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Rowan, Courtney M.; Randolph, Adrienne G.; Iyer, Narayan Prabhu; Korang, Steven Kwasi; Kneyber, Martin C.J.

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Pulmonary Specific Ancillary Treatment for Pediatric Acute Respiratory Distress Syndrome: From the Second Pediatric Acute Lung Injury Consensus Conference

Courtney M. Rowan, MD, MScr[1]

Adrienne G. Randolph, MD, MS[2,3]

Narayan Prabhu Iyer, MBBS, MD[4]

Steven Kwasi Korang, MD, PhD[5,6]

Martin C. J. Kneyber, MD, PhD, FCCM[7,8]

on behalf of the Second Pediatric Acute Lung Injury Consensus Conference (PALICC-2) of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network

OBJECTIVES: We conducted an updated review of the literature on pulmonary-specific ancillary therapies for pediatric acute respiratory distress syndrome (PARDS) to provide an update to the Pediatric Acute Lung Injury Consensus Conference recommendations and statements about clinical practice and research.

DATA SOURCES: MEDLINE (Ovid), Embase (Elsevier), and CINAHL Complete (EBSCOhost).

STUDY SELECTION: Searches were limited to children, PARDS or hypoxic respiratory failure and overlap with pulmonary-specific ancillary therapies

DATA EXTRACTION: Title/abstract review, full-text review, and data extraction using a standardized data collection form.

DATA SYNTHESIS: The Grading of Recommendations Assessment, Development, and Evaluation approach was used to identify and summarize evidence and develop recommendations. Twenty-six studies were identified for full-text extraction. Four clinical recommendations were generated, related to use of inhaled nitric oxide, surfactant, prone positioning, and corticosteroids. Two good practice statements were generated on the use of routine endotracheal suctioning and installation of isotonic saline prior to endotracheal suctioning. Three research statements were generated related to: the use of open versus closed suctioning, specific methods of airway clearance, and various other ancillary therapies.

CONCLUSIONS: The evidence to support or refute any of the specific ancillary therapies in children with PARDS remains low. Further investigation, including a focus on specific subpopulations, is needed to better understand the role, if any, of these various ancillary therapies in PARDS.

KEY WORDS: acute respiratory distress syndrome; corticosteroids; inhaled nitric oxide; pediatrics; prone positioning; surfactant

The spectrum of pediatric acute respiratory distress syndrome (PARDS) is heterogeneous. Differences in etiologies and in patient age and underlying comorbidities can influence its development and severity (1). Because there are minimal data to guide practice in PARDS, therapeutic strategies have been based on pathophysiology or extrapolated from adult or neonatal literature (2–8). The heterogeneity of PARDS can make therapies based on pathophysiology challenging to investigate. How to best incorporate the adult acute respiratory distress syndrome (ARDS) evidence into pediatric practice is unclear. Therapies, such as prone positioning and corticosteroids, commonly employed in adults with evidence of survival benefit (2, 9), must still be evaluated to determine their effect in PARDS (10–13). Despite these limitations, many

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pulmonary-specific ancillary therapies are used in children with PARDS.

Application of therapies for PARDS appear to be highly variable without a discernable pattern of use. A large, international PARDS Incidence and Epidemiology (PARDIE) observational cohort study evaluated the original Pediatric Acute Lung Injury Consensus Conference (PALICC) definitions and recommendations (14). A planned secondary analysis of PARDIE sought to describe the practice patterns of ancillary therapies (15). There was significant variability in oxygenation thresholds and timing at which each therapy was initiated and the combinations of various therapies used simultaneously. This variability was associated with comorbidities and global region, which highlights issues of the heterogeneity of PARDS and international health equity for PARDS ancillary therapies.

In this article, we address key question number 4 as outlined in the accompanying Methods article (16). What is the effectiveness and comparative effectiveness of pulmonary-specific ancillary treatments in children with PARDS? Below, we will provide an overview of the literature related to pulmonary-specific ancillary therapies for PARDS. Expert consensus recommendations made in the original PALICC recommendations (17) are updated using the findings of this systematic review that includes grading of evidence bias. Further, we will provide updated recommendations for clinical practice and future research.

METHODS

The details of the literature search are outlined in the PALICC-2 Methodology article in this supplement (16). A systematic review was conducted to identify relevant studies related to pulmonary-specific ancillary therapies in PARDS, that is, nonventilator therapies used explicitly for lung treatment. These specifically included studies related to the benefit of the following therapies: inhaled nitric oxide (iNO), surfactant, prone positioning, endotracheal suctioning, airway clearance, corticosteroids, and various other less common ancillary therapies. Adult data were excluded. The complete search strategies can be found in **Supplemental Table S1** (http://links.lww.com/PCC/C298). Details of title/abstract review, full-text review, and data extraction, and generation of clinical practice recommendations, research statements, and policy statements are outlined in the PALICC-2 Methodology article (16).

RESULTS

Of 9,934 abstracts screened, 167 underwent full-text screening and 26 articles were included (**Supplemental Fig. S1**, http://links.lww.com/PCC/C298). Complete evidence-to-decision (EtD) framework tables supporting the recommendations are also provided in the supplement and referenced below.

Inhaled Nitric Oxide

> **Recommendation 4.1.** We suggest against the routine use of iNO in PARDS as compared to selective use of iNO in PARDS.
> (Conditional Recommendation, low certainty of evidence, 98% agreement).
> Remarks: There may be clinical benefit in the use of iNO in some phenotypes such as patients with documented pulmonary hypertension or severe right ventricular dysfunction. In addition, the use of iNO may be considered in patients with severe PARDS as a rescue from, or bridge to, extracorporeal life support. When used, assessment of benefit should be undertaken within the first 4 hours and serially to minimize toxicity and to eliminate continued use in the absence of established effect.

Justification. iNO is used as an ancillary therapy in PARDS due to its pulmonary vasodilatory effects to improve ventilation/perfusion matching. Our systematic review explored the comparative effectiveness of iNO in patients with PARDS (See EtD in **Supplemental Table S2**, http://links.lww.com/PCC/C298).

Three pediatric randomized clinical trials (RCTs) informed the original PALICC recommendation (13, 18, 19). These three RCTs all demonstrated improved oxygenation with the use of iNO; however, there was no effect on mortality. A meta-analysis combining adult ARDS and PARDS data found similar results; improvement in oxygenation but no effect on mortality (20). However, this meta-analysis also found a concern for an increase in renal impairment with iNO use (risk ratio, 1.59; 95% CI, 1.2–2.2). More recently, there has been one additional pediatric RCT and two observational studies (**Table 1**). Bronicki et al (21) enrolled 55 children, randomizing subjects to either iNO or placebo. Improvement in oxygenation was noted at 12 hours after starting iNO therapy, but this

TABLE 1.

Summary of New Data for Inhaled Nitric Oxide Treatment for Pediatric Acute Respiratory Distress Syndrome, Since First Pediatric Acute Lung Injury Consensus Conference

Lead Author, Year, Sample Size	Study Design	Findings
Bronicki et al (21), 2015, $n = 55$	Randomized controlled trial: iNO vs placebo	Improved oxygenation at 12 hr (mean ± SD oxygenation index: 15±6 vs 25±22; $p = 0.03$), but not sustained at 24 hr More median VFD (15 vs 9 d; $p = 0.05$) Higher rates of extracorporeal membrane oxygenation-free survival (92% vs 52%; $p < 0.01$) No difference in overall survival (92% vs 72%; $p = 0.07$)
Gupta et al (22), 2016, $n = 1,042$	Observational database, propensity 1:1 matched analysis: iNO to controls	Less median VFD (10 vs 14 d; $p < 0.00001$) Higher median hospital costs ($150,569 vs $102,823; $p < 0.00001$) No difference in mortality (22% vs 20%; $p = 0.40$)
Bhalla et al (23), 2018, $n = 499$	Observational study, matched iNO to controls	No difference in mortality (OR, 1.3; 95% CI, 0.56–4.0; $p = 0.54$)[a] No difference in VFD (OR for 0 VFD = 1.7 [95% CI, 0.77–3.9; $p = 0.19$])[a]

iNO = inhaled nitric oxide, OR = odds ratio, VFDs = ventilator-free days.
[a]Matched analysis results presented.

was not sustained at 24 hours. While there was no difference in mortality, the iNO group had more ventilator-free days (VFDs) at 28 days and were less likely to receive cardiopulmonary support with extracorporeal membrane oxygenation (ECMO). In 2016, Gupta et al (22) published a study linking the Virtual Pediatric Systems (LLC) database and the Pediatric Health Information System of 521 patients who received iNO matched to 521 controls. There was no difference in mortality. However, the iNO group had less VFDs and higher hospital costs. In another observational study of 499 children, Bhalla et al (23) found no difference in mortality or VFD. We pooled current RCT data with previous RCTs to perform a meta-analysis. The meta-analysis revealed no statistical difference for all-cause mortality (**Fig. 1*A***), VFD (**Fig. 1*B***), ECMO use (**Fig. 1*C***), or duration of ventilation (**Supplemental Fig. S2**, http://links.lww.com/PCC/C298).

Benefits. Overall, iNO may improve oxygenation, however, the effect may not be sustained. Perhaps there is a benefit as a rescue from ECMO, however, it does not seem to improve mortality or duration of ventilation.

Harms and Burdens. There is concern for renal impairment and cost considerations for iNO. Methemoglobinemia is a rare complication, and the monitoring of methemoglobin levels is frequently considered. Not all countries or hospitals have access to iNO.

The certainty of the evidence is low with the small pediatric RCTs and the predominance of observational data. In conclusion, we cannot recommend the routine use of iNO. However, consistent with the European Society for Pediatric and Neonatal Intensive Care consensus statement, iNO can be considered in patients with known pulmonary hypertension or right ventricular dysfunction (24). It may also be considered as a rescue from or bridge to ECMO in severe PARDS cases. With the cost of the therapy and potential harm of kidney injury, it is important that assessment of iNO benefit be instituted within the first few hours to reduce unnecessary exposure and limit costs. Future investigations should focus on determining which subphenotypes may be most responsive to iNO and if iNO improves clinically relevant outcomes in severe PARDS. It is also important that future studies balance positive effects with the potential harm of renal impairment.

Surfactant

Recommendation 4.2. We suggest against the routine use of surfactant therapy in PARDS as compared to selective use of surfactant.

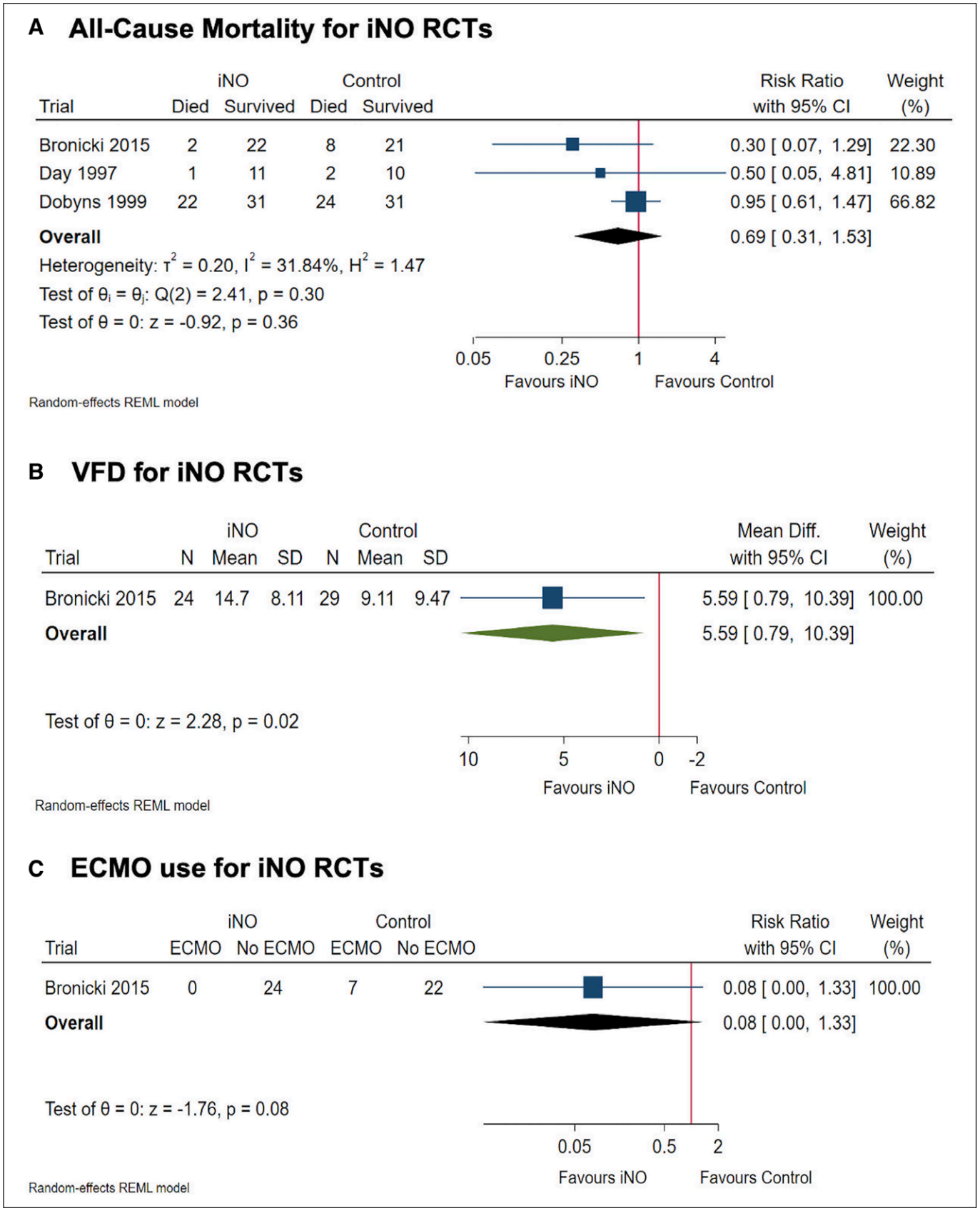

Figure 1. Results of metanalyses of randomized control trials for outcomes of inhaled nitric oxide (iNO) use in pediatric acute respiratory distress syndrome. *Forest plots comparing* iNO and placebo for the outcomes of all-cause mortality (**A**), ventilator-free days (VFDs) (**B**), and use of extracorporeal membrane oxygenation (ECMO) (**C**). Three studies were included (13, 18, 21). RCT = randomized clinical trial, REML = restricted maximum likelihood.

(Conditional Recommendation, low certainty of evidence, 100% agreement).

Remarks: There may be a role for selective use of surfactant in specific populations, however there is insufficient evidence to guide which populations may benefit.

Justification. Historically, there was significant interest in surfactant replacement therapy in PARDS due to the success in the neonatal population. This systematic review explored the comparative effectiveness of surfactant in children with PARDS (**see Supplemental Table S3**, http://links.lww.com/PCC/C298, for the EtD table).

Several well-done pediatric RCTs were conducted on the use of various types of surfactant in PARDS (25–32) and were described in detail in the original PALICC recommendations (17). In summary, almost all of these trials report an improvement in oxygenation but no effect on mortality. Some smaller trials found that surfactant was associated with a shorter duration of ventilation (26–28), but that finding was not confirmed in three larger RCTs. The first large RCT of surfactant found no difference in VFD or mortality (29), the second large follow-up RCT was stopped early for futility (31), and the third international study found no improvement in mortality or duration of ventilation (32). Since PALICC 2015, a few additional studies have been published. In 2018, Thomas et al (33) published a double-blind, placebo-controlled, RCT in children with leukemia or post-hematopoietic cell transplantation (HCT). This study was terminated early for low enrollment. There were more deaths in the surfactant group, but it was not significantly different. However, there was an excess of children post-HCT (who are noted to have a very high PICU mortality) in the group that received surfactant. In 2017, Rodriguez-Moya et al (34, 35) published two prospective RCTs. In both trials, the surfactant group had improved oxygenation and improved survival. While the results of these two studies may seem promising, the generalizability of these results should be considered with caution. The mortality in the control group is substantially higher than what is typically reported in PARDS (14). Further, there was a noted high risk of bias, with authors of these two studies reporting a financial relationship with the surfactant company.

Benefits. On compiling these data into a meta-analysis, there was no difference in mortality (**Fig. 2*A***), VFD (**Fig. 2*B***), or duration of ventilation (**Supplemental Fig. S3**, http://links.lww.com/PCC/C298) with surfactant use compared with usual care. We excluded two studies (34, 35) from this meta-analysis, due to potential for bias (vested interests) and because these two studies had markedly higher mortality compared with most studies reported in the literature. The results of a secondary meta-analysis, without exclusion of the two biased studies, are available in the supplement (**Supplemental Fig. S4**, http://links.lww.com/PCC/C298).

Harms and Burdens. The risks with surfactant administration are not negligible. Our meta-analysis also examined adverse events reported in RCTs (**Supplemental Fig. S5**, http://links.lww.com/PCC/C298). For the surfactant group, there was a higher risk of hypotension (**Supplemental Fig. S6**, http://links.lww.com/PCC/C298), hypoxia (**Supplemental Fig. S7**, http://links.lww.com/PCC/C298), and bradycardia (**Supplemental Fig. S8**, http://links.lww.com/PCC/C298), and similar risk of pneumothorax (**Supplemental Fig. S9**, http://links.lww.com/PCC/C298).

Balance of Effects. With numerous studies and well-conducted, large, multicenter trials demonstrating no significant benefit on clinical outcomes, combined with the consideration for potential harm, we cannot recommend routine use of surfactant administration for PARDS. The certainty of evidence effect was judged as low.

Other Considerations. Numerous studies have demonstrated improved oxygenation with surfactant use, which may entice investigators to consider further study. There must be a focus on specific populations that may benefit, the type of surfactant, and considerations of optimal delivery to minimize adverse events.

Prone Positioning

Recommendation 4.3. There are insufficient definitive data to support or refute the use of prone positioning in patients with PARDS.

(Conditional recommendation, low certainty of evidence, 94% agreement).

Remarks: The use of prone positioning may be considered in patients with PARDS and hypoxemia not responding to other interventions. If used, improvement in oxygenation while in the prone position should be assessed.

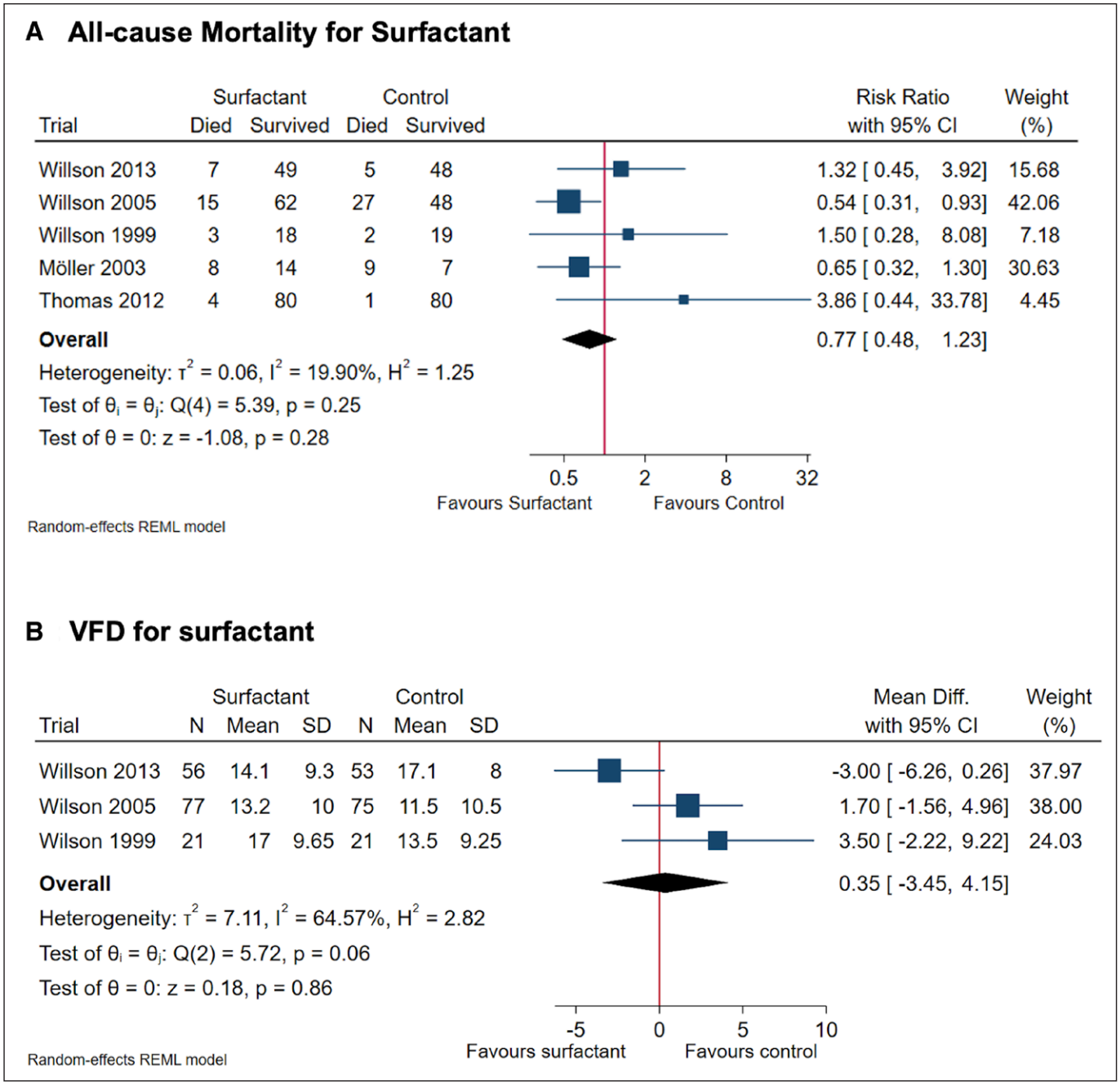

Figure 2. Results of metanalyses of randomized control trials for outcomes of surfactant use in pediatric acute respiratory distress syndrome. *Forest plots comparing* inhaled surfactant and placebo for the outcomes of all-cause mortality (**A**) and ventilator-free days (VFDs) (**B**). Five studies were included (25, 29–32). REML = restricted maximum likelihood.

We cannot make recommendations on the duration of prone positioning.

Justification. Prone positioning is employed in adults with ARDS because data demonstrate improvement in survival (2). Such data are lacking in pediatric practice. This systematic review explored the comparative effectiveness of prone positioning in children with PARDS.

Summary of Evidence. Numerous pediatric reports and trials have found that prone positioning can be done safely with improved oxygenation (11, 12, 36–40). These studies led to a RCT of 102 children randomized to supine or prone positioning within 48 hours of developing acute lung injury (12). While 90% of patients randomized to the prone position had improvement in oxygenation, the study was stopped early due to futility. There was no difference in the primary outcome of VFD or any of the secondary outcomes including mortality. Two meta-analyses, combining adult and pediatric data, suggest that prone positioning might be best for those with severe

hypoxemic respiratory failure (i.e., ratio of Pao_2/Fio_2 < 150 mm Hg) in whom low tidal volume was also used (41, 42). One of these found that prone positioning improved mortality but only for patients who had a Pao_2/Fio_2 less than 100 mm Hg (risk ratio, 0.84; 95% CI, 0.74–0.96; $p = 0.01$; seven trials, $n = 555$) (42). A large RCT in adults with severe ARDS (Pao_2/Fio_2 < 150 mm Hg) had a similar finding, demonstrating a 50% reduction in mortality at 28 days (2). A recently published meta-analysis of six pediatric trials (one trial of bronchiolitis that was not included in this recommendation, five trials published before the 2015 PALICC recommendations) found that there was not enough evidence to make a recommendation about prone positioning (43). Overall, no new studies were identified for inclusion that were published since the original PALICC recommendations on prone positioning.

Prone positioning seems to be rarely employed in PARDS. In the aforementioned secondary analysis of the PARDIE data, only 10% of patients were placed in the prone position (15). There were significant regional and geo-economic differences associated with prone use. Prone positioning was rarely used in North America ($p < 0.001$) and more often used in middle-income countries ($p < 0.001$), smaller PICUs ($p < 0.001$) and PICUs without an ECMO program ($p < 0.001$). When it was used, there was a high variability in the length of time spent in the prone position.

Benefits. Overall, there appears to be consistent evidence demonstrating oxygenation improvement in children with PARDS who are placed in the prone position.

Harms or Burdens. While there may be concern for harm with prone positioning including loss of central lines, endotracheal tube dislodgement, and pressure injuries, in general, the literature supporting its safe use is robust (11, 38, 44).

Balance of Effects. With the lack of data demonstrating improved clinical outcomes in PARDS, we cannot support or refute the routine use of prone positioning in PARDS.

The "certainty of evidence" was considered low (**Supplemental Table S4**, http://links.lww.com/PCC/C298).

Implementation Considerations. Prone positioning, unlike some other ancillary supportive therapies, may be easier to implement across different geo-economic health settings, resulting in increased global health equity. Aside from the presence of experienced staff, it is an inexpensive therapy that requires no special equipment.

Conclusions. The strong data supporting use of prone positioning in adults with ARDS, and the consistent improvement in oxygenation in PARDS, demands further investigation in children. Future studies should focus on severe PARDS, with attention to time in the prone position. Additionally, with the different physiologic respiratory mechanics seen across age groups, a focus on impact on various age strata may be important. The ongoing PRone and OScillation Pediatric Clinical Trial (NCT03896763) is recruiting worldwide and may provide definitive answers for patients 2 weeks to 20 years old. In a 2 × 2 factorial design, it is investigating prone positioning combined with either conventional or high frequency oscillatory mechanical ventilation in children with moderate-to-severe PARDS.

Endotracheal Suctioning

Good practice statement 4.4.1. In intubated patients with PARDS, an unobstructed airway should be maintained.

(Ungraded good practice statement, 98% agreement).

Remark: Endotracheal suctioning must be performed with caution to minimize the risk of de-recruitment.

Research statement 4.4.2. We cannot make a recommendation on the use of a closed versus an open suctioning system. Future research should focus on the impact of closed and open suctioning systems on outcomes.

(Ungraded research statement, 90% agreement).

Remarks: In severe PARDS, consideration should be given to the technique of suctioning with careful attention to minimize the potential for de-recruitment.

Good practice statement 4.4.3. The routine instillation of isotonic saline prior to endotracheal suctioning should not be used in patients with PARDS.

(Ungraded good practice statement, 94% agreement).

Remarks: The instillation of isotonic saline prior to endotracheal suctioning may be considered for lavage to remove thick tenacious secretions.

Endotracheal tube suctioning has clear benefits. It is necessary to maintain a clear airway for adequate oxygenation and ventilation. While it is frequently used in the PICU, there is little evidence to support the exact method or frequency of suctioning. Observational studies have demonstrated loss of lung volume with endotracheal suctioning (45), and this was particularly noticeable with open endotracheal suction (46–48). Loss of lung recruitment must be considered, particularly in PARDS where lung compliance is poor. Isotonic saline has been used to clear secretions from the endotracheal tube; however, there are considerations for harm. In intubated children, not specifically with PARDS, McKinley et al (49) randomized 427 to one of three endotracheal suctioning treatment groups: no saline, 0.2% saline, and 0.9% saline instillation. No saline use was just as effective as either saline instillation. Again, not specific to PARDS, an integrative review of three pediatric studies found that endotracheal suction led to a transient decrease in oxygen saturation (50). The American Association of Respiratory Care (AARC) published clinical guidelines for caring for intubated children (51). The AARC recommended as-needed suctioning only, using breath sounds, secretion visualization, and a sawtooth pattern on ventilator waveforms as indicators for the need for suctioning. The organization also recommended that normal saline should generally be avoided with suctioning. With the current paucity of data in children with PARDS, we cannot recommend the routine use of an open versus closed system or the instillation of isotonic saline with suction. We do recognize that intermittent suctioning, particularly in the clear presence of secretions will be needed to maintain a clear airway and that thick, tenacious secretions may require isotonic saline lavage for clearance. Lung volume loss must be considered when suctioning, particularly if using open suctioning. Further investigation regarding routine endotracheal suctioning and optimal techniques may benefit the care of the PARDS patient.

Airway Clearance

Research statement 4.5. We cannot make a recommendation on the use of specific methods of airway clearance (such as chest physiotherapy and mucolytics) in patients with PARDS. Future research should focus on the impact of specific airway clearance methods on outcomes, and on specific populations likely to benefit from these methods.
(Ungraded research statement, 96% agreement).

Various mechanical methods, such as manual chest physiotherapy, percussive vest therapy, or intrapulmonary percussive therapy are sometimes used for airway clearance. These mechanical therapies are often combined with pharmacologic therapies such as beta-agonists and mucolytics (52). There is no evidence to support or refute these therapies in PARDS. There are also potential negative effects, such as the side effect profile of the various medications used and the associated financial costs. Despite the lack of evidence of benefit and the potential harm, these therapies are often applied. In the PARDIE cohort, over 50% of the children received bronchodilators in the first 72 hours of PARDS (15). Further investigation is needed to better understand the role airway clearance strategies may have in the care of children with PARDS.

Corticosteroids

Recommendation 4.6. We suggest against the routine use of corticosteroids in patients with PARDS as compared to selective use of steroids.
(Conditional Recommendation, low certainty of evidence, 96% agreement).
Remarks: There may be some benefit in patients with PARDS caused by SARS-CoV-2, however we cannot make recommendations regarding other specific populations for use.

Justification. Corticosteroids have been proposed as treatment for adults with ARDS to combat the known inflammatory process that occurs in the lungs. While there is evidence that glucocorticoid administration in children with PARDS results in decreased inflammatory markers (53), there is little evidence that it improves outcomes. This systematic review explored the comparative effectiveness of corticosteroids in children with PARDS.

Summary of Evidence. Since the original 2015 PALICC recommendations (17), a few additional studies have been published (**Table 2**). In 2015, Yehya et al (54) published an observational study of 283 children

TABLE 2.

Summary of New Data for Corticosteroids for Treatment of Pediatric Acute Respiratory Distress Syndrome, Since First Pediatric Acute Lung Injury Consensus Conference

Lead Author, Year, and Sample Size	Study Design	Findings
Yehya et al (54), 2015, $n = 283$	Observational study, steroids for > 24 hr ($n = 169$) vs others	Less ventilator-free days (coefficient: −0.12 [95% CI, −0.18 to −0.07; $p < 0.001$)[a] Longer ventilation duration in survivors (log coefficient, 0.02; 95% CI, 0.01–0.03; $p < 0.001$)[a] No difference in mortality (OR, 1.02; 95% CI, 1.00–1.04; $p = 0.101$)[a]
Drago et al (55), 2015, $n = 35$	Randomized controlled trial; methylprednisolone (2 mg/kg loading followed by 1 mg/kg/d × 7 d) vs placebo	Less likely to need supplemental O_2 at PICU transfer (76% vs 100%; $p = 0.01$) No difference in mean (± SD) duration of ventilation (9.7 ± 6.6 vs 9.6 ± 5.2 d; $p = 0.94$) No difference in mean (± SD) PICU length of stay (13.5 ± 6.6 vs 15.2 ± 8.3 d; $p = 0.51$) No difference in hospital survival (100% vs 88%; $p = 0.15$)
Mitting et al (56), 2019, $n = 78$	Observational study of children with pediatric acute respiratory distress syndrome receiving IV methylprednisolone	Steroid "responders" had improved survival (74% vs 41%; OR, 4.14 [1.57–10.87]; $p = 0.004$)

OR = odds ratio.

[a]Propensity adjusted analysis presented.

with PARDS, 60% of whom received corticosteroids (predominantly hydrocortisone and methylprednisolone) for over 24 hours. On multivariable and propensity score-adjusted analysis, exposure to corticosteroids was associated with fewer VFD at 28 days (odd ratio, –2.98 d [95% CI, –5.09 to –0.88 d]; $p = 0.009$) and longer duration of mechanical ventilation in survivors ($p = 0.011$). While on univariable analysis, those with steroid exposure had a higher mortality (17% vs 8%, $p = 0.03$), this difference was no longer significant on adjusted analysis. In 2015, Drago et al (55) published a small double-blind RCT of 35 children who were randomized to either methylprednisolone ($n = 17$) or placebo ($n = 18$). In this small study, there was no difference in duration of ventilation, length of stay, or mortality. However, those that received steroids were less likely to require supplemental oxygen at transfer out of the PICU. Finally, another observational study also suggests that children with PARDS who have an improvement in oxygenation following steroid administration have greater odds of survival (74% vs 41%; OR, 4.14; 95% CI, 1.57–10.87; $p = 0.004$) (56).

While the data for PARDS is lacking, data has emerged supporting the use of early dexamethasone in adults with ARDS. Villar et al (9) published a multicenter RCT of 277 adults with moderate-to-severe ARDS randomized to either IV dexamethasone (20 mg daily from days 1 to 5 and then 10 mg daily from days 6 to 10) or to placebo. The dexamethasone group had 4.8 more VFDs ($p < 0.0001$) and a lower mortality (21% vs 36%; $p = 0.0047$). In this study, there was no increase in the occurrence of hyperglycemia or new infections.

Balance of Effects. Overall, there is not enough data in PARDS to support the routine use of corticosteroids, and the "certainty of evidence" was considered low (**Supplemental Table S5**, http://links.lww.com/PCC/C298, EtD corticosteroids).

Other Considerations. Recent adult ARDS data and emerging data from patients with COVID-19 (57–59) suggest there may be a role in certain populations. However, many questions remain, including type of steroid, dosage, timing of initiation, and duration of therapy. Future investigation must focus on answering these questions. Additionally, any benefit of corticosteroid use must be carefully balanced with any risk, in particular, the risk of immunosuppression and new infections.

Other Ancillary Therapies

> **Research statement 4.7.** We cannot make a recommendation on the use of the following ancillary treatment in patients with PARDS: helium-oxygen mixture, inhaled or IV prostaglandins therapy, plasminogen activators, fibrinolytics or other anticoagulants, inhaled β-adrenergic receptor agonists or ipratropium, or IV N-acetylcysteine for antioxidant effects. Future research should focus on the impact of these treatments and on specific populations likely to benefit from them.
> (Ungraded research statement, 96% agreement).

Therapies such as helium-oxygen mixture, inhaled or IV prostaglandins therapy, plasminogen activators, fibrinolytics or other anticoagulants, inhaled β-adrenergic receptor agonists or ipratropium, or IV N-acetylcysteine for antioxidant effects have, in general, not been well-studied in PARDS.

In children with acute lung injury, one observational study and a small RCT have investigated the use of inhaled prostaglandin (60, 61). Improvement in oxygenation was noted but no other patient outcomes have been studied. More recently, there was a small RCT of 66 children with PARDS randomized to oral Ambroxol (40 mg/kg/d divided into four doses) or placebo for 10 days (62). As a mucolytic with anti-inflammatory properties, Ambroxol is an attractive therapeutic option, in particular, because of its low cost. In this small RCT, Ambroxol appeared safe, but there was no difference in VFD or mortality between groups. Experimental therapies have been investigated in groups that are high risk for PARDS, such as children post-allogeneic HCT. Etanercept, a soluble tumor necrosis factor alpha binding protein, has been studied in this population and found to improve outcomes in idiopathic pneumonia syndrome (63–65). However, this has not been studied in other pediatric populations with PARDS. With the paucity of data, we are not able to make a recommendation for these therapies. Further study is needed to determine their efficacy in treatment of patients with PARDS.

CONCLUSIONS

The evidence to support or refute use of these specific ancillary therapies remains low. Data demonstrating improvement in adults with ARDS with the use of prone positioning and corticosteroids have not been replicated in children. While there are data in PARDS demonstrating improvement in oxygenation with iNO, surfactant, and prone positioning, there is a lack of data to support improvement in clinically relevant outcomes, namely mortality or duration of ventilation. It is unclear how this improvement in oxygenation is associated with long-term neurologic, pulmonary or quality-of-life outcomes. Further investigation, including a focus on specific subpopulations, is needed to better understand the role, if any, of these various ancillary therapies in PARDS.

1 *Department of Pediatrics, Division of Critical Care Medicine, Indiana University School of medicine, Riley Hospital for Children at IU Health, Indianapolis, IN.*

2 *Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Boston, MA.*

3 *Departments of Anaesthesia and Pediatrics, Harvard Medical School, Boston, MA.*

4 *Fetal and Neonatal Institute, Division of Neonatology, Children's Hospital Los Angeles, Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA.*

5 *Department of Anesthesiology and Critical Care, Children's Hospital Los Angeles, Los Angeles, CA.*

6 *Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region of Denmark, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.*

7 *Department of Paediatrics, Division of Paediatric Critical Care Medicine, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.*

8 *Critical care, Anesthesiology, Peri-operative & Emergency medicine (CAPE), University of Groningen, Groningen, The Netherlands.*

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For information regarding this article, E-mail: coujohns@iu.edu

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The Second Pediatric Acute Lung Injury Consensus Conference (PALICC-2) group members are listed in ***Appendix 1*** *(http://links.lww.com/PCC/C298).*

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