13) In the section PAH-CHD – Pathophysiology, the last sentence of the third paragraph is an open-ended statement. How does the correlation between apoptosis resistance,

intimal proliferation and PAH irreversibility open new perspectives in management?
New drugs under current PAH trials active on remodeling/proliferative pathways, SMAD and TGFb signaling (including sotatercept).
No changes made.

14) In the section PAH-CHD - classification, the 5th line, please specify that targeted treatment means targeted at the pulmonary vascular disease ie pulmonary vasodilators.
Agree
Modified in the text

15) In the section PAH-CHD - classification, the 11th line, regarding the third group PAH with a small defect. There is now evidence from the Danish, Dutch and German registries supporting a lifetime risk of PH that is higher than the general population, in patients with small hemodynamically insignificant shunts. This signal maybe contaminated with PH related to LV dysfunction, but it seems to be present even after excluding left side heart disease. So, it is unclear if the PH in this group is truly unrelated to the shunt since the lifetime risk is higher than the general population. (Eckerstrom et al, J Am Heart Assoc. 2022;11:e027477 / A.E. Lammers et al. Int J of Cardiolog 308 (2020) 28–32 / Van Riel et al, JACC, Vol 66, Issue 9, 1 September 2015, Pages 1084-1086)
Firstly, this is a review of PH in pediatrics, and those paper are on adults. Secondly, we believe that children with PH and a small coincidental defect have actually another disease, and mutations in Sox17 and TBX4 have been found in children with ASD and PAH.
No modification made.

16) In the section PAH-CHD – Diagnosis and risk assessment, the first paragraph. I am not sure that I agree that the evaluation can be limited to clinical, oxygen saturation, CXR and echo. This could be the preliminary evaluation, but one needs to rule out all other causes of PAH including developmental lung disease, genetics, thyroid disease, HIV depending on prevalence in population. Right heart cath also serves to differentiate between PAH and postcapillary PH than can occur in longstanding CHD and can help design a management plan.
Sentence added about exclusion of other cause of PH and about postcapillary component.

17) In the section PAH-CHD – Diagnosis and risk assessment, the second paragraph, I would add to the list of predictors of PVD, good weight gain or absence of failure to thrive, presence of comorbidities suggesting genetic disorders even if not specifically diagnosed. For the evaluation, I would add oxygen saturation with activity or 6MWT as well as presence of lower oxygen saturation in the lower limbs in relation to the upper limbs in patients with a PDA, especially with exercise.
Accepted.
Changes in text

18) In the section PAH-CHD – treatment, the first paragraph, line 6 – benefit is misspelt.
Agree
Changed in the text

19) In the section PAH-CHD – treatment, the first paragraph, line 7 – consider removing epoprostenol infusion since Treprostinil can also be given via IV infusion.
Agree
Changed for prostacyclin analogues

20) The higher risk of iron deficiency anemia should be specified that it is in Eisenmenger patients due to higher stroke risk.
According to the 2022 guidelines, iron deficiency screening and iron supplementation is recommended in all PAH, not only Eisenmenger syndrome.
No change made.

21) In the section PAH-CHD – treatment, the fourth paragraph can be added to the end of the second paragraph as both address Eisenmenger syndrome.
Section contructed with first some general statement, then specific situations.
No change made.

22) In the section PAH-CHD – treatment, the third paragraph, regarding the intent to treat strategy- please add reference for the intent to treat being primarily used in pre-tricuspid valve shunts. There are many case reports of use of pulmonary vasodilators prior to VSD repair whether for improving postoperative course or to try to address longer term reversibility.
My statement is corroborated by a review of literature, reference added.

23) In the section PH-LHD – pathophysiology: It is important to highlight that extrapolation from adult studies is not applicable in children born with left sided heart disease since the disease is present in utero and can affect pulmonary vascular development e.g. in HLHS with atrial restriction where patients are born with "nutmeg lungs" and have significantly worse prognosis than patients without atrial restrictions.
Accepted, sentence added in the text.

24) In the section PH-LHD – pathophysiology: third paragraph, the second sentence is missing a reference.
Reference at the end of the paragraph (same).
No change made.

25) In the section PH-LHD – treatment: It is important to highlight that this whole section is based on adult data. It is unclear that LHD present in-utero would also be reversible and what the response to pulmonary vasodilators would be.
There is no data showing that pulmonary vasodilators work in any circumstances in

LHD so far.
No change added

26) In the section PVD in Fontan circulation: the fourth paragraph – line 4, the sentence starting with “Ageing is also a potential …” requires a reference.
Accepted.
Reference added.

27) In the section PVD in Fontan circulation: the results of the FUEL study should probably be highlighted separately as a well-designed study in this patient population.
Accepted. Sentence added.

28) In the Conclusion – line 4: the word “pre-operatory” should be replaced by “preoperative”.
Agree
Modified in the text