Published in final edited form as:

Pediatr Crit Care Med. 2017 November ; 18(11): 1019–1026. doi:10.1097/PCC.0000000000001305.

Association of Response to Inhaled Nitric Oxide and Duration of Mechanical Ventilation in Pediatric Acute Respiratory Distress Syndrome

Jasmine C. Dowell, MD¹, Neal J. Thomas, MD, MSc², and Nadir Yehya, MD¹

¹Children's Hospital of Philadelphia and University of Pennsylvania, Department of Anesthesiology and Critical Care Medicine, Suite 7C-26, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104

²Penn State Hershey Children's Hospital, Department of Pediatrics and Public Health Science, Division of Pediatric Critical Care Medicine, 500 University Drive, Hershey, PA 17033

Abstract

Objective—Literature regarding appropriate use of inhaled nitric oxide (iNO) for pediatric acute respiratory distress syndrome (PARDS) is sparse. This study aims to determine if positive response to iNO is associated with decreased mortality and duration of mechanical ventilation in PARDS.

Design—Retrospective cohort study

Setting—Large pediatric academic medical center

Patients or Subjects—161 children with PARDS and iNO exposure for 1 hour within 3 days of PARDS onset.

Interventions—Patients with 20% improvement in oxygenation index (OI) or oxygen saturation index (OSI) by 6 hours after iNO initiation were classified as “responders.”

Measurements and Main Results—OI, OSI, and ventilator settings were evaluated prior to iNO initiation and 1, 6, 12, and 24 hours following iNO initiation. Primary outcomes were mortality and duration of mechanical ventilation. Baseline characteristics, including severity of illness, were similar between responders and non-responders. Univariate analysis showed no

---

Corresponding Author: Jasmine C. Dowell, MD, Children's Hospital of Philadelphia, Department of Anesthesiology & Critical Care Medicine, 34th St. & Civic Center Blvd, Philadelphia, PA 19104, dowellj@email.chop.edu, 267-331-1042. Reprints will be ordered and should be shipped to: Jasmine C. Dowell, MD, 1515 N. Van Buren St, Unit 501, Milwaukee, WI 53202.

Author Contributions: Drs. Dowell and Yehya had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Drs. Dowell and Yehya

Acquisition, analysis, and interpretation of data: Drs. Dowell and Yehya

Drafting of the manuscript: Dr. Dowell

Critical revision of the manuscript for important intellectual content: Drs. Dowell, Thomas, and Yehya, Statistical analysis: Dr. Yehya

Statistical analysis: Dr. Yehya

Obtained funding: Dr. Yehya

Conflict of Interest Disclosures: They have no financial interest or interaction with providers of iNO. Dr. Thomas presented a one-time educational webinar on the new PARDS definitions for the company employees that included no promotional content, but only the proceedings of the Pediatric Acute Lung Injury Consensus Conference. Drs. Jasmine C. Dowell and Nadir Yehya have no conflicts of interest to report.

difference in mortality between responders and non-responders (21% vs 21%, $p=0.999$). Ventilator days were significantly lower in responders (10 vs 16, $p<0.001$). Competing risk regression (competing risk of death) confirmed association between iNO response and successful extubation (SHR=2.11, 95% CI 1.41 to 3.17, $p<0.001$). Response to iNO was associated with decreased utilization of high frequency oscillatory ventilation (HFOV) and extracorporeal membrane oxygenation (ECMO), and lower hospital charges (difference in medians of \$424,000).

Conclusions—Positive response to iNO was associated with fewer ventilator days, without change in mortality, potentially via reduced use of HFOV and ECMO. Future studies of iNO for PARDS should stratify based on oxygenation response, given the association with favorable outcomes.

Keywords

acute respiratory failure; inhaled nitric oxide; ARDS; hypoxia; PARDS

Introduction

Pediatric acute respiratory distress syndrome (PARDS) is a common illness requiring admission to the pediatric intensive care unit (PICU) and a significant contributor to PICU mortality[1-3]. Though always defined by hypoxemia and respiratory distress, the etiology, patient population affected, and natural history of the illness can be quite heterogeneous[4]. Due to this heterogeneity and lack of data to guide treatment, management of PARDS varies widely across institutions and between providers. An exemplar of this is the use of inhaled nitric oxide (iNO), a pulmonary vasodilator and modulator of endothelial function, to treat refractory PARDS. Despite multiple adult and pediatric studies showing no improvement in mortality with iNO therapy[5-10], this expensive therapy is used in up to 13% of PARDS cases[4] in an effort to improve hypoxemia. Additionally, a meta-analysis[10] of the available data only included 3 pediatric patients and a recent pediatric propensity matched study[11] was unable to match based on patient illness measures, leading to exclusion of many iNO-exposed patients from analysis. Therefore, it is difficult to extrapolate conclusions from either study to clinical practice. Furthermore, all studies have analyzed patients as a homogenous cohort despite the known heterogeneity of disease severity and course. There is also evidence of variability at the cellular level, as exemplified by angiotensin 2 (Ang2), a biomarker of endothelial dysfunction whose levels are variable across patients and highest in PARDS non-survivors[12]. In addition to physiologic and pathophysiologic heterogeneity in PARDS, therapeutic response to iNO varies across patients[1, 13-17]. Given this heterogeneity, it is plausible that some patient populations may benefit from iNO therapy while others may not[13]. An approach for determining which patients may benefit is to stratify patients by response to iNO, rather than simply exposure to iNO. This retrospective observational cohort study aimed to determine whether patients with PARDS who respond to iNO have decreased mortality and duration of mechanical ventilation, relative to non-responders. We hypothesized that patients who respond to iNO would have lower mortality and duration of mechanical ventilation. Additionally, given the variability of the endothelial biomarker Ang2 in PARDS and the putative effects of iNO on pulmonary vasculature, we

sought to determine whether Ang2 levels differed between iNO responders and non-responders, as an exploratory aim.

Materials and Methods

Study Design, Patient Selection, and Data Collection

This retrospective study was approved by the Children's Hospital of Philadelphia's (CHOP) Institutional Review Board, and the requirement for informed consent waived. The PARDS cohort evaluated in this study has been previously described in detail[18]. The cohort consists of prospectively enrolled intubated children aged 1 month to 17 years admitted to the CHOP PICU between July 1, 2011 and June 30, 2016 who met American-European Consensus Conference (AECC) criteria for acute lung injury[19]. The AECC definition was used because the study was initiated prior to the 2012 Berlin definition. However, as our institution does not utilize positive end-expiratory pressure (PEEP) less than 5 cmH₂O, all patients met Berlin criteria for of ARDS[20]. Similarly, as the study was initiated prior to the 2015 Pediatric Acute Lung Injury Consensus Conference (PALICC), we did not utilize the PALICC definition of PARDS; however, all patients met PALICC criteria[21].

Patients were included if exposed to iNO of any dose for at least 1 hour, within 3 days of PARDS onset, as the focus of this study was early PARDS. Absent a standard protocol in the CHOP PICU, iNO initiation is left to the discretion of the attending physician. In this cohort, iNO was universally initiated and maintained at 20 ppm for the 24 hours during which oxygenation data was collected. Duration of iNO therapy and weaning in both responders and non-responders was also left to the discretion of the treating physician. Our institution does not employ a standard practice for iNO initiation, duration, or weaning strategy, or for weaning of mechanical ventilation. However, iNO and mechanical ventilation are weaned independently of each other—i.e. patients do not remain intubated solely to allow iNO weaning and are frequently extubated to iNO delivery via non-invasive means once invasive mechanical ventilation is deemed no longer necessary by the attending physician.

Demographic information and clinical data were collected prospectively and compiled into a database, including PARDS etiology, comorbidities, ventilator settings, use of ancillary therapies (advanced ventilator modes, extracorporeal membrane oxygenation (ECMO), iNO duration, mortality, and duration of mechanical ventilation. The severity of illness score used was the Pediatric Risk of Mortality (PRISM) III at 12 hours. Charts were retrospectively reviewed for echocardiographic evidence of pulmonary hypertension (PHTN), defined by stated diagnosis in written report by designated pediatric cardiologist or estimated right ventricular pressure greater than half systemic mean arterial pressure. Plasma brain natriuretic peptide (BNP) levels were also recorded. Hospital charges were extracted from the CHOP billing database. Oxygenation index (OI), oxygenation-saturation index (OSI), and mean airway pressure (mP_{aw}) were abstracted retrospectively for the following timepoints: prior to iNO initiation and at 1 hour, 6 hours, 12 hours, and 24 hours following iNO initiation.

A subset of patients (n = 44) were prospectively enrolled in an ongoing cohort study of plasma Ang2 levels in PARDS[12]. Blood was collected within 24 hours of PARDS onset in

citrated tubes (Becton, Dickinson and Company; Franklin Lakes, NJ), centrifuged within 30 minutes of collection (2000 g, 20 minutes, 20C) to generate platelet-poor plasma, and stored at -80C. Ang2 was measured in duplicate using an enzyme-linked immunosorbent assay (ELISA; R & D Systems, Minneapolis, MN). Inter-assay coefficient of variation was 5.3%.

Definitions

The primary metric of oxygenation used was OI ($\text{mP}_{\text{aw}} \times \text{FiO}_2 \times 100/\text{PaO}_2$). A positive response to iNO was defined as 20% improvement in OI by 6 hours after iNO initiation. For patients in whom OI was not computable at initiation or at 6 hours—typically due to lack of an arterial line—OSI ($\text{mP}_{\text{aw}} \times \text{FiO}_2 \times 100/\text{SpO}_2$) [22] was used, ensuring that only SpO_2 values between 80% and 97% were utilized [23].

The designation “immunocompromised” required presence of an immunocompromising diagnosis (oncologic, immunologic, rheumatologic, or transplant) and active immunosuppressive chemotherapy, or a congenital immunodeficiency [24].

The primary outcomes were PICU mortality and duration of mechanical ventilation. All mention of “mechanical ventilation” in this study implies invasive ventilation, and non-invasive support was not counted toward total ventilator days. “Day 1” was initiation of invasive ventilation. Liberation from invasive ventilation for >24 hours defined duration of mechanical ventilation. Patients requiring re-initiation of invasive ventilation after 24 hours of extubation had the extra days counted towards total ventilator days.

Data Analysis

Data are expressed as percentages or median [interquartile range]. Categorical variables were analyzed by Fisher's exact test. Continuous variables were compared using Wilcoxon rank sum. Changes in OI, OSI, and mP_{aw} over time were tested using Kruskal-Wallis ANOVA with post-hoc comparisons, corrected for multiple testing. Analyses were conducted with Stata SE 14.2.

Multivariable logistic regression was performed to test for independent association between respiratory or oxygenation variables and mortality, after adjusting a priori for PRISM III, immunocompromised status, and OSI at iNO initiation. We have previously demonstrated that PRISM III and immunocompromised status are strongly associated with mortality in PARDS [25, 26]. OSI at iNO initiation was included to control for baseline PARDS severity, and for univariate association with mortality ($p = 0.039$). Additional potential confounders were also considered, such as organ failures, vasopressor score, and fluid balance. These confounders were co-linear with PRISM III and were not included. Additionally, no excluded variable improved model fit by likelihood ratio test. Model fit was assessed using Hosmer-Lemeshow statistics.

Competing risk regression was used to model the independent association of respiratory or oxygenation variables with duration of ventilation, using extubation as the primary outcome and death as the competing risk. Observations were censored at 28 days. Competing risk analysis using the Fine and Gray method [27] calculates a subdistribution hazard ratio (SHR) to estimate the risk of extubation, while accounting for the competing risk of death. The

competing risk models were similarly adjusted for PRISM III, immunocompromised status, and OSI at iNO initiation. The proportional hazard assumption was assessed by testing for interaction with a time-dependent covariate.

Results

161 patients met inclusion criteria and were categorized as either iNO responders (n = 98) or non-responders (n = 63). Based on the availability of arterial blood gases, OI was used to classify response in 135 children (84%), whereas OSI was used in 26 (16%) of children. Population characteristics, illness severity, and PARDS etiology were similar between iNO responders and non-responders (Table 1). Additionally, there was no difference in the incidence of pHTN markers in responders and non-responders, such as elevated brain natriuretic peptide (385 [138, 1664] vs. 209 [75, 1967] pg/mL, $p = 0.295$) and echocardiographic findings suggestive of pHTN (29% vs. 29%, $p = 0.999$). Furthermore, while cardiac evaluation was only available in a limited number of patients within our cohort, patients with documented evidence of pHTN were not more likely to show response to iNO than the overall cohort: 60% of patients with pHTN were responders and 60% of the entire cohort were responders.

Responders and nonresponders had similar durations of iNO therapy (4 [2, 7] vs. 5 [2, 10] days, $p = 0.150$). iNO response was associated with higher Ang2 levels (12.1 [5.3, 19.5] vs. 5.3 [4, 11.5] ng/mL, $p = 0.048$, Table 1, Supplemental Figure 1A), though levels of this biomarker were only available in 44 patients. Ang2 discriminated iNO response with an area under the receiver operating curve (AUROC) of 0.67 (95% CI 0.51 to 0.84, Supplemental Figure 1B).

At 6, 12, and 24 hours following iNO initiation, responders had significantly lower OI and OSI (Figure 1A, 1B). There was no difference in mP_{aw} between the two groups at any timepoint. However, iNO non-responders had higher mP_{aw} at 6 ($p = 0.006$) and 12 hours ($p = 0.045$) after iNO initiation relative to time 0 (Kruskal-Wallis ANOVA with post-hoc comparisons corrected for multiple testing), whereas mP_{aw} did not change at all over the first 24 hours in responders (Figure 1C).

iNO responders had significantly less exposure to high frequency oscillatory ventilation (HFOV) (26% vs. 41%, $p = 0.039$) and ECMO (5% vs. 17%, $p = 0.034$). There was no difference in mortality between groups (21% vs. 21%, $p = 0.999$) and response to iNO was not independently associated with PICU mortality in multivariable logistic regression (Table 2, Hosmer-Lemeshow χ^2 13.2, 8 df, $p = 0.110$). iNO responders had significantly lower hospital charges than non-responders (\$664,000 vs. \$1,088,000, $p = 0.002$).

Response to iNO was associated with significantly fewer ventilator days (10 [7, 20] vs. 16 [10, 39], $p < 0.001$). Competing risk regression analyses, accounting for competing risk of death, demonstrated that response to iNO was independently associated with earlier successful extubation (Table 3. SHR = 2.11, CI 1.41 to 3.17, $p < 0.001$) after adjusting for PRISM III, immunocompromised status, and OSI at iNO initiation (Figure 2). Inclusion of echocardiographic evidence of pHTN in the model revealed an independent association with

prolonged intubation (SHR = 0.57, 95% CI 0.35 to 0.93, $p = 0.025$). However, the association between response to iNO and earlier extubation was not substantially modified (SHR 2.46, 95% CI 1.54 to 3.93, $p < 0.001$).

Discussion

While there was no difference in mortality, iNO response—defined by 20% improvement in OI or OSI at 6 hours—was associated with earlier successful separation from ventilator. Responders to iNO also had less frequent use of HFOV and ECMO, which may explain the shorter duration of ventilation and lower associated hospital costs.

This study suggests there exists potential for a significant decrease in PARDS-associated morbidity with iNO therapy. Our mortality results agree with those of previous studies[4-10], though it has been argued that mortality in PARDS is usually secondary to non-pulmonary causes, making it unsurprising that improved oxygenation would have little effect on overall mortality[28]. However, previous studies did not evaluate for morbidity effects and selectively excluded certain populations of patients—such as those with immunocompromise, sepsis, and multisystem organ dysfunction—from analysis, which limits generalizability of the results to a significant portion of PICU patients[29, 30]. The largest study of iNO in PARDS to date propensity matched 521 PARDS patients who received iNO to those who did not, and found no improvement in mortality or ventilator free days[11]. However, limitations in the database prevented matching patients by severity of hypoxemia or assessing change in oxygenation with therapy. Furthermore, the study excluded patients who received iNO for less than 1 day, although the effects of iNO may be seen within minutes or hours[10, 31]. Also excluded were a subset of patients unable to be propensity matched, such that ultimately only 40% of enrolled patients documented as having received iNO were included in the final data analysis. Finally, statistical techniques can only match on available variables, and the possibility of unmeasured confounding affecting the results remains. For all these reasons, the study results are difficult to interpret or apply to clinical practice.

Our group's study adds data from a large PARDS cohort to the literature—the largest iNO exposed PARDS cohort with patient-level data—as well as a nuanced approach to evaluating the potential benefit of this salvage therapy in decreasing ventilator-associated morbidity. A previous attempt to separate adult ARDS patients by response to iNO in a randomized control trial only used improvement in PaO₂ to stratify patients, which can be confounded by changes in ventilator strategy[5]. Another randomized trial in adult ARDS noted differential iNO response between exposed patients, but evaluated outcomes based on the combined sample of responders and non-responders[10]. Additionally, the patients receiving iNO were exposed to different doses, as low as 1.25 ppm. The patients who received the lowest doses did not show an oxygenation response, but the outcomes of these patients were still pooled with those of the patients who received higher doses and did show oxygenation response. Another randomized trial of iNO in PARDS had a crossover design that made it difficult to evaluate survival and ventilation outcomes[16]. Finally, a pediatric randomized control trial by Bronicki et al had a small number of iNO exposed patients (24 patients), as compared to the 161 patients in the present study. Additionally, patients in the Bronicki trial

were not stratified by iNO response, possibly secondary to the limited sample size. Without an adequate randomized control trial available in the literature, our findings of decreased duration of ventilation in a large iNO-responsive PARDS cohort is a significant addition to the PARDS literature.

Our results also show that, in addition to decreased duration of mechanical ventilation, iNO responders were less exposed to other sources of PICU morbidity that are frequently employed in the setting of refractory PARDS, such as HFOV and ECMO. These results are in keeping with those of some previous studies, such as a publication by Kinsella et al[32] demonstrating decreased need for ECMO in these patients and the previously mentioned trial by Bronicki et al.[30], which found decreased ECMO usage, as well as increased ventilator free days for the iNO arm. Lower usage of HFOV may be an additional mechanism for the observed decrease in duration of mechanical ventilation, as HFOV is associated with increased ventilator days[33]. The impact of decreasing ventilator and ECMO exposures may extend past hospital discharge. A recent paper on adult veno-veno ECMO outcomes found decreased quality of life even 6 months after ECMO exposure[34]. In addition to sparing responders from potential long term effects of ECMO exposure, iNO itself may have lasting benefits. A 2012 study found that adult ARDS survivors who had been exposed to iNO had better pulmonary function test results 6 months after recovery than ARDS survivors without iNO exposure[35]. Furthermore, the data shows stratifying patients by response is cost effective, as iNO responders had lower hospital charges, potentially due to shorter ventilation, less HFOV, and less ECMO.

Within our cohort, demographic variables were not predictive of iNO response. However, plasma Ang2 levels within 24 hours of iNO initiation were significantly higher in the patients who demonstrated iNO response. Ang2 is a protein that destabilizes the endothelium[36], and has previously been shown to predict mortality in PARDS[12]. A possible mechanism for this finding is that more severe endothelial dysfunction, as indicated by elevated Ang2 levels, may lead to increased likelihood of sensitivity to the effects of iNO. Though our results need to be validated in a larger study, they suggest Ang2 is a potential predictor of iNO response and can possibly be used to stratify patients in future iNO trials. While Ang2 requires further study given the overlap between responders and non-responders in the present sample, it is an attractive candidate for risk stratification in future iNO trials as it demonstrates both prognostic (higher risk of mortality) and predictive (higher chance of iNO response) enrichment.

This study is limited by its retrospective design and variability in physician practice among our group with regards to timing of iNO initiation and duration of iNO usage. This variability is secondary to lack of a standard institutional practice for iNO usage during the study time period. Our finding of continued use of iNO in non-responders likely represents hesitation to discontinue therapies in patients with persistent hypoxia. This is an area in which quality improvement projects may be indicated. Our study is also limited by the extensive use of non-conventional ventilation, which precludes end-tidal CO₂ monitoring. Accordingly, we could not assess changes in alveolar dead space in response to iNO. A lack of serial echocardiography precludes longitudinal assessment of cardiac function after iNO initiation.

Future work in this cohort would include identification of predictors of iNO response, which could serve as basis for forming guidelines as to which patients are most likely to benefit from iNO therapy. However, it should be noted that neither demographic nor severity of illness variables predicted response to iNO in our cohort, and the finding that Ang2 discriminated iNO response is only preliminary. Continued enrollment will be necessary to power these additional analyses and potentially permit matching of responders and non-responders for further analysis. Enrollment and generalizability of results may be augmented by development of a multicenter registry. Additionally, it is difficult to compare or propensity match iNO exposed and unexposed PARDS patients due to considerable differences in the characteristics of those populations.

As this is a retrospective study, we are unable to ascribe causality to the observed association of iNO response and shorter duration of mechanical ventilation. Thus, a randomized control trial will be necessary to discriminate if iNO response is causative of the observed decrease in morbidity or simply prognosticates which patients are likely to be liberated from mechanical ventilation faster, irrespective of whether the improved oxygenation is responsible for the shortened duration of ventilation. The fact that patients with documented pHTN were not more likely to be responders suggests that response to iNO is not simply a marker of reversible pHTN. Future studies may also consider usage of inhaled eprostanil to evaluate if cost differences persist between treatment responders and non-responders when using this less expensive pulmonary vasodilator.

Conclusions

In conclusion, these data suggest that a trial of iNO should be considered in patients with PARDS, given the positive association between iNO response and decreased ventilator days and hospital charges, as well as less exposure to ECMO and HFOV. The data also suggest discontinuation of iNO therapy should be considered if there is no response and that there is room for improvement in development of iNO usage protocols. This therapy-response stratification approach is in keeping with the call for new ARDS treatment paradigms personalized to individual patient physiology[37]. Future studies on iNO and morbidity in PARDS should stratify patients based on oxygenation response to iNO, as it is associated with iNO response and poor outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support: This study is supported by National Institutes of Health grant K12HL109009.

Role of the Funder/Sponsor: The National Institutes of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data.

Dr. Neal J. Thomas reports personal fees from Therabron and CareFusion, and grants from the Federal Drug Association, all outside of the submitted work. CareFusion is a medical technology company that includes a series of mechanical ventilators (LTV, Avea).

References

1. Dobyns EL, A N, Fortenberry JD, et al. Interactive effects of high-frequency oscillatory ventilation and inhaled nitric oxide in acute hypoxemic respiratory failure in pediatrics. *Critical care medicine*. 2002; 30(11):2425–2429. [PubMed: 12441749]
2. Schouten LR, V F, Bos AP, et al. Incidence and Mortality of Acute Respiratory Distress Syndrome in Children: A Systematic Review and Meta-Analysis. *Critical care medicine*. 2016; 44(4):819–829. [PubMed: 26509320]
3. Cornfield D. Acute respiratory distress syndrome in children: physiology and management. *Current opinion in pediatrics*. 2013; 25(3):338–343. [PubMed: 23657244]
4. Munshi L, R G, Wunsch H. Adjuvants to mechanical ventilation for acute respiratory distress syndrome. *Intensive care medicine*. 2016; 42(5):775–778. [PubMed: 27022981]
5. Lundin S, M H, Smithies M, Stenqvist O, Frostell C. Inhalation of nitric oxide in acute lung injury: results of a European multicentre study. The European Study Group of Inhaled Nitric Oxide. *Intensive care medicine*. 1999; 25(9):911–919. [PubMed: 10501745]
6. Adhikari NK, B K, Friedrich JO, Granton JT, Cook DJ, Meade MO. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. *BMJ British medical journal (Clinical research ed)*. 2007; 334(7597):779–779.
7. Afshari ABJ, B J, Møller AM, Wetterslev J. Inhaled nitric oxide for acute respiratory distress syndrome and acute lung injury in adults and children: a systematic review with meta-analysis and trial sequential analysis. *Anesthesia and analgesia*. 2011; 112(6):1411–1421. [PubMed: 21372277]
8. Karam O, G F, Wetterslev J, Afshari A. The effect of inhaled nitric oxide in acute respiratory distress syndrome in children and adults: a Cochrane Systematic Review with trial sequential analysis. *Anaesthesia*. 2016; doi: 10.1111/anae.13628.
9. Gebistorf F, K O, Wetterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. *Cochrane database of systematic reviews*. 2016; (6):CD002787. [PubMed: 27347773]
10. Adhikari NK, D R, Lundin S, et al. Inhaled nitric oxide does not reduce mortality in patients with acute respiratory distress syndrome regardless of severity: systematic review and meta-analysis. *Critical care medicine*. 2014; 42(2):404–412. [PubMed: 24132038]
11. Gupta P, R T, Hall M, et al. Effect of Inhaled Nitric Oxide on Outcomes in Children With Acute Lung Injury: Propensity Matched Analysis From a Linked Database. *Critical care medicine*. 2016; 44(10):1901–1909. [PubMed: 27163193]
12. Yehya N, Thomas NJ, Meyer NJ, Christie JD, Berg RA, Margulies SS. Circulating markers of endothelial and alveolar epithelial dysfunction are associated with mortality in pediatric acute respiratory distress syndrome. *Intensive Care Med*. 2016; 42(7):1137–1145. [PubMed: 27101828]
13. Bohn D. Nitric oxide in acute hypoxic respiratory failure: from the bench to the bedside and back again. *The Journal of pediatrics*. 1999; 134(4):387–389. [PubMed: 10190909]
14. Timmons OD, D J, Vernon DD. Mortality rates and prognostic variables in children with adult respiratory distress syndrome. *The Journal of pediatrics*. 1991; 119(6):896–899. [PubMed: 1960603]
15. Gerlach H, K D, Semmerow A, et al. Dose-response characteristics during long-term inhalation of nitric oxide in patients with severe acute respiratory distress syndrome: a prospective, randomized, controlled study. *American journal of respiratory and critical care medicine*. 2003; 167(7):1008–1015. [PubMed: 12663340]
16. Dobyns EL, C D, Anas NG, et al. Multicenter randomized controlled trial of the effects of inhaled nitric oxide therapy on gas exchange in children with acute hypoxemic respiratory failure. *The Journal of pediatrics*. 1999; 134(4):406–412. [PubMed: 10190913]
17. Davis SL, F D, Costarino AT. Adult respiratory distress syndrome in children: associated disease, clinical course, and predictors of death. *The Journal of pediatrics*. 1993; 123(1):35–45. [PubMed: 8320623]
18. Yehya NSS, S S, Thomas NJ. Characterizing degree of lung injury in pediatric acute respiratory distress syndrome. *Critical care medicine*. 2015; 43(5):937–946. [PubMed: 25746744]

19. Hernu R, W F, Thiollere F, et al. An attempt to validate the modification of the American-European consensus definition of acute lung injury/acute respiratory distress syndrome by the Berlin definition in a university hospital. *Intensive Care Med.* 2013; 39(12):2161–2170. [PubMed: 24114319]
20. R V, Rubenfeld GD, et al. ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. *JAMA : the journal of the American Medical Association.* 2012; 307(23):2526–2533. [PubMed: 22797452]
21. Group PALICC. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med.* 2015; 16(5):428–439. [PubMed: 25647235]
22. Thomas NJ, Shaffer ML, Willson DF, Shih MC, Curley MA. Defining acute lung disease in children with the oxygenation saturation index. *Pediatr Crit Care Med.* 2010; 11(1):12–17. [PubMed: 19561556]
23. Khemani R, T N, Venkatachalam V, et al. Comparison of SpO₂ to PaO₂ based markers of lung disease severity for children with acute lung injury. *Crit Care Med.* 2012; 40(4):1309–1316. [PubMed: 22202709]
24. Yehya N, T A, Thomas N, Friess S. Improved oxygenation 24 hours after transition to airway pressure release ventilation or high-frequency oscillatory ventilation accurately discriminates survival in immunocompromised pediatric patients with acute respiratory distress syndrome*. *Pediatr Crit Care Med.* 2014; 15(4):e147–156. [PubMed: 24413319]
25. Yehya N, B A, Thomas N, Khemani R. Alveolar Dead Space Fraction Discriminates Mortality in Pediatric Acute Respiratory Distress Syndrome. *Pediatr Crit Care Med.* 2016; 17(2):101–109. [PubMed: 26669646]
26. Yehya N, S S, Thomas N, Nadkarni V, Srinivasan V. Corticosteroid exposure in pediatric acute respiratory distress syndrome. *Intensive Care Med.* 2015; 41(9):1658–1666. [PubMed: 26160728]
27. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American statistical association.* 1999; 94(446):496–509.
28. Yehya N, T N. Relevant Outcomes in Pediatric Acute Respiratory Distress Syndrome Studies. *Frontiers in pediatrics.* 2016; 4(4):51. [PubMed: 27242980]
29. Taylor RW, Z J, Dellinger RP, et al. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. *JAMA : the journal of the American Medical Association.* 2004; 291(13):1603–1609. [PubMed: 15069048]
30. Bronicki RAFJ, F J, Schreiber M, Checchia PA, Anas NG. Multicenter randomized controlled trial of inhaled nitric oxide for pediatric acute respiratory distress syndrome. *The Journal of pediatrics.* 2015; 166(2):365–369.e361. [PubMed: 25454942]
31. Abman SH, G J, Parker DK, Schmidt JM, Swanton D, Kinsella JP. Acute effects of inhaled nitric oxide in children with severe hypoxemic respiratory failure. *The Journal of pediatrics.* 1994; 124(6):881–888. [PubMed: 8201471]
32. Kinsella JP, A S. Inhaled nitric oxide therapy in children. *Paediatric respiratory reviews.* 2005; 6(3):190–198. [PubMed: 16153568]
33. Bateman S, B S, Asaro LA, et al. Early High-Frequency Oscillatory Ventilation in Pediatric Acute Respiratory Failure. A Propensity Score Analysis. *American journal of respiratory and critical care medicine.* 2016; 193(5):495–503. [PubMed: 26492410]
34. Fan EGL, G L, Combes A, et al. Venovenous extracorporeal membrane oxygenation for acute respiratory failure : A clinical review from an international group of experts. *Intensive care medicine.* 2016; 42(5):712–724. [PubMed: 27007108]
35. Dellinger RP, T S, Criner GJ, et al. Association between inhaled nitric oxide treatment and long-term pulmonary function in survivors of acute respiratory distress syndrome. *Critical care (London, England).* 2012; 16(2):R36.
36. Parikh SM, Mammoto T, Schultz A, Yuan HT, Christiani D, Karumanchi SA, Sukhatme VP. Excess circulating angiopoietin-2 may contribute to pulmonary vascular leak in sepsis in humans. *PLoS Med.* 2006; 3(3):e46. [PubMed: 16417407]
37. Beitler JR, G E, Schmidt M, et al. Personalized medicine for ARDS: the 2035 research agenda. *Intensive care medicine.* 2016; 42(5):756–767. [PubMed: 27040103]

Figure 1. Comparison of oxygenation index (1a), oxygen saturation index (1b), and mean airway pressure (1c) of responders (blue) and non-responders (red) in the first 24 hours after inhaled nitric oxide (iNO) initiation

Figure 2.

Cumulative incidence function (CIF) for successful extubation in immunocompetent (2a) and immunocompromised (2b) responders (blue lines) and non-responders (red lines) after adjustment for PRISM III and OSI at iNO initiation, accounting for the competing risk of death (SHR = 2.11, 1.41 to 3.17, $p < 0.001$)

Table 1
Characteristics of the PARDS cohort exposed to iNO

Patient Characteristics	All patients (n = 161)	Responders (n = 98)	Non-responders (n = 63)	p value
Age (years)	3.9 [1.3, 9.1]	4.1 [1.2, 10.5]	3 [1.3, 8.2]	0.762
Male/female (%/%)	87/74 (54/46)	54/44 (55/45)	33/30 (53/47)	0.749
PRISM III at 12 hours	11 [4, 20]	12 [5, 20]	11 [3, 19]	0.492
Cause of PARDS (%)				
Infectious pneumonia	100 (62)	58 (59)	42 (67)	0.891
Aspiration pneumonia	16 (10)	10 (10)	6 (10)	
Non-pulmonary sepsis	29 (18)	19 (19)	10 (16)	
Trauma	5 (3)	3 (3)	2 (3)	
Other	11 (7)	8 (8)	3 (5)	
Co-morbidities				
Prematurity	25 (16)	14 (14)	11 (17)	0.658
Immunocompromised	36 (22)	23 (23)	13 (21)	0.703
Stem cell transplant	18 (11)	11 (11)	7 (11)	0.999
At initiation of iNO				
OI (n = 135)	25.8 [18.5, 38.5]	27.4 [18.4, 44.3]	24.4 [18.7, 29.9]	0.128
OSI (n = 161)	18.7 [13.7, 25.9]	20.5 [14, 26.6]	17.3 [12.9, 23.6]	0.058
mPaw	20 [17, 24]	20 [17, 25]	19 [16, 23]	0.143
BNP (pg/mL, n = 122)	336 [116, 1708]	385 [138, 1664]	209 [75, 1967]	0.295
Pulmonary hypertension on TTE (% , n = 128)	37 (29)	22 (29)	15 (29)	0.999
Angiotensin 2 (ng/mL, n = 44)	7.2 [4.6, 18.2]	12.1 [5.3, 19.5]	5.3 [4, 11.5]	0.048
Duration of iNO therapy (days)	4 [2, 8]	4 [2, 7]	5 [2, 10]	0.150
Alternative ventilator modes				
APRV	13 (8)	9 (9)	4 (6)	0.571
HFOV	51 (32)	25 (26)	26 (41)	0.039
HFPV	38 (24)	25 (26)	13 (21)	0.570
Hospital charges (\$1000 US dollars)	772 [490, 1565]	664 [416, 1277]	1088 [670, 2165]	0.002
Outcomes				
ECMO	17 (11)	6 (6)	11 (17)	0.034
Ventilator days (all)	13 [8, 23.5]	10 [7, 20]	16 [10, 39]	< 0.001
Ventilator days (survivors)	14 [9, 25]	11 [8, 20]	17.5 [13, 44]	< 0.001
PICU/hospital deaths (%)	34 (21)	21 (21)	13 (21)	0.999

Table 2
Logistic regression testing the association between response to iNO at 6 hours and PICU mortality

Variable	Odds ratio	95% CI	p value
PRISM III at 12 hours	1.07	1.03 to 1.11	0.001
Immunocompromised (yes)	9.94	3.93 to 25.11	< 0.001
OSI at iNO initiation	1.03	0.99 to 1.08	0.243
Response to iNO at 6 hours (yes)	0.82	0.32 to 2.08	0.675

Table 3
Competing risk regression testing the association between response to iNO at 6 hours and successful extubation by 28 days (SHR > 1 means faster extubation)

Variable	Sub-distributional hazard ratio	95% CI	p value
PRISM III at 12 hours	0.99	0.97 to 1.01	0.266
Immunocompromised (yes)	0.35	0.20 to 0.61	< 0.001
OSI at iNO initiation	0.98	0.96 to 1.00	0.057
Response to iNO at 6 hours (yes)	2.11	1.41 to 3.17	< 0.001