

Peer Review File

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Reviewer A:

Comment: it is a bit unusual for this type of an article that they directly connect this review to their own current research work (Ref. 31/34/35) and even include already published illustrations. Clearly, predicting lung maturity and also risk for RDS and also BPD from gastric aspirates taken at birth using modern mass spectrometry methods is only one of the strategies.

Reply: The reason that we write in details about our new spectroscopic FTIR method combined with AI is that the method is the first and pro. temp. the only method allowing targeted intervention treatment of BPD (and RDS) at birth. The method is very fast. The FTIR spectroscopy register all the molecules present in gastric aspirate and the AI algorithm identify the spectral data correlated to development of BPD. Our method is not mass spectrometry, see also ref 69. These explanations are clarified in the revised manuscript.

Changes in the text "Manuscript (MS) with revisions": p 12 line 15-22.

Reviewer B:

We have followed most of the Reviewers recommendations.

Comment 1:

Sentence (line) 17, p2 in the revised MS: Delete "are reviewed with this" leaving the sentence "The present review focuses on early prediction and both current and possible future pharmacologic interventions, highlighting the potential to improve the outcome of BPD."

Reply 1: OK. Change: see *line16-18, p2.*

Comment 2: *line 25, p2:* change sentence to read "...with gestational age ≥ 31 weeks the incidence decreases to 4 percent (1)".

Reply 2: OK.

Comment 3 & 4: *line 1-2, p3:* "BPD has a high mortality and morbidity, as well as high treatment costs, particularly as the severity of disease increases."

Line 2-3, p3: Delete "All severity degrees of the disease are seen."

Reply 3 & 4: OK

Comment 5: *Line5-6, p3:* "The first clinical symptoms, increasing the need of oxygen and lung edema, are normally seen about 10 days after birth (new ref. 16,17)." This sentence doesn't fit with the flow here. I recommend moving it to page 4 which I'll discuss below (*line24-25, p4*).

Reply 5: OK

Comment 6: *Line8, p3:* Change "hits" to "insults".

Reply 6: OK

Comment 7: *Line7, p4:* "First Description of BPD – Old and New BPD" change to say "Description of BPD – Old and New".

Reply 7: Text is deleted to shorten the text following recommendation from Reviewer D.

Comment 8: Line11, p4: Per-cent does not need a hyphen and should read “percent”.

Reply 8: Word (text) deleted.

Comment 9: Line23, p4: To-day does not need a hyphen and should read “today”.

Reply 9: OK

Comment 10-12: Line22-25 , p4 and Line 1, p5: Change to read “The new BPD we now see is normally preceded by increased alveolar-capillary permeability in the first 1-2 weeks after birth (16) with increasing need for oxygen due to lung edema as early clinical findings within 10 days after birth” – this last piece is the replaced information from above.

Line 1-3, p4: Change to read “...within 10 days after birth. Radiographically, hazy ground-glass opacities seen on film within 12-24 hours (17) promotes presumption of a preceding intrauterine infection as the start of BPD.”

Line7, p5: delete the word “relatively”

Reply 10-12: OK

Comment 13: Line 6-11-6, p5: why has this condition largely disappeared except in Japan? Is it due to differences in practice, difference in patient population? Also, why did Wilson-Mikity syndrome decrease as it did? Is it due to gentler ventilation and the current measures in practice?

Reply 13: As explained in the text we suggest that the condition has largely disappeared in our countries due to gentler ventilation and that the condition in Japan seem to be linked to higher leucocyte elastase and low α 1-antitrypsin.

Comment 14: Line19-21, p5: There should be a period after the word discharge, so as to read “...36 weeks postmenstrual age (PMA) or at discharge. BPD can be graded as mild,”.

Reply 14: The text has been deleted to shorten the manuscript following advice from Reviewer D.

Comment 15: Line15-19, p5: Change to read “A concise and clearly-defined consensus BPD definition, outlining risk severity, would be beneficial for both clinical purposes and for research. With such a definition, methods to accurately predict BPD severity may help individualize early treatment therapies.”

Reply 15: OK

Comment 16: Line3, p6: Change sentence to read “Early targeted treatment of BPD may improve outcomes.”

Reply 16: The text has been deleted to shorten the manuscript following advice from Reviewer D.

Comment 17-19: Line3, p7: Delete “probably because of” and replace with “possibly due to”

Line11-13, p7: Change sentence to read “If necessary, nasal intermittent positive pressure ventilation (NIPPV) can often be used with success prior to mechanical ventilation (37).”

Line15-16, p6: Update sentence to read “...to decrease the combined outcome of death and BPD compared to pressure-limited ventilation (38).”

Reply 17-19:OK

Comment 20 &21: Line18-25 p : Move sentence to the beginning of the paragraph: “Caffeine is recommended prophylactically in very preterm infants (36) and has been shown to reduce the risk of BPD (39) with minimization of barotrauma from reduced duration of mechanical ventilation. Caffeine is a competitive adenosine receptor antagonist..... In addition, caffeine increases the likelihood of successful extubation reducing the duration of mechanical ventilation.”

Line2, p8: Delete “and need for supplemental oxygen.”

Reply 20 & 21: OK

Comment22: Line20,21, p9: Delete “the”, so sentence reads “Also, postnatal iNO in a fetal baboon model of BPD has reduced incidence of the disease (45).”

Reply 22: The was kept.

Comment 23: Line8-14, p9: Please clarify this statement “no important differences in the rates of BPD were found in randomized controlled trials targeting low saturations (85-89%) versus high saturations (91-95%) (49)”. Askie’s study reports no important differences in the composite outcome of death and BPD between the two groups. But there was a statistically significant difference in the rates of BPD (or supplemental oxygen at 36 weeks PMA) favoring lower SpO2 target.

Reply 23: We have changed the text as recommended.

Comment 24: Line 24-25, p9: Sentence 5, p8: Please add to the final sentence “....also been associated with the development of BPD, but studies on prophylactic treatment and risk/benefit analysis have not, to our knowledge, been undertaken.”

Reply 24: OK have been added.

Comment 25: Line 5-8, p10: This section is extremely sparse and, though this is a narrative summary of various approaches to ameliorate the severity of BPD, the nutrition literature is expansive and so a few more sentences on nutritional approaches through TPN or early enteral feeding would be helpful.

Reply 25: Therefore, early nutritional approaches through total parenteral nutrition and/or early enteral feeding are important in the very tiny babies to diminish BPD. Exclusive human milk-based nutrition has been shown to impact microbiome and decrease BPD risk.

Comment 26: Line 11-18, p10: Update paragraph to read “The literature about BPD prediction is extensive. Early prediction of BPD would allow intervention to stop or slow progression of disease. Many authors have reported data on various biomarkers”.

Reply 26: The text is updated and rewritten.

Comment 27: p10: Delete (old sentence 13-16, p8) as you talk about Faleh's study further down in the paragraph.

Reply 27: There is no double text about Faleh's study.

Comment 28: Line24, p10: Please provide a reference for your definition of a biomarker.

Reply 28: Ref. 48 added in the text.

Comments 29: line 18-19, p10: Sentence 3, p9: Update sentence to read "Four recent reports are subsequently described."

Reply 29: The text here is deleted.

Comments 30-31: Line18, p11: Delete the word "in" in the following sentence "from a single Chinese center studied in 44 preterm infants...."

Line23, p11: Delete "probably" and change sentence to read "...clinical complications are likely related to RDS and to the....."

Reply 30-31: OK.

Comment 32: Line12-18, p13 in the revised MS: I would delete the entire paragraph. This review is set up to discuss the importance and benefit of early prediction of BPD, as well as current therapeutics for early BPD and potential future or upcoming treatments being studied. While highlighting several studies on p9 describing several predictive risk scores, and then moving on to discuss a new model of prediction at birth using FTIR, I think the description on p10 sentence 13 through p11 sentence 4 suffices. The purpose should be to describe a few predictive models without focusing on one primary method of prediction. This paper is not the appropriate platform to promote this one method FTIR as a predictive model, but merely a means to describe that this model exists as one of the various models used or in development.

Reply 32: In the manuscript we have described the most effective methods to predict BPD. We describe also why it is important to treat the PBD infants as early as possible. Therefore, we find it natural to describe the FTIR spectroscopic method combined with AI we are working with. See also the reply to Reviewer A include the text *p12 line 15-21* and especially reference 69 about mid-infrared spectroscopy and why it is a very important diagnostic method also in neonatology. Furthermore see the comments and reply to Reviewer D. Line 16-18 p 13 in the manuscript is deleted.

Reviewer C:

Comment/Suggestion 1:

I would suggest the authors divide the review into these segments (headers):

- a. Introduction
- b. Background
- c. Current Management Strategies of BPD
- d. Early predictors of BPD
- e. Potential early therapies in at-risk infants

The authors can then create sub-headers to emphasize and organize the review better drawing the attention of the reader to each segment.

Reply 1: OK. We have divided the review as suggested.

Comment/Suggestion 2:

Introduction: Please mention Stoll BJs NICHD study as it is a larger study of importance. The citation is: Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, Hale EC, Newman NS, Schibler K, Carlo WA, Kennedy KA, Poindexter BB, Finer NN, Ehrenkranz RA, Duara S, Sánchez PJ, O'Shea TM, Goldberg RN, Van Meurs KP, Faix RG, Phelps DL, Frantz ID 3rd, Watterberg KL, Saha S, Das A, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics*. 2010 Sep;126(3):443-56. doi: 10.1542/peds.2009-2959. Epub 2010 Aug 23. PMID: 20732945; PMCID: PMC2982806.

Reply 2: We have added the reference as Ref.3.

Comment/Suggestion 3:

Although a narrative review, the paper will improve immensely if the authors include a “methods” section wherein the type, scope and approach of choosing the studies are detailed. Please include a flow chart of the literature review steps. The authors should explain how they attempted to minimize bias in choosing the studies in order to strengthen their paper.

Reply 3: *In the revised MS - In Introduction p 4 line 3-6* we have instead added the following text: “The article is divided in the following segments: Introduction – Background – Current management strategies of BPD – Early predictors of BPD – Potential early therapies in at-risk infants. The literature in the review are hand searched and derivate from published studies”.

Comment/Suggestion 4:

Page 2, Line 8-10: Change sentence to – “It is generally accepted that BPD is a multifactorial disease often associated with intrauterine infections and placental perfusion disorders”

Reply 4: OK

Comment/Suggestion 5:

Page 2, line 16-18: The word review is used twice in this sentence. Please switch to the following sentence: “The present review focuses on early prediction and the existing pharmacologic interventions highlighting the potential to improve the outcome of BPD.”

Reply 5: OK. Same revision is suggested by Reviewer B.

Comment/Suggestion 6:

Page 3, Line4-7: Please change the sentence to... “The etiology of BPD is multifactorial and not fully understood because several different hits both pre- and postnatal may contribute to the evolution and progression of BPD”.

Reply 6: OK. hits is changed to insults as suggested by reviewer B.

Comment/Suggestion 7:

Page 3, Line 7: Change to “microorganisms are invading the infant’s lungs” to “microorganisms invade the infant’s lung”.

Reply 7: OK

Comment/Suggestion 8:

Page 3, line 14: Please use the word “associated” instead of “causing”.

Reply 8: OK

Comment/Suggestion 9:

The authors are suggested to provide a header called “Background” which should include the first sub-header as “Definition of BPD” and then discuss “Old and New BPD”. This will organize and keep the reader on track. The suggested headers are described under point 1).

Reply 9: The text about Old and New BPD and Definition of BPD have been shorted substantial as suggested by Reviewer D and there are no longer a sub-header about Old and New BPD.

Comment/Suggestion 10,11,12:

Page 10, line 11-16: Please change the sentence to “The ideal approach would be to predict BPD as early as possible and intervene to stop progression of the disease”.

Page 10, line 11-16 : The sentence: “following on from this it will be possible to develop very early treatments for BPD before the development of permanent sequelae.” This is entirely speculative. Instead, I would suggest; “Based on the predictors it may be possible to develop early interventions before the development of permanent sequelae.”

Reply 10-12: We have changed the sentences as suggested by Reviewer B to: “Early prediction and intervention of the disease ideally may allow to stop or slow progression of the disease before development of permanent sequelae”.

Page 10, line 23: Instead of “includes” use the word “include”. Reply: OK.

Comment/Suggestion 13:

Page 12: Please switch the order of the sentences: “The sensitivity was 88% and the specificity 91% of the BPD model in a clinical study including preterm infants. Gastric aspirate in the newborn is the fluid produced mainly in the fetal lungs with contributions from the fetal kidneys and cells of the amniotic sac and therefore may include biomarkers linked to infection in cases with chorioamnionitis and correlated with intrauterine pneumonia.”

To..... *Page 12, line 22 - Page 13, line 2:*

“Gastric aspirate in the newborn is a fluid produced mainly in the fetal lungs with contributions from the fetal kidneys and cells of the amniotic sac and therefore may include biomarkers linked to infection in cases with chorioamnionitis and correlated with intrauterine pneumonia. The sensitivity was 88% and the specificity 91% of the BPD model in a clinical study including preterm infants.”

Reply 13: OK.

Comment/Suggestion 14:

Page 14, line 12: Why is SP-D in bold?

Reply 14: It should not be bold, and it is changed now.

Comment/Suggestion 15:

Page 14, Line 15-16: Please provide reference for the statement – “Addition of antibiotics to surfactants may also be a potential therapeutic avenue to explore.”

Reply 15: This matter is too controversial, and the text has been deleted now.

Comment/Suggestion16:

Please edit the following sentence *Page 14 line 20-21*: "However only recently has this therapy re-emerged as a potential mean of disease modification in BPD" to "However, recently this therapy has re-emerged as a potential means of disease modification in BPD".

Reply 16: OK. (and the word "Hower" is deleted).

Comment/Suggestion17:

Page 15, line 15-16: Change the sentence to - "Macrolide therapy has previously been used as a potential strategy for infants at risk of BPD with ureaplasma colonization".

Reply 17: OK.

Comment/Suggestion18:

Page 16, Line 2-3: Change the sentence to - "Many clinical trials with MSC are currently ongoing."

Reply 18: OK

Comment/Suggestion19:

Page 15, Line 8-9: "These treatments are late treatments and will not be dealt with in this review." Change to: These are late treatments of BPD which will not be discussed in this review".

Reply 19: OK.

Reviewer D:

Comment/Suggestion 1: The narrative review aim was "The present review focuses on early prediction, and the existing pharmacologic interventions are reviewed with this highlighting the potential to improve the outcome of BPD." the manuscript is long, and some aspects are not helpful to answer the main question; therefore, I suggest taking off the following article parts:
First description of BPD – Old and New BPD(One phrase is enough, it is not the objective)
Definition of BPD (One phrase is enough, it is not the objective).

Reply 1: We agree with the Reviewer and have substantially shortened the suggested sentences. See *Page 4, 5 and 6* in the reviewed MS.

Reply 1: We agree with the Reviewer and have substantially shortened the suggested sentences. See *Page 4, 5 and 6* in the reviewed MS.

Comment/Suggestion 2:

General Treatment in the Early Phases of BPD: What is the association between these factors and the review aim? The early prediction can change the management regarding these variables?

Reply 2: This is described in the Introduction *Page 3 line21-24*. In short, early prediction and treatment of BPD better the outcome.

Comment/Suggestion 3: Prediction and Prevention: This section is excellent and according to the proposal. *Page 12 line 12-* "Recently it has been possible to predict BPD at birth (31) using mid-infrared Fourier Transform Infrared

Spectroscopy (FTIR) (69) as dry transmission on gastric aspirate combined with clinical data and analyzed by artificial intelligence (AI)." What are the advantages of FTIR compared with the other predictors presented in the prediction and prevention section?

Reply 3: We have added new extra text about the advantages of FTIR in *Prediction at birth Page 12.*

"Recently it has been possible to predict BPD at birth (31) using Fourier Transform Mid-infrared Spectroscopy (FTIR) (69) as dry transmission on gastric aspirate combined with clinical data and analysed by artificial intelligence (AI). This technology which is very rapid (results are obtained within 10-15 minutes) is reagent free and low cost. It has been pervasive in the process industry and thus well suited for deployment in acute point of care settings where speed is critical. The FTIR spectroscopy is pro tempore the only method which can produce predictive results from analyses of many molecules immediately after birth. Other methods such as mass spectroscopy are lab methods, and the results are earliest available days (in best cases many hours) after birth."

Comment/Suggestion 4:

Page 13 Linea 1-2 "The sensitivity was 88% and the specificity 91% of the BPD model in a clinical study including 61 preterm infants", Do you can, based on your BPD prediction, recommend avoiding the early treatments to prevent BPD (CAFFEINE, SURFACTANT, ETC)?

Reply 4: No. This is explained in new text in CLINICAL TREATMENT IN THE EARLY PHASES OF BPD *Page 6 line 10-12*: "Many of the current clinically treatments of BPD as early nasal continuous positive airway pressure (CPAP), surfactant, caffeine and optimal nutrition are necessary early therapies together with new early therapies in at risk babies."

Comment/Suggestion 5:

In the same way, do you can, based on your early BPD prediction, recommend the early treatments to prevent BPD (Surfactant with added Budesonide, etc.)? Should postnatal steroids be performed at birth?

Reply 5: Concerning corticosteroids see the section on *Page 8*. Very early steroid treatment can't be recommended *see Page 8* and this is now also written in the section "Surfactant with added Budesonide" *Page 14, line 8-9.*

Comment/Suggestion 6:

These questions are to a better understanding of the proposal of narrative review; the manuscript is a little wordy and should be rewritten focusing on early prediction and the usefulness.

Reply 6: This is now done in the MS as described above.

Comment/Suggestion 7:

What can be the concerns about the early BPD prediction?

Reply 7: Very early steroid treatment as described above. Safety trials are necessary in most of the potential early therapies and prevention of BPD in at risk babies. This is mentioned in the text for Stem cell therapy *Page 16, for SP-D Page 14*, and for prophylactic treatments of coagulase negative staphylococci and cytomegalovirus *Page 9.*

Comment/Suggestion 8:

The review must focus on the early prediction of BPD, practical, and the possible treatments at birth (24h -72h?).

Reply 8: This is now done, see also reply to Comment no 6. Treatment within 24-28 hours are now possible and necessary as mentioned on *Page 13 line 28 to Page 15 line 3.*