Inhaled Steroids for the Treatment of Early Pediatric Acute Respiratory Distress Syndrome (PARDS), a Randomized Pilot Trial

NCT04064684

Version Date: 12/16/2019

Inhaled steroids for the treatment of early Pediatric Acute Respiratory Distress Syndrome (PARDS), a randomized pilot trial

A. Coronado Munoz, MD[1]; R. Mosquera, MD[2]; M. Nares, MD[3]; V. Modem, MBBS, MS[1]; J. Meliones, MD[1]; Jon Tyson, MD, MPH[4]

1 University of Texas at Houston, Memorial Hermann Children's Hospital, Division of Pediatric Critical Care Medicine

2 University of Texas at Houston, Memorial Hermann Children's Hospital, Division of Pediatric Pulmonary Medicine

3 University of Miami, Jackson Memorial Hospital, Division of Pediatric Critical Care.

4 University of Texas at Houston, Vice Dean Clinical Research, Director Center for Clinical Research and Evidence-Based Medicine

ABSTRACT

Background:

PARDS has high mortality and has no specific treatment. Inhaled steroids (IS) could help reducing the alveolar inflammation. Multiple animal studies examining IS for ARDS show decreased inflammation. One pilot trial in adults showed improvement of oxygenation immediately after IS administration. We believe that **there is enough data to study IS as treatment for PARDS.**

Hypothesis:

Budesonide 0.5 mg q 12 hours nebulized in mechanical ventilators (started within 72 hours of diagnosis of PARDS and administered for up to 10 days while ventilated) increases ventilator-free days during the first 28 days.

Methods:

Blinded randomized pragmatic trial, intend-to-treat analysis. Inclusion criteria: PARDS by PALICC definition [1], 30 days to 18 years old, mechanical ventilation <72 hours. Exclusion criteria: alveolar hemorrhage, hospice care or prior steroids use. After informed parental consent, patients will be stratified by severity of PARDS mild-moderate versus severe, randomized (random number table, block of 10, 1:1) to either nebulized budesonide or normal saline (identical appearance). The clinical team will manage the patients with our PARDS protocols. The medication will be administered for a maximum of 10 days and it will be stopped if patients have pulmonary bleeding. Variables and outcomes will be largely obtained from the EMR. We will aim to enroll 60 patients over 2 years. If our hypotheses are confirmed, **the trial will justify, facilitate the design, and provide an evidence-based hypothesis for multicenter trial.**

BACKGROUND

Acute Respiratory Distress Syndrome (ARDS) is a clinical syndrome of non-cardiogenic pulmonary edema caused primarily by damage to the alveolar epithelial-endothelial barrier. The disruption of this barrier results in accumulation of fluid in the alveolar space and the initiation of a complex inflammatory process [1-4]. Despite the numerous therapeutic studies performed for ARDS, the only therapy that has shown to improve outcomes is protective mechanical ventilation strategies. The clinical management in pediatrics has been historically based on extrapolation from adult data [2-4]. Investigated therapies without positive results in pediatrics include the use of Nitric Oxide, surfactant replacement, prone positioning and systemic steroids [5-13]. Inhaled steroids have been tried in animal studies with positive results and there is a single center pilot trial that has used inhaled steroids (IS), budesonide, for the treatment of ARDS in adults, that shows improved oxygenation immediate to the administration [14].

In June 2015, the Pediatric Acute Lung Injury Consensus Conference published specific definitions and evidence on outcomes, management and pathophysiology specific for Pediatric

Acute Respiratory Distress Syndrome (PARDS). That publication included the use of oxygenation measurements to define the severity of PARDS. Severity was divided in mild, moderate and severe depending on the Oxygenation Index or Oxygenation Saturation Index. An international multicenter prevalence study using those definitions found that patients with severe PARDS have a 90 day-mortality of 34%, versus mild 14.3% and moderate 14.5%. The rate of new cases of PARDS in that study was 3% of patients treated in the participating critical care units. Majority of those cases were secondary to pneumonia (63%) and trauma (19%). [1, 15].

Based on animal models of lung injury there are differences in the pathophysiology of PARDS with age [16]. These differences may be related to different stages of alveolarization and lung development and the maturation of the immune system in children. The inflammation produced in the alveolar space is mediated by neutrophils. In children, there are few studies looking at the cytokine response in PARDS [17-19]. Two different studies have demonstrated elevated levels of interleukins (IL), specifically IL-6 and IL-8 [20-22]. Another study found that elevated levels of soluble intercellular adhesion molecule-1 are associated with prolonged duration of mechanical ventilation and a higher mortality [23]. Elevated proteases (matrix metalloproteinases, MMP) like MMP-8 and MMP-9 have been shown in adult and pediatric studies to play key roles in the neutrophilic lung inflammation and are associated with prolonged mechanical ventilation [24, 25]. There is, however, poor understanding of the role that these mediators play as therapeutic targets and whether decreasing the inflammatory response in the alveolar space with the use of corticosteroids would change the clinical course of those patients [26, 27]. Inhaled steroids could decrease this inflammatory response in PARDS.

There is a recently published study in adults using budesonide for ARDS, compared to normal saline. 60 patients were divided equally between both cohorts and they showed improvement of oxygenation in the group of budesonide but only in the immediate effect post administration [14]. Alsara et al. examined the use of preoperative inhaled steroids in adults and the occurrence of ALI in the postoperative period. In this patient population and when adjusting for COPD, the use of steroids was not associated with the development of early ALI [28]. Festic et al. examined the use of pre-hospital inhaled steroid use and the incidence of ALI in at-risk patients. The results did not show an association of lower incidence of ALI in patients receiving inhaled steroids. The authors concluded that the results could be affected by the population size leading to a Type II error [29]. There are several studies evaluating inhaled steroids in animal models of ARDS. A systematic review of those studies was presented in the *Society of Critical Care Medicine* conference [30]. The results are varied related to the variability of lung injury models. One study showed less pulmonary granulocyte accumulation in the pigs treated with the steroids as compared to the placebo group. Two other studies using the same treatment and model of lung injury, showed improved oxygenation, pulmonary compliance and survival in the steroid group [31-34]. Another study showed that animals receiving budesonide prior to the injury had less production of Tumor Necrosis Factor α (TNF α), IL-1, IL-6 and MCP-1. Overall, the use of IS in animal models showed less formation of lung edema, better oxygenation, less degree of acute lung injury and decreased leukocyte migration [35]. In pediatrics, Drago et al. published a pilot-study in 2015 using low dose intravenous methylprednisolone. The results were limited since it was a pilot study and it was an underpowered one. There was no statistical significance on the main outcome, which was days on mechanical ventilation. The duration of days was similar in both groups, 9.74 ± 6.62 versus 9.59 ± 5.21. That study showed the feasibility of developing a larger randomized-controlled trial using systemic steroids in pediatric patients with ARDS [9]. **There are no studies referring to the use of inhaled steroids for PARDS.**

The use of inhaled steroids has been studied in asthma, Chronic Obstructive Pulmonary Disease (COPD), Cystic Fibrosis (CF) and neonatal respiratory distress syndrome. Most of the studies evaluating inhaled steroids anti-inflammatory effects have been performed in asthmatic patients.

The only inhaled steroid approved for patients younger than 4 years of age is Budesonide [36-40]. Another advantage of budesonide is the ability to deliver the medication via nebulization in mechanically ventilated patients [41-45]. The immediate anti-inflammatory effects have been well described in asthmatic patients [46, 47]. **More importantly, the safety profile of inhaled**

steroids has been studied in large pediatric, neonatal including preterm , and adult populations [36, 37, 48]. Inhaled steroids have also been studied in patients with cystic fibrosis, which are at higher risk of pulmonary infections, and have not been associated with a higher risk of infection [49, 50]. Recent studies have looked at inhaled steroids in very low birth weight preterm neonates for the prevention of chronic lung disease. A recent study in preterm neonates, ventilator-dependent infants concluded that the use of inhaled budesonide was associated with less incidence of bronchopulmonary dysplasia (BPD). However, there was higher mortality in the budesonide group (16.9% vs. 13.6%, gestational age - stratified relative risk 1.24, CI 0.91 – 1.69) [51]. A large Cochrane metanalysis, published in 2012, did not find evidence of advantages of inhaled steroids over systemic steroids in the management of ventilator-dependent preterm infants, but did show fewer side effects than with the use of systemic steroids [52]. Two recent Cochrane publications for early < 8 days and late > 7 days systemic steroids use in pre-term newborns for prevention of BPD concluded that the use of steroids did not outweigh the adverse effects. For both groups there was a faster improvement of the respiratory status assessed by weaning-off mechanical ventilation. In the early group, patients that received hydrocortisone had a higher survival rate, and for the late group the data suggests that it reduces mortality. Both groups had adverse events like gastrointestinal bleeding or perforation and poor neurological outcomes [53, 54]. A recent Cochrane publication for the use of inhaled steroids for BPD failed to show reduced mortality or BPD. However, this metanalysis was based in eight studies. Further studies are necessary to draw conclusions regarding the usefulness or not of inhaled steroids for this population [55].

We believe there is enough data to conduct a study examining the treatment of PARDS with inhaled steroids in a safe manner. This proposal is to perform a pilot study, the largest feasible trial in the time proposed, and conduct a Bayesian analysis, to estimate the probability of benefits of this treatment, and assess whether a multicenter is warranted [56]. We will examine clinical outcomes of pediatric patient with PARDS who will receive inhaled budesonide as a therapy.

RESEARCH AIMS

Primary Hypothesis: Budesonide 0.5 mg q 12 hours nebulized in mechanical ventilators (started within 72 hours of diagnosis of PARDS and administered for up to 10 days while ventilated) increases ventilator-free days during the first 28 days

AIMS:

- To show that inhaled steroids in patient with PARDS can decrease the days on mechanical ventilator measured by ventilator-free days.
- To improve the oxygenation index (OI) or oxygenation saturation index (OSI) by 30% in patients receiving inhaled steroids, by day 10 or the last day of mechanical ventilation if this happen before day 10, starting the treatment within 72 hours of diagnosis.
- To show the relevance and feasibility of a larger study by assessing the hypothesis in a small cohort of patients.
- To show that inhaled steroids can improve residual lung disease evaluated by Pulmonary Function Test (PFTs) and Impulse Oscillometry (IOS)
- To reduce inflammatory markers (IL6, IL8, TNF α, MMP 8 and MMP9) and neutrophil counts from tracheal aspirates.
- To reduce the length of stay (LOS) in the PICU and hospital admissions.

STUDY DESIGN AND METHODS

Blinded randomized pragmatic pilot trial. We will include pediatric patients with Pediatric Acute Respiratory Distress Syndrome, diagnosed <72 hours, on mechanical ventilation. The severity of ARDS will be determined using established PALICC criteria determined by Oxygenation Index

(OI) and Oxygenation saturation index (OSI) [1]. The definitions are presented in Figure 1. This study is pending IRB approval, University of Texas, HSC at Houston.

Age	Exclude patients with peri-natal related lung disease			
Timing	Within 7 days of known clinical insult			
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	**Non Invasive mechanical ventilation**	**Invasive mechanical ventilation**		
	PARDS (No severity stratification)	Mild	Moderate	Severe
	Full face-mask bi-level ventilation or CPAP ≥5 cm H_20 [2] PF ratio ≤ 300 SF ratio ≤ 264 [1]	4 ≤ OI < 8 5 ≤ OSI < 7.5[1]	8 ≤ OI < 16 7.5 ≤ OSI < 12.3[1]	OI ≥ 16 OSI ≥ 12.3[1]
Special Populations				
Cyanotic Heart Disease	Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease. [3]			
Chronic Lung Disease	Standard Criteria above for age, timing, and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above.[3]			
Left Ventricular dysfunction	Standard Criteria for age, timing and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction.			

Figure 1: PALICC Definition of PARDS

OI = oxygenation index = (FiO_2* mean airway pressure*100)/ PaO_2

OSI = oxygen saturation index = (FiO_2* mean airway pressure*100) /SpO_2

[1] Use PaO_2 based metric when available. If PaO_2 not available, wean FiO_2 to maintain SpO_2 ≤ 97% to calculate OSI or SF ratio

[2] For non-intubated patients treated with supplemental oxygen or nasal modes of non-invasive ventilation see Figure 3 for At Risk Criteria

[3] ARDS severity groups stratified by OI or OSI should not be applied to children with chronic lung disease who normally receive invasive mechanical ventilation or children with cyanotic congenital heart disease

Inclusion Criteria:

- Pediatric patients older than 30 days and up to 18 years of age admitted to the PICU with a diagnosis of PARDS enrolled within 72 hours of diagnosis.
- Patients requiring invasive mechanical ventilation.
- Criteria of PARDS as defined by the Pediatric Acute Lung Injury Consensus Conference (PALICC), on June 2015 in Pediatric Critical Care Journal [1] Figure 1.

Exclusion Criteria:

- Patients with diffuse alveolar hemorrhage.
- Patients terminally ill with limitation of care or in hospice care.
- Patients receiving inhaled steroids or systemic steroids as chronic therapy before admission.
- Patients with high dose systemic steroids for anti-inflammatory purposes. We will not exclude patients receiving hydrocortisone for shock.
- Patients with hypersensitivity reactions documented to budesonide or other inhaled steroids like fluticasone, beclomethasone or others or other systemic steroids like prednisone, hydrocortisone, prednisolone and methylprednisolone.

Enrollment:

Patients with PARDS will be identified in the PICU of Memorial Hermann Children's Hospital. PICU attendings, fellows and nurses will be informed about the study and they will inform the research team about potential patients. One person for the research team will be on-call to review daily admissions to the PICU to identify potential patients. Parents or legal guardians of eligible patients will be approached for consent. **Once consent is obtained the patients will be stratified by severity of PARDS OI < 16 (mild or moderate) and OI > 16 (severe). The randomization will be generated by a computer and the random number table will be performed by the Memorial Hermann Research Pharmacy. The patients will be blocked randomized, blocks of ten patients, 1:1, two blinded groups: budesonide vs placebo (normal saline)**. The research pharmacy of Memorial Hermann Hospital will deliver the medication according to the randomization list. They will distribute the medication to the patient's bin in the Automated Medication Cabinet in the PICU. The medications will be distributed in identical syringes, identical label with the number of the study and patient information.

Medication delivery:

Enrolled patients will be treated with Pulmicort Repsules®, Budesonide inhalation suspension [57], at a dose of 0.5 mg, nebulized twice daily through the mechanical ventilator. That budesonide dose is the one recommended for treatment of pediatric asthmatic patients [40]. Normal saline is commonly used as a solution to dilute secretions and facilitate suctioning of those secretions. There are no trials of normal saline in patients with PARDS but it is thought to be harmless and it is currently used for clearing respiratory secretions. Studies *In vitro* for hypertonic saline have showed that sodium chloride in the airway does not get absorbed systemically [58, 59]. The research team, medical management team, bedside nurse and respiratory therapist will be blinded to the medication versus placebo. Both are clear liquids of similar consistency. They are also stable medications and can be distributed bedside by research pharmacy in identical syringes. The medication will be ordered in the Electronic Medical Record (EMR) as a research medicine. The medication will be administered to the patient by the respiratory therapist with the single-patient-use medication nebulizer attached to the mechanical ventilator circuit. The maximum length of treatment will be 10 days. If the patient improves and can be weaned-off mechanical ventilation, invasive or non-invasive, prior to 10 days of therapy the medication will be discontinued on the last day of ventilatory support [60]. If the patients require reintubation, we will continue the study medication until completing the 10-day treatment. If the patient has pulmonary bleeding the treatment will be discontinued. **All these patients will be included in an intention-to-treat analysis.**

Risk

The risks associated with this treatment are not considered clinically relevant taking in consideration the evidence described in susceptible subjects as described in the Background section. The short time duration of the treatment proposed also minimizes the risk of side effects. General side effects associated to steroids use are discussed in the following paragraph explaining why these effects are not considered to pose a risk to our patients.

Inhaled steroids have been associated with Candida albicans in the oral mucosa. However, this medication is going to be administered directly in the lungs. There is a known and well described immunosuppressant effect of steroids. However, this risk has only been described in studies involving long term treatment with systemic steroids. There is no data that demonstrates an immunosuppressive effect of budesonide in patients with asthma that use it chronically. Another risk associated with steroids is the possibility adrenal suppression. However, this risk has not been demonstrated in inhaled steroids. Finally, effects on growth have been demonstrated in pediatric patient receiving inhaled steroids like budesonide but these studies have been done in patients with prolonged treatments with budesonide.

Medical management:

The management of the mechanically ventilated patients with PARDS will be at the discretion of the on-service team. This includes the use of open lung strategy, permissive hypercapnia and low tidal volume ventilation. The standard of care of the patients with ARDS in our unit is evidence-based: Tidal volumes between 6-8 ml/kg (ideal body weight), permissive hypercapnia tolerating pCO2 as high as 70 Torr as long as the pH is 7.25 or higher and FiO2 titrated to maintain

oxygenation saturations between 92 – 94% and adjusting Positive end-expiratory pressure (PEEP) and inspiratory : expiratory ratios accordingly. [61-64] The extubation is decided by the Extubation readiness trial protocol of our unit [65]. **All that information will be variables recorded for each patient enrolled along with the outcomes.** The physicians, faculty and fellows, of the pediatric critical care division will adhere to PARDS management recommendation for mechanical ventilation lung protection and to the extubation readiness trial protocols. This will be reminded during our weekly patient discussion meetings and monthly research meetings. Fellows will be available to help with data collection and will be invited to directly participate in the trial.

Data and outcomes:

The clinical information will be largely extracted from the EMR. **Ventilator-free days (VFD)**: The number of days between weaning off the mechanical ventilation and day 28 after enrollment in study. If the patient dies before day 28 or if the patient requires mechanical ventilation for more than 28 days the value VFD will be 0. It will be measured two ways: for IMV and for a combination of IMV + NIMV. For patients reintubated within 48 hours it will be considered a continuous ventilation [15, 66]. The secondary outcome is **Oxygenation index and Oxygenation saturation index** are routinely measured in ventilated patients. We will obtain the measurements twice a day while the patients continue requiring invasive mechanical ventilation (IMV) and non-invasive mechanical ventilation (NIMV) up to 28 days. **Length of stay in PICU and in hospital** will be also measured until patients are transferred, discharged or decease. Tracheal aspirates will be obtained on day 1, day 3 and on the last day of treatment or last day of invasive mechanical ventilation. It will be processed in the critical care research laboratory with the use of custom ordered commercial laboratory assays compatible with EPOCH microplates [67]. This will include ELISA test for **TNF α levels, IL-1, IL-6, IL-8 and MMP-8 and MMP-9**. A cell count will be performed in each sample to obtain a neutrophil count. A vial of tracheal aspirate will be stored for genetic testing on protein expression for future translational research; these samples will be stored in a subzero freezer. The values obtained will be recorded daily since enrollment until completion of treatment or until discontinuation of mechanical ventilation or for 28 days if patients remain on mechanical ventilation (IMV or NIMV). The values will be obtained daily and a 4 am and 4 pm value will be included for every day of treatment. Before discharge from PICU patients will be referred to the High-Risk Clinic at one month after PICU discharge to evaluate for **residual lung disease measured by PFTs and IOS**. These studies will be performed by the Pediatric Pulmonary Division research team. [68] The rest of the variables to be collected are listed in Appendix A.

DATA ANALYSIS PLAN

Sample size: largest feasible study in 2 years; 60 patients expected, and we commit to enrolling 60 even if three years are required

Since this is a pilot single center trial, we propose performing a **Bayesian analysis for the primary outcome and for the ventilator free days outcome** [56]. This will allow us to enroll the maximum number of patients feasible in two years. According to the number of admissions in the PICU at Children's Memorial Hermann (around 1200 patients per year) and incidence of PARDS, we estimate we could enroll 60 patients

This will be a pilot study and will estimate the probability of benefits and assess whether a multicenter trial is warranted. Bayesian analysis will be performed using a neutral prior (50% probability of benefit). Bayesian posterior probability of benefit ≥ 75%, showing increased VFDs, will be required to propose a larger multicenter trial. These analyses will be performed by Claudia Pedroza, PhD, a Bayesian statistician.

The rest of variables will be analyzed with frequentist statistics and will include t-test for continuous variables, chi-square for categorical, Mann Whitney U test for nonparametric statistics.

DATA MANAGEMENT COMMITTEE

A Data Safety Monitoring Board (DSMB) will review this study yearly. They will perform an unblinded review of patients for possible unforeseen complications associated to the treatment arm including worst clinical outcomes for any of the groups. The composition of this board will have Doctor Konstantinos Boukas, Medical Director Pediatric Critical Care, as chair and doctor Syed Hashmi, statistician, and doctor Ankur Kamdar, rheumatologist, expert on steroid medications. The DSMB report will be sent to the principal investigator and to the IRB. All the detailed information is attached in the document called DSMB charter.

Additionally, the progress on the execution, data collection, safety and data analysis of this project will be supervised monthly by doctor Jon Tyson, doctor Jon Meliones, doctor Claudia Pedroza and doctor Ricardo Mosquera. This group will supervise and receive updates from the PI and will review the data collected and evaluate the safety of the study. The progress will also be discussed with the directors of the Center for Clinical and Translational Sciences KL2 program at UTH every 3 months. A review document will be completed at the time of the continuous reviews by the IRB and it will include Adverse Events. Serious Adverse Events will be informed to the IRB within 7 days.

PRIVACY AND SECURITY

The information will be obtained from EMR Care4. The relevant clinical identifiers as MRN, date of birth and date of admission will be linked with a code. This code will be assigned and recorded in the Linking log document. This document will be stored in a separate locked cabinet, in a safe locked office and password and privacy protected computer. The data will be collected in Red Cap as demonstrated in CRF.

1. Khemani, R.G., et al., *Pediatric acute respiratory distress syndrome: definition, incidence, and epidemiology: proceedings from the Pediatric Acute Lung Injury Consensus Conference.* Pediatr Crit Care Med, 2015. **16**(5 Suppl 1): p. S23-40.
2. Force, A.D.T., et al., *Acute respiratory distress syndrome: the Berlin Definition.* JAMA, 2012. **307**(23): p. 2526-33.
3. Ferguson, N.D., et al., *The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material.* Intensive Care Med, 2012. **38**(10): p. 1573-82.
4. De Luca, D., et al., *The use of the Berlin definition for acute respiratory distress syndrome during infancy and early childhood: multicenter evaluation and expert consensus.* Intensive Care Med, 2013. **39**(12): p. 2083-91.
5. Essouri, S., C. Carroll, and G. Pediatric Acute Lung Injury Consensus Conference, *Noninvasive support and ventilation for pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference.* Pediatr Crit Care Med, 2015. **16**(5 Suppl 1): p. S102-10.
6. Adhikari, N., K.E. Burns, and M.O. Meade, *Pharmacologic therapies for adults with acute lung injury and acute respiratory distress syndrome.* Cochrane Database Syst Rev, 2004(4): p. CD004477.
7. Calfee, C.S. and M.A. Matthay, *Nonventilatory treatments for acute lung injury and ARDS.* Chest, 2007. **131**(3): p. 913-20.
8. Peter, J.V., et al., *Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis.* BMJ, 2008. **336**(7651): p. 1006-9.
9. Drago, B.B., et al., *Double-blind, placebo-controlled pilot randomized trial of methylprednisolone infusion in pediatric acute respiratory distress syndrome.* Pediatr Crit Care Med, 2015. **16**(3): p. e74-81.

10. Jeon, K., et al., *Predictors of response to corticosteroid treatment in patients with early acute respiratory distress syndrome: results of a pilot study.* Yonsei Med J, 2015. **56**(1): p. 287-91.
11. Tang, B.M., et al., *Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis.* Crit Care Med, 2009. **37**(5): p. 1594-603.
12. Tamburro, R.F., M.C. Kneyber, and G. Pediatric Acute Lung Injury Consensus Conference, *Pulmonary specific ancillary treatment for pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference.* Pediatr Crit Care Med, 2015. **16**(5 Suppl 1): p. S61-72.
13. Rimensberger, P.C., I.M. Cheifetz, and G. Pediatric Acute Lung Injury Consensus Conference, *Ventilatory support in children with pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference.* Pediatr Crit Care Med, 2015. **16**(5 Suppl 1): p. S51-60.
14. Mohamed, H. and M. Meguid, *Effect of nebulized budesonide on respiratory mechanics and oxygenation in acute lung injury/acute respiratory distress syndrome: Randomized controlled study.* Saudi Journal of Anaesthesia, 2017. **11**(1): p. 9-14.
15. Khemani, R.G., et al., *Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study.* The Lancet Respiratory Medicine, 2019. **7**(2): p. 115-128.
16. Smith, L.S., J.J. Zimmerman, and T.R. Martin, *Mechanisms of acute respiratory distress syndrome in children and adults: a review and suggestions for future research.* Pediatr Crit Care Med, 2013. **14**(6): p. 631-43.
17. Yehya, N., et al., *Circulating markers of endothelial and alveolar epithelial dysfunction are associated with mortality in pediatric acute respiratory distress syndrome.* Intensive Care Med, 2016. **42**(7): p. 1137-45.
18. Wong, H.R., et al., *Pediatric Sepsis Biomarker Risk Model-II: Redefining the Pediatric Sepsis Biomarker Risk Model With Septic Shock Phenotype.* Crit Care Med, 2016.
19. Orwoll, B.E. and A. Sapru, *Biomarkers in Pediatric ARDS: Future Directions.* Front Pediatr, 2016. **4**: p. 55.
20. Todd, D.A., et al., *Surfactant phospholipids, surfactant proteins, and inflammatory markers during acute lung injury in children.* Pediatr Crit Care Med, 2010. **11**(1): p. 82-91.
21. Dobyns, E., et al., *Elevated plasma endothelin-1 and cytokine levels in children with severe acute respiratory distress syndrome.* The Journal of Pediatrics, 1999. **135**(2 (1)): p. 246 - 249.
22. Flori, H., et al., *A prospective investigation of interleukin-8 levels in pediatric acute respiratory failure and acute respiratory distress syndrome.* Critical Care, 2019. **23**(1): p. 128.
23. Flori, H.R., et al., *Early elevation of plasma soluble intercellular adhesion molecule-1 in pediatric acute lung injury identifies patients at increased risk of death and prolonged mechanical ventilation.* Pediatr Crit Care Med, 2003. **4**(3): p. 315-21.
24. Kong, M., et al., *Matrix Metalloproteinase Activity in Pediatric Acute Lung Injury.* International Journal of Medical Sciences, 2009. **6**(1): p. 9-17.
25. Kong, M.Y., et al., *Early elevation of matrix metalloproteinase-8 and -9 in pediatric ARDS is associated with an increased risk of prolonged mechanical ventilation.* PLoS One, 2011. **6**(8): p. e22596.
26. Sapru, A., et al., *Pathobiology of acute respiratory distress syndrome.* Pediatr Crit Care Med, 2015. **16**(5 Suppl 1): p. S6-22.
27. Reade, M. and E. Milbrandt, *Is there evidence to support a phase II trial of inhaled corticosteroids in the treatment of incipient and persistent ARDS? .* Critical Care and Resuscitation, 2007. **9**(3): p. 10.
28. Alsara, A., et al., *Preoperative Inhaled Steroids Did not Protect Against Early Postoperative Acute Lung Injury*. 2010, American Journal of Respiratory and Critical Care Medicine. p. A1702.

29. Festic, E., et al., *Prehospital use of inhaled steroids and incidence of acute lung injury among patients at risk.* J Crit Care, 2013. **28**(6): p. 985-91.
30. Munoz, A.C., et al., *1144: INHALED STEROIDS FOR THE TREATMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME IN ANIMAL STUDIES.* Critical Care Medicine, 2018. **46**(1): p. 556.
31. Walrther, S., et al., *Corticosteroid by aerosol in septic pigs - effects on pulmonary function and oxygen transport.* Intensive Care Medicine, 1993. **19**: p. 155 - 160.
32. Walther, S., et al., *Nebulized corticosteroid improves pulmonary function and outcome in experimental porcine septicemia.* Acta Anaesthesiologica Scandinavica, 1991. **35**: p. 635 - 641.
33. Walther, S., et al., *Pulmonary Granulocyte accumulation is reduced by nebulized corticosteroid in septic pigs.* Acta Anaesthesiologica Scandinavica, 1992. **36**: p. 651 - 655.
34. Yan, Y.M., et al., *Therapeutic effects of inhaling aerosolized surfactant alone or with dexamethasone generated by a novel noninvasive apparatus on acute lung injury in rats.* J Trauma Acute Care Surg, 2012. **73**(5): p. 1114-20.
35. Jansson, A.H., C. Eriksson, and X. Wang, *Effects of budesonide and N-acetylcysteine on acute lung hyperinflation, inflammation and injury in rats.* Vascul Pharmacol, 2005. **43**(2): p. 101-11.
36. Sheffer, A., et al., *Long-term safety of once-daily budesonide in patients with early-onset mild persistent asthma: results of the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study.* Annals of Allergy, Asthma and Immunology, 2005. **94**: p. 48 - 54.
37. Silverman, M., et al., *Safety and tolerability of inhaled budesonide in children in the Steroid Treatment As Regular Therapy in early asthma (START) trial.* Pediatric Allergy and Immunology, 2006. **17**(Suppl 17): p. 14 - 20.
38. Vikre-Jørgensen, J., L. Agertoft, and S. Pedersen, *Dose Titration of Nebulized Budesonide in Young Children.* Pediatric Pulmonology, 1997. **23**: p. 270 - 277.
39. Volovitz, B. and M. Nussinovitch, *Effect of High Starting Dose of Budesonide Inhalation Suspension on Serum Cortisol Concentration in Young Children with Recurrent Wheezing Episodes.* Journal of Asthma, 2003. **40**(6): p. 625-629.
40. National Heart, L.a.B.I. and N.A.E.a.P. Program, *Expert Panel report 3: Guidelines for the diagnosis and management of asthma. .* U.S. Dept. of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute. , 2007.
41. Miller, D.D., et al., *Aerosol delivery and modern mechanical ventilation: in vitro/in vivo evaluation.* Am J Respir Crit Care Med, 2003. **168**(10): p. 1205-9.
42. Hess, D., et al., *Medication Nebulizer Performance Effects Of Diluent Volume, Nebulizer Flow, and Nebulizer Brand.* Chest, 1996. **110**: p. 498-505.
43. Longest, P.W., et al., *Improving Aeorol Drug Delivery During Invasive Mechanical Ventilation With Redesigned Components.* Respiratory Care, 2014. **59**(5): p. 686-698.
44. Longest, P.W., M. Azimi, and M. Hindle, *Optimal delivery of aerosols to infants during mechanical ventilation.* J Aerosol Med Pulm Drug Deliv, 2014. **27**(5): p. 371-85.
45. Longest, P.W. and G. Tian, *Development of a new technique for the efficient delivery of aerosolized medications to infants on mechanical ventilation.* Pharm Res, 2015. **32**(1): p. 321-36.
46. Mendes, E.S., et al., *Immediate antiinflammatory effects of inhaled budesonide in patients with asthma.* Ann Am Thorac Soc, 2014. **11**(5): p. 706-11.
47. Volovitz, B., et al., *Rapid induction of clinical response with a short-term high-dose starting schedule of budesonide nebulizing suspension in young children with recurrent wheezing episodes* Journal of Allergy and Clinical Immunology, 1998. **101**(4): p. 464 - 469.
48. DiSantostefano, R.L., et al., *Risk of pneumonia with inhaled corticosteroid/long-acting beta2 agonist therapy in chronic obstructive pulmonary disease: a cluster analysis.* Int J Chron Obstruct Pulmon Dis, 2014. **9**: p. 457-68.
49. Balfour-Lynn, I.M. and K. Welch, *Inhaled corticosteroids for cystic fibrosis.* Cochrane Database Syst Rev, 2014. **10**: p. CD001915.

50. BISGAARD, H., et al., *Controlled Trial of Inhaled Budesonide in Patients with Cystic Fibrosis and Chronic Bronchopulmonary Pseudomonas aeruginosa Infection.* American Journal of Respiratory and Critical Care Medicine, 1997. **156**(4): p. 1190-1196.
51. Bassler, D., et al., *Early Inhaled Budesonide for the Prevention of Bronchopulmonary Dysplasia.* N Engl J Med, 2015. **373**(16): p. 1497-506.
52. Shah, S., et al., *Inhaled versus systemic corticosteroids for preventing chronic lung disease in ventilated very low birth weight preterm neonates.* Cochrane Database of Systemic Reviews, 2012(5).
53. Doyle, L.W., et al., *Early (< 8 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants.* Cochrane Database Syst Rev, 2017. **10**: p. CD001146.
54. Doyle, L.W., et al., *Late (> 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants.* Cochrane Database Syst Rev, 2017. **10**: p. CD001145.
55. Onland, W., M. Offringa, and A. van Kaam, *Late (>/= 7 days) inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm infants.* Cochrane Database Syst Rev, 2012(4): p. CD002311.
56. Amrhein V, Greenland S, and M. B, *Scientists rise up against statistical significance.* Nature, 2019. **567**(7748): p. 305-307.
57. AstraZeneca, *Pulmicort Repsules ®, (budesonide, inhalation suspension)*, in *http://www.azpicentral.com/pulmicort-respules/pulmicortrespules.pdf#page=1*. 2010.
58. Zhang, L., et al., *Nebulised hypertonic saline solution for acute bronchiolitis in infants.* Cochrane Database of Systematic Reviews, 2017(12).
59. Elkins, M.R. and P.T.P. Bye, *Mechanisms and applications of hypertonic saline.* Journal of the Royal Society of Medicine, 2011. **104 Suppl 1**(Suppl 1): p. S2-S5.
60. Kurachek, S.C., et al., *Extubation failure in pediatric intensive care: a multiple-center study of risk factors and outcomes.* Crit Care Med, 2003. **31**(11): p. 2657-64.
61. THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK, A., *Ventilation With Lower Tidal volumes As Compares With Traditional Tidal volumes For Acute Lung Injury And the Acute Respiratory Distress Syndrome.* The New England Journal of Medicine, 2000. **342**(18): p.1301-8.
62. Britos, M., et al., *The value of positive end-expiratory pressure and Fio(2) criteria in the definition of the acute respiratory distress syndrome.* Crit Care Med, 2011. **39**(9): p. 2025-30.
63. Thompson, B.T., et al., *Clinicians' Approaches to Mechanical Ventilation in Acute Lung Injury and ARDS.* Chest, 2001. **120**: p. 1622-1627.
64. Chacko B, et al., *Pressure-controlled versus volume-controlled ventilation for acute respiratory failure due to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS).* Cochrane Database of Systematic Reviews, 2015(1).
65. Khemani, R.G., et al., *Pediatric extubation readiness tests should not use pressure support.* Intensive Care Med, 2016. **42**(8): p. 1214-22.
66. Schoenfeld, D.A.B., GR.; for the ARDS Network, *Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome.* Critical care medicine, 2002. **30**(8): p. 1772-1777.
67. Biotek Intruments, I. *Epoch Microplate Spectrophotometer*. 2012; Available from: http://daytam.atauni.edu.tr/uploads/dosya/3ac576d0f36adc27e263009054d53719.pdf.
68. Ward, S.L., et al., *Long-Term Pulmonary Function and Quality of Life in Children After Acute Respiratory Distress Syndrome: A Feasibility Investigation.* Pediatr Crit Care Med, 2017. **18**(1): p. e48-e55.
69. Wong, J.J., et al., *Risk Stratification in Pediatric Acute Respiratory Distress Syndrome: A Multicenter Observational Study.* Crit Care Med, 2017. **45**(11): p. 1820-1828.

Appendix A

Variable	**Unit**	**Range of Scale**
Subject ID		1 – x
Subject age	Months	1 – 264
Date of admission	Date format	Mm/dd/yy
Gender	Nominal	1 Male 2 Female
Weight	(kg)	
Days in PICU	Days	0 – x
Days in Hospital	Days	0 – x
Primary Diagnosis – etiology of ARDS *Sepsis/Pneumonia*	Dichotomy	1 Sepsis 2 Pneumonia
Secondary Diagnosis	Nominal	Each diagnosis will be coded
Day of diagnosis of ARDS (documented on chart, day 1 control group)	Date format	Mm/dd/yy
Disposition after PICU	Nominal	1 Transfer to floor 2 Discharge home 3 Deceased
PRISM III Admission score to PICU:	Continuous	0-72
Date of first dose of intervention	Date format (dd/mm/yy)	

Days on treatment	Numeric	
All following values will be recorded from 4 am and 4 pm measurements on days 1 – 5		
Oxygenation index	[FiO2 x Mean Airway Pressure x 100] / PaO2	4 – 8 mild 8 – 16 moderate > 16 severe
PEEP	cmH2O	
Tidal volume	Volume per breath per kilo, ideal weight (ml/Kg)	
pH	Continuous	
pCO2	Continuous Torr	
pO2	Continuous Torr	
O2 sat (blood gas)	Continuous Percentage	