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STATE-OF-THE-ART

Delivery room interventions to prevent bronchopulmonary dysplasia in extremely preterm infants

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Bronchopulmonary dysplasia (BPD) is the most common chronic respiratory complication of preterm birth. Preterm infants are at risk for acute lung injury immediately after birth, which predisposes to BPD. In this article, we review the current evidence for interventions applied during neonatal transition (delivery room and first postnatal hours of life) to prevent BPD in extremely preterm infants: continuous positive airway pressure (CPAP), sustained lung inflation, supplemental oxygen use during neonatal resuscitation, and surfactant therapy including less-invasive surfactant administration. Preterm infants should be stabilized with CPAP in the delivery room, reserving invasive mechanical ventilation for infants who fail non-invasive respiratory support. For infants who require endotracheal intubation and mechanical ventilation soon after birth, surfactant should be given early ($<$ 2 h of life). We recommend prudent titration of supplemental oxygen in the delivery room to achieve targeted oxygen saturations. Promising interventions that may further reduce BPD, such as sustained inflation and non-invasive surfactant administration, are currently under investigation.

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BACKGROUND

Extremely preterm infants are at high risk for acute lung injury and subsequent chronic lung disease or bronchopulmonary dysplasia (BPD). BPD affects approximately 25 to 40% of surviving very low birth weight infants,[1,2] with the highest incidence among those born at the lowest gestational ages (GAs).[3,4] BPD is associated with impaired lung function that persists into adolescence and adulthood.[5–8] In addition, BPD is an important risk factor for adverse non-respiratory outcomes, including growth failure,[9,10] neurodevelopment impairment[11,12] and poor school-age performance.[13]

Considerable data suggest that early lung and systemic inflammation contribute to the pathogenesis of BPD.[14–17] These discoveries led to significant research into early postnatal interventions to prevent or ameliorate early lung inflammation and injury in extremely preterm infants. Immediately after birth, the newborn infant must open and aerate the lung to initiate the transition from a fetal to a postnatal circulation and physiology. However, most extremely preterm infants struggle to independently aerate the lung, owing to a compliant chest wall,[18,19] weak respiratory muscles, altered epithelial sodium channels[20] and immature surfactant.[21] Consequently, most extremely preterm infants require positive pressure ventilation and/or supplemental oxygen after birth. Although these therapies are often necessary to ensure adequate gas exchange, they may induce acute lung injury from barotrauma and volutrauma and oxygen-free radical formation. Therefore, ideal strategies for BPD prevention should start immediately after preterm birth to limit lung injury and oxidative stress.

ABOUT THIS ARTICLE

The focus of this narrative review is an analysis of the current literature describing interventions applied during neonatal transition to prevent BPD in extremely preterm infants. We present the current evidence for therapies used in the delivery room or initial hours of life: continuous positive airway pressure (CPAP), sustained lung inflation, supplemental oxygen use during resuscitation, surfactant therapy (via endotracheal tube), and less-invasive surfactant administration (LISA). Subsequent therapies to prevent BPD have been reviewed elsewhere and are not the focus of this article.[22–24]

We included high-quality randomized controlled trials (RCTs), meta-analyses and key observational studies. Further, we conducted a meta-analysis of published RCTs comparing LISA vs control therapies in infants born $\leqslant$32 weeks GA with a reported outcome of BPD or the composite of BPD or death as an outcome. This analysis was performed with Review Manager (RevMan) Version 5.3 (Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

CONTINUOUS POSITIVE AIRWAY PRESSURE

Use of non-invasive CPAP immediately after birth facilitates lung recruitment and formation of a functional residual capacity. Non-invasive CPAP mitigates lung injury by avoiding barotrauma–volutrauma from mechanical ventilation or atelecto-trauma that can result from repeated collapse and expansion of the alveoli during room air breathing. Early observational data from 1987 suggested that aggressive early use of CPAP reduced BPD.[25] Protocols describing the successful use of CPAP for delivery room

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resuscitation of extremely low birth weight infants with selective intubation and surfactant administration reserved for infants who failed CPAP followed soon after.[26]

Some 10 to 15 years after these initial descriptions, several large multicenter randomized trials of respiratory management after birth compared an initial strategy of early CPAP with immediate intubation and surfactant administration. The largest of these were COIN,[27] SUPPORT[28] and the Vermont Oxford Network delivery room management trial.[29]

In the COIN trial, Morley *et al.*[27] randomized 610 infants from 25 to $28^{6/7}$ weeks gestation to initial respiratory management of either initial CPAP therapy or mechanical ventilation. The SUPPORT trial enrolled 1316 infants between 24 and $27^{6/7}$ weeks gestation who were randomized before birth to initial CPAP therapy with subsequent selective surfactant administration and a limited ventilation strategy vs mechanical ventilation and prophylactic surfactant therapy.[28] Last, in the Vermont Oxford Network trial, Dunn *et al.*[29] randomized 648 infants between 26 and $29^{6/7}$ weeks gestation to the following modes of respiratory support: prophylactic surfactant followed by mechanical ventilation, prophylactic surfactant followed by extubation to CPAP, or initial CPAP therapy with selective surfactant treatment.

Many study design elements varied between these trials, including enrollment size, the GAs of enrolled infants, antenatal vs postnatal randomization, timing of respiratory interventions and initial CPAP settings (ranging from 5 cm H_2O to 8 cm H_2O). Despite these differences, all three trial results were consistent for the outcome of BPD. Each trial demonstrated a non-significant reduction in the rate of death or BPD at 36 weeks PMA among infants treated with CPAP, compared with empirical intubation and mechanical ventilation. In pooled analyses of these RCTs, there was a small but statistically significant reduction in the risk for death or BPD in the CPAP-treated infants. The number needed to treat (NNT) reported by these meta-analyses (some of which included smaller RCTs) ranged from 20 to 35.[30–32]

Although the rate of pneumothorax was higher in CPAP-treated infants in the COIN trial,[27] neither of the other trials reported increased risk for air leaks among infants treated with initial CPAP. In meta-analysis, initial CPAP with selective surfactant was not associated with increased risk for pneumothorax or other adverse events.[31,32]

Based on these findings, the American Academy of Pediatrics Committee on Fetus and Newborn subsequently published a policy statement concluding that, 'the early use of CPAP with subsequent selective surfactant administration in extremely preterm infants results in lower rates of BPD/death when compared with treatment with prophylactic or early surfactant therapy'.[33]

SUSTAINED INFLATION (SI)

SI is a lung recruitment strategy used immediately after birth. SI holds an inflating pressure for a prolonged duration to achieve lung fluid clearance and to establish the functional residual capacity. In 1981, Vyas *et al.*[34] described a 5-s SI to asphyxiated term newborns after birth. Subsequent observational studies demonstrated the feasibility and safety of performing SI in preterm infants during neonatal transition.

Five randomized trials of SI in extremely preterm infants have been published to date (Table 1).[35–39] Harling *et al.*[35] randomized 52 infants < 31 weeks gestation to receive either a 5-s SI or a 2-s 'conventional' lung inflation as the initial positive pressure inflation delivered after birth. There were no significant differences between groups for the primary outcome, bronchoalveolar lavage cytokine levels or secondary outcomes of death, BPD or major neonatal morbidities.[35] As there was only a 3-s difference in duration of the initial lung inflation, the SI maneuver in this trial

Table 1. Published randomized trials comparing SI with IPPV in extremely preterm infants

Study	*Population*	*Comparison*	*Primary outcome*	*Comments*
Lindner *et al.*, 2005[36]	61 infants 25–$28^{6/7}$ weeks GA	Up to three SI (20–30 cm $H_2O \times 15$ s) vs IPPV, both via NP tube	Intubation at 48 HOL: SI (61%) vs IPPV (70%), OR 0.68 (95% CI 0.23–1.97)	Closed early for slow recruitment; under powered to detect a significant difference in primary outcome rates
Harling *et al.*, 2005[35]	52 infants < 31 weeks GA	One SI (25–30 cm $H_2O \times 5$ s) vs IPPV (2 s inflation), via facemask or ETT	Cytokine concentrations from BAL at 12 h of life: no significant differences between groups	Minimal treatment difference between groups. Non-clinical primary outcome
te Pas and Walther 2007[37]	207 infants 25–$32^{6/7}$ weeks GA	Up to two SI (20–25 cm $H_2O \times 10$ s) with PEEP via NP tube vs IPPV without PEEP via facemask	Intubation within 72 HOL: SI (37%) vs IPPV (51%), OR 0.57 (95% CI 0.32–0.98)	No PEEP during IPPV for the control group, different devices and interfaces used between groups
Lista *et al.*, 2015[38]	291 infants 25–$28^{6/7}$ weeks GA	Up to two prophylactic SI (25 cm $H_2O \times 15$ s) via facemask vs nasal CPAP with subsequent resuscitation per NRP guidelines	Intubation within 72 HOL: SI (53%) vs CPAP (65%), OR 0.62 (95% CI 0.38–0.99)	Infants received prophylactic SI, regardless of respiratory status after birth
Jiravisitkul *et al.*, 2017[39]	81 infants 25–32 weeks GA	Up to two SI (25 cm $H_2O \times 15$ s) via facemask vs IPPV with PEEP via facemask	Mean FiO_2 at 10 min after birth: SI (0.28, 95% CI: 0.26–39) vs control (0.47, 95% CI: 0.43–0.52), $P < 0.001$	Proximal primary outcomes. Heart rate and pulse oximetry in first 10 min and delivery room intubation: no significant differences between groups

Abbreviations: BAL: bronchoalveolar lavage; BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous positive airway pressure; GA, gestational age; HOL, hours of life; IPPV, intermittent positive pressure ventilation; NRP, neonatal resuscitation program; OR, odds ratio; PEEP, positive end expiratory pressure; SI, sustained inflation.

may not have been long enough to demonstrate significant differences between groups.

In a RCT stopped early for slow recruitment, Lindner *et al.*[36] randomized 61 preterm infants to treatment with up to three 15-s SIs vs intermittent positive pressure ventilation (IPPV) with positive end expiratory pressure. There was no significant difference between treatment groups in the primary outcome, intubation in the first 48 h of life, or secondary outcomes of death or chronic lung disease.[36]

te Pas *et al.*[37] enrolled 207 infants <33 weeks gestation who required positive pressure ventilation after birth in a single-site RCT comparing one to two SIs (10 s each) with IPPV. Infants treated with SI experienced a reduced rate of the primary outcome, intubation in the first 72 h of life, and the secondary outcome of moderate/severe BPD (9% vs 19%, odds ratio 0.41, 95% confidence interval (CI) 0.18 to 0.96). Unfortunately, different interfaces and respiratory devices were used between treatment groups, making it difficult to isolate SI as the single cause of improved outcomes.[37]

The multisite SLI (Sustained Lung Inflation) trial randomized infants between 25 and $28^{6/7}$ weeks gestation to receive up to two 15-s SIs or nasal CPAP, with subsequent resuscitation according to Neonatal Resuscitation Program guidelines.[38] The primary outcome of this trial, mechanical ventilation within the first 72 h after birth, was significantly lower in infants treated with SI. This trial was not powered for the outcome of BPD, and BPD rates did not significantly differ between groups.[38]

Jiravisitkul *et al.*[39] performed a single-site RCT of 81 infants between 25 and 32 weeks gestation who were randomized to receive up to two 15-s SIs or IPPV with subsequent resuscitation per neonatal resuscitation program guidelines. The mean fraction of inspired oxygen 10 min after birth—a primary outcome—was lower in the SI group compared with infants in the IPPV group. There were no significant differences in the other primary outcomes (heart rate and SpO_2 in the first 10 min of life or rates of delivery room intubation) between groups. There was no significant difference between treatment groups in the secondary outcome of BPD.[39]

A meta-analysis, comprising 611 preterm infants from four of these trials, found no significant differences in the rates of BPD, death or the composite outcome of BPD or death among those treated with SI compared with the control therapy.[40] However, these results should be interpreted cautiously, as the individual trials varied considerably with regards to the duration and peak pressures of the SI, the administered control therapies, resuscitation devices and demographic characteristics of the enrolled infants (Table 1). Two ongoing trials of SI with the primary outcome of BPD or death will provide important information on the safety and efficacy of SI for the prevention of BPD in extremely preterm infants.[41,42]

SUPPLEMENTAL OXYGEN DURING RESUSCITATION

The transition from the relatively hypoxemic fetal state to a normal postnatal oxygen saturation (SpO_2) is a gradual process after birth. To adequately support gas exchange while avoiding hyperoxia-related toxicity to developing organs, such as the lungs and retina, clinicians try to judiciously regulate supplemental oxygen use in preterm infants. This effort is hampered by the lack of robust data on the normal SpO_2 transition in extremely preterm infants, which in turn complicates efforts to determine the optimal approach to FiO_2 titration after birth.

Dawson *et al.*[43] published nomograms of SpO_2 after birth, which were generated from 468 infants who did not require respiratory support after birth. However, only 39 (8%) of the infants included in the Dawson curves cohort were born preterm (<32 weeks GA). To address this gap, Vento *et al.*[44] recorded serial SpO_2 measurements in 102 preterm infants (median GA 29 weeks) who were stabilized using CPAP without supplemental O_2 after birth. Infants in that study achieved reference values of SpO_2 faster than the preterm infants in the study by Dawson *et al.*[43] (who received no respiratory support).[44] In contrast, Mian *et al.*[45] found that rise in SpO_2 lagged behind both the Dawson and Vento nomograms in their cohort of 55 preterm infants (mean GA 31 weeks) supported on CPAP, despite provision of supplemental oxygen to many of these infants. Importantly, the normative ranges for SpO_2 rise described in all these studies were derived mostly in moderately preterm infants. They therefore may not be generalizable to the most extremely preterm infants, who are at highest risk for both impaired gas exchange due to immature lungs as well as injury from oxygen toxicity.

Several RCTs have compared an initial approach of low vs high oxygen administration during delivery room resuscitation of preterm infants.[46–54] These trials varied considerably in study design and many are limited by small sample sizes and use of only very proximal outcomes (Table 2). Two of these RCTs reported a significant reduction in BPD among infants in whom resuscitation was initiated with lower FiO_2.[49,52] However, a meta-analysis comprising RCTs conducted in preterm infants ($\leqslant$32 weeks GA) demonstrated no significant difference in the risks for BPD (relative risk (RR) 1.11, 95% CI 0.73 to 1.68) or mortality (RR 0.62, 95% CI 0.37 to 1.04) between infants treated with low vs high initial concentrations of supplemental oxygen.[55] More recently, Oei *et al.*[56] performed a meta-analysis restricted to RCTs comparing low ($\leqslant$0.3) vs high ($\geqslant$0.6) FiO_2 for resuscitation in infants born $\leqslant 28$ weeks GA. There was no significant difference between groups for the outcomes of BPD among survivors (37% low oxygen vs 41% high oxygen, RR 0.88, 95% CI 0.68 to 1.14) or mortality (14% low oxygen vs 12% high oxygen, RR 0.99, 95% CI 0.52 to 1.91).[56]

The meta-analysis by Oei *et al.*[54] included results from the TO_2RPIDO trial, which randomized infants <32 weeks gestation to delivery room resuscitation started with 21% vs 100% oxygen. This was an early-stopped trial, which ceased recruitment after just 292 of the targeted 1986 subjects were recruited (of which 287 were included in the analysis). An un-prespecified subgroup analysis of infants <28 weeks gestation in this trial demonstrated higher mortality in the 21% FiO_2 group (22% vs 6%, $P=0.01$).[54] In an observational study, Rabi *et al.*[57] studied 2326 infants $\leqslant 27$ weeks GA born in Canada before and after local practice changed from initiating resuscitation with 100% FiO_2 to lower oxygen concentrations (typically 21% to 40%) with subsequent titration. Rates of BPD were similar between the two epochs. However, the composite outcome of death or severe neurological injury was significantly more frequent among infants resuscitated with an initially lower FiO_2 (adjusted odds ratio 1.36, 95% CI 1.11 to 1.66).[57]Results from both of these studies should be interpreted cautiously, owing to limitations from stopping early[58] (the TO_2RPIDO trial)[54] and the before/after study design relying on an exposure of reported policy changes (Rabi *et al.*[57]).

Although the pooled available data do not suggest that initial FiO_2 during resuscitation influences the outcome of BPD, the optimal initial concentration of supplemental oxygen used during neonatal resuscitation and time to reach 'normal' SpO2 in extremely preterm infants remains an important evidence gap. The 2015 International Liaison Committee on Resuscitation recommended starting resuscitation for preterm infants with a low FiO_2 concentration (21% to 30%) but acknowledged the need for more evidence.[59] The ongoing PreSOX trial[60] may provide more information about the optimal use of oxygen during resuscitation to minimize mortality and morbidity in preterm infants.

Table 2. Published randomized trials comparing low vs high FiO_2 during delivery room stabilization

Author	*Population*	*Comparison*	*Primary outcome*	*Comments*
Lundstrøm *et al.*, 1995[46]	70 infants < 33 weeks GA	Initial FiO_2 21% vs 80%, titrated clinically by response in HR.	Cerebral blood flow (measured by xenon clearance) at 2 HOL higher in low oxygen group (median 15.9 vs 12.3 ml 100 g^{-1} min^{-1}), $P < 0.0001$	FiO2 titrated based on HR not SpO_2. Secondary outcome: no significant difference in supplemental O_2 at 28 days
Harling *et al.*, 2005[47]	52 infants < 31 weeks GA	FiO_2 50% vs 100%	Cytokine concentrations in BAL collected at 12 HOL: no significant differences	Secondary outcome: no significant difference in survival without BPD
Wang *et al.*, 2008[48]	41 infants 23–31[6/7] weeks GA	Initial FiO_2 21% vs 100%, titrated per protocol	SpO_2 values during stabilization. SpO_2 significantly lower in 21% FiO_2 group from 2 to 10 MOL	Secondary outcome: no significant difference in supplemental O_2 at 36 weeks PMA
Vento *et al.*, 2009[49]	78 infants 24–28 weeks GA	Initial FiO_2 30% vs 90%, titrated per protocol	Neonatal death (< 28 days) and BPD at 36 weeks PMA. No difference in neonatal death. Less BPD among survivors in low FiO_2 group (15% vs 32%, $P < 0.05$).	Secondary outcomes: low FiO_2 group had significantly fewer days of supplemental O_2 and mechanical ventilation and lower markers of oxidative stress and inflammation
Rabi *et al.*, 2011[50]	106 infants ⩽32 weeks GA	FiO_2: high (100% static), moderate (initial 100%, titrated), or low (initial 21%, titrated)	Time within target SpO_2 85–92%. No differences in time to reach target SpO_2. Moderate group with greater proportion of time spent in target SpO_2 range than high group	Secondary outcomes: no significant difference in BPD, death or duration of mechanical ventilation
Armanian and Badiee, 2012[51]	32 infants 29–34 weeks GA	Initial FiO_2 30% vs 100%, titrated per protocol	Outcomes reported: SpO_2 and HR per minute of life. More infants In 100% FiO_2 with HR > 100 b.p.m at 2 MOL (94% vs 50%, $P = 0.008$)	Unclear primary outcome. All proximal outcomes (within first 5 MOL). Clinically relevant in-hospital outcomes not reported
Kapadia *et al.*, 2013[52]	88 infants 24–34[6/7] weeks GA	Initial FiO_2 21% vs 100%, titrated per protocol	Improved oxidative balance ratio (serum (BAP/TH)) at 1 HOL in 21% FiO_2 group (median 13 vs 8, $P < 0.01$)	Secondary outcome: 21% FiO_2 with less BPD (7% vs 25%, $P < 0.05$)
Rook *et al.*, 2014[53]	193 infants < 32 weeks GA	Initial FiO_2 30% vs 65%, titrated per protocol	BPD at 36 weeks PMA: no significant difference between groups, 24% (low FiO_2) vs 17% (high FiO_2), $P = 0.15$	Secondary outcomes: no differences in duration of mechanical ventilation or markers of oxidative stress
Oei *et al.*, (2017)[54]	287 infants < 32 weeks GA	Initial FiO_2 21% vs 100%, titrated per protocol	Primary outcome (death or major disability at 2 years) not yet reported	No significant difference in BPD between groups. Ancillary analysis of 119 enrolled infants revealed higher oxidative stress markers in the 100% FiO_2 group[91]

Abbreviations: BAL, bronchoalveolar lavage; BAP, biological antioxidant potential; BPD, bronchopulmonary dysplasia; BPM, beats per minute; FiO_2, fraction of inspired oxygen; GA, gestational age; HOL, hour(s) of life; HR, heart rate; MOL, minute(s) of life; PMA, postmenstrual age; SpO_2, oxygen saturation (pulse oximetry); TH, total hydroperoxide.

SURFACTANT ADMINISTRATION AFTER STANDARD ENDOTRACHEAL INTUBATION

Beginning in the 1980s, several high-quality RCTs assessed the safety and timing of surfactant administration in preterm infants.[61–63] Early RCTs demonstrated that administration of surfactant to preterms with established respiratory distress syndrome (RDS) reduced pulmonary air leak and lowered the risk of death or supplemental oxygen use at 28 days of age (the standard definition of BPD at that time).[61–63] Subsequent studies found that prophylactic administration of surfactant soon after birth also reduced pulmonary morbidity and improved BPD-free survival.[61,62] However, most of these RCTs were conducted prior to the routine use of antenatal corticosteroids and aggressive use of non-invasive CPAP. As discussed above in the section on CPAP, prophylactic intubation and surfactant administration, compared with early non-invasive CPAP therapy, does not reduce BPD risk in preterm infants.[30–32]

Unfortunately, stabilization with non-invasive respiratory support is not possible in all preterm infants. Up to 65% of spontaneously breathing extremely preterm babies require intubation and mechanical ventilation despite early CPAP therapy.[31] In these instances, early rescue surfactant therapy is appropriate. Providing early rescue surfactant (within the first 2 h of life) to mechanically ventilated preterm infants, as compared with delayed surfactant administration (after second hour of life), reduces the risk of BPD (RR 0.69, 95% CI 0.55 to 0.86) and the composite of death or BPD (RR 0.83, 95% CI 0.75 to 0.91).[64]

When surfactant is indicated, there are several animal-derived (modified or purified from the bovine or porcine lungs) and synthetic formulations available for use. Animal-derived surfactants compared with first-generation protein-free surfactants are associated with a marginal reduction in mortality (RR 0.89, 95% CI 0.79 to 0.99) and death or BPD (RR 0.95, 95% CI 0.91 to 1.00).[65] Meta-analysis of trials comparing modified bovine-minced lung surfactant to porcine-minced lung surfactant raised concern that bovine surfactant may increase the risk for mortality, BPD and other adverse outcomes.[66] However, in a subgroup analysis, the improvement in morbidity and mortality risk was limited to the trials using a higher initial dose of porcine-minced lung surfactant (>100 mg kg^{-1}).[66] It is uncertain whether the differences in outcome risks are from differences in the surfactant dose or extraction source. A second-generation synthetic surfactant (lucinactant) containing a peptide analog of surfactant protein-B is also now available and has similar efficacy as animal-derived products.[67,68]

To maximize the potential benefits of early surfactant administration without undergoing prolonged mechanical ventilation, Victorin *et al.*[69] introduced the technique of INtubation, SURfactant administration during brief mechanical ventilation, followed by Extubation (INSURE approach). Initial RCTs found that the INSURE approach compared with selective administration of surfactant to infants with established RDS reduced the need for mechanical ventilation and use of supplemental oxygen at 28 days of life.[70] However, when compared with early stabilization with CPAP alone, INSURE does not reduce BPD. In a meta-analysis of 9 RCTs that included a total of 1551 preterm infants, Isayama *et al.*[71] reported that INSURE compared with CPAP did not significantly affect the risk for death or BPD (RR 0.88, 95% CI 0.76 to 1.02).

LESS-INVASIVE SURFACTANT ADMINISTRATION

In an effort to avoid standard endotracheal intubation, several less invasive techniques of surfactant administration have been developed. These include intratracheal instillation of surfactant with a thin catheter (for example, nasogastric tube), aerosolized administration, intrapartum pharyngeal instillation and delivery via a laryngeal mask airway.[72]Of these strategies, surfactant instillation via thin catheter, often referred to as LISA or minimally

invasive surfactant therapy, is the most studied. Verder *et al.*[73] first published their experience with LISA in the early 1990s. In a large, multicenter observational study ($n = 2206$) of preterm infants treated with LISA vs matched controls, LISA was associated with lower rates of mechanical ventilation (41% vs 62%, $P < 0.001$) and death or BPD (14% vs 21%, $P < 0.001$).[74]

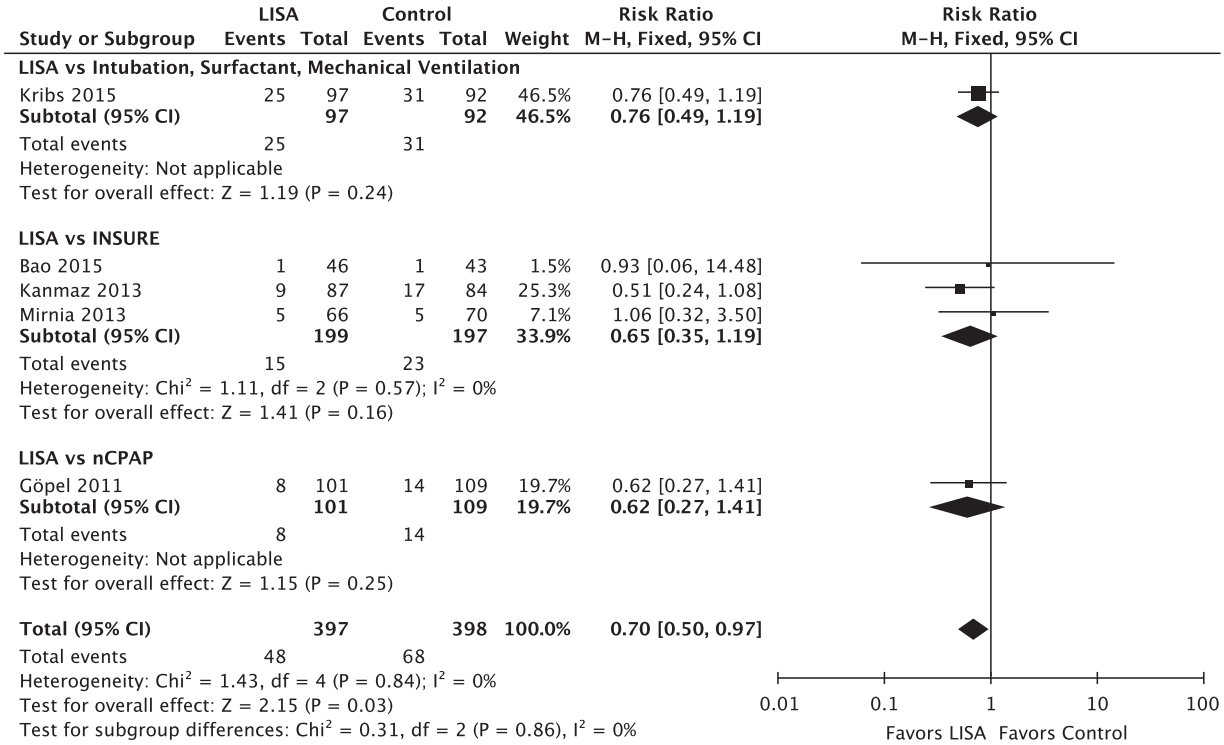

Figure 1. Forrest plot for the outcome of bronchopulmonary dysplasia among survivors, comparing less-invasive surfactant administration (LISA) vs control therapy in extremely preterm infants. CI, confidence interval; INSURE, INtubation, SURfactant administration during brief mechanical ventilation, followed by Extubation; nCPAP, nasal continuous positive airway pressure.

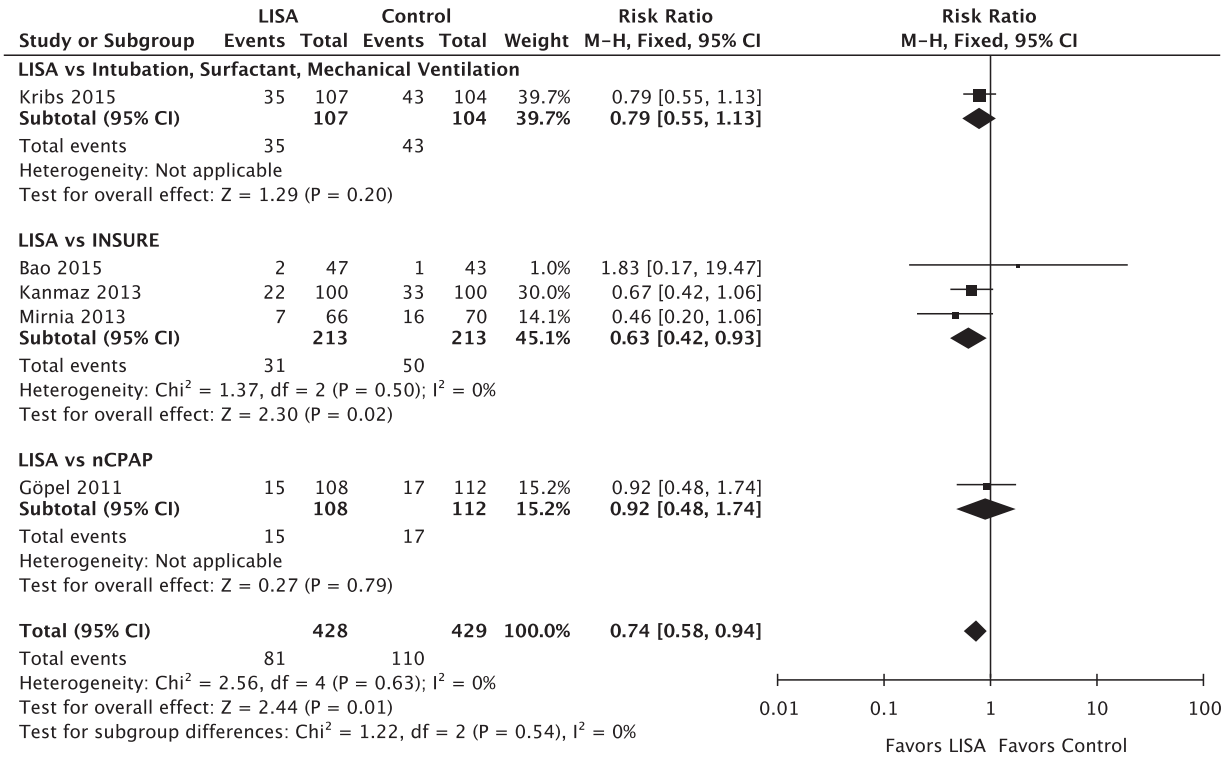

Figure 2. Forrest plot for the outcome of death or bronchopulmonary dysplasia, comparing less-invasive surfactant administration (LISA) vs control therapy in extremely preterm infants. CI, confidence interval; INSURE, INtubation, SURfactant administration during brief mechanical ventilation, followed by Extubation; nCPAP, nasal continuous positive airway pressure.

Four RCTs conducted in extremely preterm infants compared LISA with surfactant administration via endotracheal tube (three vs INSURE, one vs continued mechanical ventilation after surfactant therapy)[75–78] and one compared LISA to ongoing nasal CPAP therapy.[79] Here we report a meta-analysis of data combined from these five RCTs (total $n = 857$). Using data combined from all 5 trials, LISA vs control therapy reduced the risk for BPD among survivors to at least 36 weeks PMA (RR 0.70, 95% CI 0.50 to 0.97; typical risk difference − 0.05, 95% CI − 0.10 to − 0.01; NNT 19; 95% CI 10 to 189) (Figure 1) and the composite of death or BPD (RR 0.74, 95% CI 0.58 to 0.94; typical risk difference − 0.07; 95% CI − 0.12 to − 0.01; NNT 15; 95% CI 8 to 70) (Figure 2). When compared with INSURE therapy alone (3 trials, $n = 426$), LISA also reduced the risk for death or BPD (RR 0.63, 95% CI 0.42 to 0.93; typical risk difference − 0.09, 95% CI − 0.16 to − 0.015; NNT 12, 95% CI 6 to 66) but not BPD among survivors (RR 0.65, 95% CI 0.35 to 1.19, typical risk difference − 0.04; 95% CI − 0.10 to 0.02). Of note, one published RCT comparing LISA to INSURE ($n = 38$) was excluded from this analysis owing to enrollment of moderate and extremely preterm infants (GA < 35 weeks).[80] Two meta-analyses inclusive of this RCT were recently reported.[81,82]

Isayama *et al.*[83] recently reported a Bayesian random-effects network meta-analysis evaluating the efficacy of six early ventilation strategies (mechanical ventilation, nasal CPAP, non-invasive positive pressure ventilation, INSURE, LISA and nebulized surfactant administered via laryngeal mask airway) for prevention of BPD in infants born < 33 weeks gestation. This approach allowed for simultaneous estimation of the relative effects of multiple interventions regardless of whether they were directly compared in individual trials. The study results indicated that LISA was associated with the largest reduction in the risk for death or BPD (odds ratio 0.49; 95% credible interval 0.30 to 0.79) of any of the evaluated interventions.[83] However, the authors noted the findings were limited by the overall low quality of the available evidence. An ongoing trial (anticipated $n = 606$ for a primary composite outcome of death or physiological BPD) comparing LISA to sham treatment in extremely preterm infants without a history of prior intubation will provide additional important data on this topic.[84]

OTHER STRATEGIES

Intratracheal budesonide

Yeh *et al.*[85] recently randomized 265 very low birth weight infants with RDS who were mechanically ventilated in the first 4 h of life to treatment with intratracheal surfactant vs intratracheal budesonide and surfactant. Infants treated with budesonide and surfactant experienced a significant reduction in the outcome of death or BPD (any supplemental O_2 requirement) at 36 weeks (42% vs 66%, $P < 0.001$).[85] Further, interleukin concentrations in tracheal aspirates were transiently lower among infants in the intervention arm, suggesting intratracheal budesonide may diminish BPD risk through local anti-inflammatory effects.[85] Notably, the effect size of this trial is rather large (NNT, 4.1; 95% CI 2.8 to 7.8).[85] Thus, while these study results are promising, further large RCTs of intratracheal budesonide plus surfactant are needed before this therapy should be introduced into clinical practice.

Caffeine

In the Caffeine for Apnea of Prematurity trial, > 2000 infants with birth weight 500 to 1250 g were randomized to receive to caffeine or placebo within the first 10 days of life.[86] Infants randomized to caffeine experienced significantly less BPD than placebo infants, which was largely attributed to the fact that caffeine-treated

Box 1 Summary of Evidence for Perinatal Interventions to Prevent BPD

Continuous positive airway pressure (CPAP) vs mechanical ventilation

- Evidence: Cochrane meta-analysis of 3 large RCTs ($n = 2358$) reporting outcome of BPD or death at 36 weeks PMA[32]
- Results: Primary CPAP therapy compared with mechanical ventilation reduced the risk of BPD/death.
- Treatment effect: Relative risk 0.89 (95% CI: 0.81 to 0.97)
- Number needed to treat: 20 (95% CI: 11 to 100)

Sustained inflation vs intermittent positive pressure ventilation or CPAP

- Evidence: Meta-analysis of 4 RCTs ($n = 611$ infants) comparing SI with IPPV or CPAP reporting the outcome of BPD or death at 36 weeks PMA[40]
- Results: Neither SI or IPPV was superior to reduce the risk of BPD/death.
- Treatment effect: Relative risk 0.92 (95% CI: 0.66 to 1.29)

Supplemental oxygen during delivery room resuscitation

- Evidence: Meta-analysis of 10 RCTs ($n = 677$ infants ⩽32 weeks gestation) comparing low (⩽30%) with high (⩾60%) initial FiO_2 for delivery room resuscitation reporting outcome of BPD[55]
- Results: Neither approach to supplemental FiO_2 was superior to reduce the risk of BPD
- Treatment effect: Relative risk 1.11 (95% CI: 0.73 to 1.68)

Surfactant

INSURE vs nasal CPAP

- Evidence: Meta-analysis of 6 RCTs ($n = 1250$) reporting the outcome of BPD or death at 36 weeks PMA[71]
- Results: Neither INSURE or nasal CPAP was superior to reduce the risk of BPD/death.
- Treatment effect: Relative risk 0.88 (95% CI: 0.76 to 1.02)

Early (< 2 h of life) vs Late (⩾2 h of life) administration among infants receiving invasive mechanical ventilation

- Evidence: Cochrane meta-analysis of 3 RCTs ($n = 3050$) reporting the outcome of BPD or death at 36 weeks PMA[64]
- Results: Early compared with late surfactant reduced the risk of BPD/death.
- Treatment effect: Relative risk 0.83 (95% CI: 0.75 to 0.91)
- Number needed to treat: 16 (95% CI: 11 to 34)

Less-invasive surfactant administration (LISA) vs all control therapies

- Evidence: Meta-analysis of 5 RCTs ($n = 857$) reporting the outcome of BPD or death at 36 weeks PMA (Figure 2)
- Results: LISA compared with control therapy reduced the risk of BPD/death.
- Treatment effect: Relative risk 0.74 (95% CI 0.58 to 0.94).
- Number needed to treat: 15 (95% CI 8 to 70)

Less-invasive surfactant administration (LISA) vs INSURE

- Evidence: Meta-analysis of 3 RCTs ($n = 426$) reporting the outcome of BPD or death at 36 weeks PMA (Figure 2)
- Results: LISA compared with INSURE reduced the risk of BPD/death.
- Treatment effect: Relative risk 0.63 (95% CI 0.42 to 0.93)
- Number needed to treat: 12 (95% CI 6 to 66)

infants received an average of 1 less week of positive pressure ventilation.

Caffeine is now a standard of care therapy in the respiratory management for preterm infants. Early initiation of caffeine is especially critical in the CPAP era, as more preterm infants are managed via non-invasive support immediately after birth and require a sustained respiratory drive to avoid intubation and mechanical ventilation.[87] A meta-analysis comprising both cohort studies and RCT demonstrated that early caffeine administration is associated with a reduction in BPD, when compared with later administration. The timing of 'early' caffeine administration varied from the first 2 h after birth to the first 3 days after birth.[88]

Two small RCTs demonstrated that caffeine administration within the first minutes[89] to first 2 h of life[90] is feasible and may improve short-term physiological outcomes.[89,90] Neither trial was designed or powered to detect differences in BPD. Although caffeine therapy should be administered early in the neonatal intensive care unit to prevent BPD in preterm infants, there are insufficient RCT data to recommend immediate caffeine administration in the delivery room to prevent BPD.

CONCLUSIONS

Acute lung injury sustained in the immediate perinatal period directly contributes to the development of BPD in premature infants. Strategies to decrease lung injury and inflammation should begin prior to and continue following preterm delivery (Box 1). Initial stabilization of all infants at risk for RDS should begin with CPAP, reserving endotracheal intubation and surfactant administration for infants who fail non-invasive support. Prudent titration of supplemental oxygen in the delivery room is also recommended. Promising interventions that may further reduce BPD risk are currently under investigation and include SI and non-invasive surfactant administration.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1 Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S *et al.* Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA* 2015; **314**: 1039–1051.
2 Horbar JD, Carpenter JH, Badger GJ, Kenny MJ, Soll RF, Morrow KA *et al.* Mortality and neonatal morbidity among infants 501 to 1500 grams from 2000 to 2009. *Pediatrics* 2012; **129**: 1019–1026.
3 Laughon MM, Langer JC, Bose CL, Smith PB, Ambalavanan N, Kennedy KA *et al.* Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants. *Am J Respir Crit Care Med* 2011; **183**: 1715–1722.
4 Klinger G, Sokolover N, Boyko V, Sirota L, Lerner-Geva L, Reichman B *et al.* Perinatal risk factors for bronchopulmonary dysplasia in a national cohort of very-low-birthweight infants. *Am J Obstet Gynecol* 2013; **208**: 115.e1–9.
5 Doyle LW, Faber B, Callanan C, Freezer N, Ford GW, Davis NM. Bronchopulmonary dysplasia in very low birth weight subjects and lung function in late adolescence. *Pediatrics* 2006; **118**: 108–113.
6 Fawke J, Lum S, Kirkby J, Hennessy E, Marlow N, Rowell V *et al.* Lung function and respiratory symptoms at 11 years in children born extremely preterm: the Epicure study. *Am J Respir Crit Care Med* 2010; **182**: 237–245.
7 Sanchez-Solis M, Garcia-Marcos L, Bosch-Gimenez V, Pérez-Fernandez V, Pastor-Vivero MD, Mondéjar-Lopez P. Lung function among infants born preterm, with or without bronchopulmonary dysplasia. *Pediatr Pulmonol* 2012; **47**: 674–681.
8 Vollsæter M, Røksund OD, Eide GE, Markestad T, Halvorsen T. Lung function after preterm birth: development from mid-childhood to adulthood. *Thorax* 2013; **68**: 767–776.
9 Natarajan G, Pappas A, Shankaran S, Kendrick DE, Das A, Higgins RD *et al.* Outcomes of extremely low birth weight infants with bronchopulmonary dysplasia: impact of the physiologic definition. *Early Hum Dev* 2012; **88**: 509–515.
10 Wang L-Y, Luo H-J, Hsieh W-S, Hsu C-H, Hsu H-C, Chen P-S *et al.* Severity of bronchopulmonary dysplasia and increased risk of feeding desaturation and growth delay in very low birth weight preterm infants. *Pediatr Pulmonol* 2010; **45**: 165–173.
11 Schmidt B, Asztalos EV, Roberts RS, Robertson CMT, Sauve RS, Whitfield MF *et al.* Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. *JAMA* 2003; **289**: 1124–1129.
12 Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA *et al.* Validation of the national institutes of health consensus definition of bronchopulmonary dysplasia. *Pediatrics* 2005; **116**: 1353–1360.
13 Short EJ, Klein NK, Lewis BA, Fulton S, Eisengart S, Kercsmar C *et al.* Cognitive and academic consequences of bronchopulmonary dysplasia and very low birth weight: 8-year-old outcomes. *Pediatrics* 2003; **112**: e359.
14 Björklund LJ, Ingimarsson J, Curstedt T, John J, Robertson B, Werner O *et al.* Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lambs. *Pediatr Res* 1997; **42**: 348–355.
15 Hillman NH, Moss TJM, Kallapur SG, Bachurski C, Pillow JJ, Polglase GR *et al.* Brief, large tidal volume ventilation initiates lung injury and a systemic response in fetal sheep. *Am J Respir Crit Care Med* 2007; **176**: 575–581.
16 Albertine KH, Jones GP, Starcher BC, Bohnsack JF, Davis PL, Cho SC *et al.* Chronic lung injury in preterm lambs. Disordered respiratory tract development. *Am J Respir Crit Care Med* 1999; **159**: 945–958.
17 Wallace MJ, Probyn ME, Zahra VA, Crossley K, Cole TJ, Davis PG *et al.* Early biomarkers and potential mediators of ventilation-induced lung injury in very preterm lambs. *Respir Res* 2009; **10**: 19.
18 Heldt GP, McIlroy MB. Distortion of chest wall and work of diaphragm in preterm infants. *J Appl Physiol (1985)* 1987; **62**: 164–169.
19 Heldt GP, McIlroy MB. Dynamics of chest wall in preterm infants. *J Appl Physiol (1985)* 1987; **62**: 170–174.
20 Barker PM, Gowen CW, Lawson EE, Knowles MR. Decreased sodium ion absorption across nasal epithelium of very premature infants with respiratory distress syndrome. *J Pediatr* 1997; **130**: 373–377.
21 Obladen M. Factors influencing surfactant composition in the newborn infant. *Eur J Pediatr* 1978; **128**: 129–143.
22 Jensen EA, Foglia EE, Schmidt B. Evidence-based pharmacologic therapies for prevention of bronchopulmonary dysplasia: application of the grading of recommendations assessment, development, and evaluation methodology. *Clin Perinatol* 2015; **42**: 755–779.
23 Shinwell ES, Portnov I, Meerpohl JJ, Karen T, Bassler D. Inhaled corticosteroids for bronchopulmonary dysplasia: a meta-analysis. *Pediatrics* 2016; **138**: e20162511.
24 Lemyre B, Laughon M, Bose C, Davis PG. Early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants. *Cochrane Database Syst Rev* 2016; **12**: CD005384.
25 Avery ME, Tooley WH, Keller JB, Hurd SS, Bryan MH, Cotton RB *et al.* Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. *Pediatrics* 1987; **79**: 26–30.
26 Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birth weight infants: spontaneous breathing or intubation? *Pediatrics* 1999; **103**: 961–967.
27 Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB *et al.* Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med* 2008; **358**: 700–708.
28 Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Laptook AR *et al.* Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010; **362**: 1970–1979.
29 Dunn MS, Kaempf J, de Klerk A, de Klerk R, Reilly M, Howard D *et al.* Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. *Pediatrics* 2011; **128**: e1069–e1076.
30 Fischer HS, Bührer C. Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis. *Pediatrics* 2013; **132**: e1351–e1360.
31 Schmolzer M, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung -Y. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. *BMJ* 2013; **347**: f5980.
32 Subramaniam P, Ho JJ, Davis PG. Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants. *Cochrane Database Syst Rev* 2016; **6**: CD001243.
33 Committee on fetus and newborn. Respiratory support in preterm infants at birth. *Pediatrics* 2014; **133**: 171–174.

34 Vyas H, Milner AD, Hopkin IE, Boon AW. Physiologic responses to prolonged and slow-rise inflation in the resuscitation of the asphyxiated newborn infant. *J Pediatr* 1981; **99**: 635–639.
35 Harling AE, Beresford MW, Vince GS, Bates M, Yoxall CW. Does sustained lung inflation at resuscitation reduce lung injury in the preterm infant? *Arch Dis Child Fetal Neonatal Ed* 2005; **90**: F406–F410.
36 Lindner W, Högel J, Pohlandt F. Sustained pressure—controlled inflation or intermittent mandatory ventilation in preterm infants in the delivery room? A randomized, controlled trial on initial respiratory support via nasopharyngeal tube. *Acta Paediatr* 2005; **94**: 303–309.
37 te Pas AB, Walther FJ. A randomized, controlled trial of delivery-room respiratory management in very preterm infants. *Pediatrics* 2007; **120**: 322–329.
38 Lista G, Boni L, Scopesi F, Mosca F, Trevisanuto D, Messner H *et al.* Sustained lung inflation at birth for preterm infants: a randomized clinical trial. *Pediatrics* 2015; **135**: e457–e464.
39 Jiravisitkul P, Rattanasiri S, Nuntnarumit P. Randomised controlled trial of sustained lung inflation for resuscitation of preterm infants in the delivery room. *Resuscitation* 2017; **111**: 68–73.
40 Schmölzer GM, Kumar M, Aziz K, Pichler G, O'Reilly M, Lista G *et al.* Sustained inflation versus positive pressure ventilation at birth: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2014; **100**: F361–F368.
41 Foglia EE, Owen LS, Thio M, Ratcliffe SJ, Lista G, Te Pas A *et al.* Sustained aeration of infant lungs (SAIL) trial: study protocol for a randomized controlled trial. *Trials* 2015; **16**: 95.
42 Assessment of Lung Aeration at Birth. Clinicaltrials.Gov Identifier NCT01739114. Available at https://clinicaltrials.gov/ct2/show/NCT01739114?term = assessment +lung+aeration&rank = 3. Accessed 31 March 2017.
43 Dawson JA, Kamlin CO, Vento M, Wong C, Cole TJ, Donath SM *et al.* Defining the reference range for oxygen saturation for infants after birth. *Pediatrics* 2010; **125**: e1340–e1347.
44 Vento M, Cubells E, Escobar JJ, Escrig R, Aguar M, Brugada M *et al.* Oxygen saturation after birth in preterm infants treated with continuous positive airway pressure and air: assessment of gender differences and comparison with a published nomogram. *Arch Dis Child Fetal Neonatal Ed* 2013; **98**: F228–F232.
45 Mian QN, Pichler G, Binder C, O'Reilly M, Aziz K, Urlesberger B *et al.* Tidal volumes in spontaneously breathing preterm infants supported with continuous positive airway pressure. *J Pediatr* 2014; **165**: 702–706.
46 Lundstrom E, Pryds O, Greisen G. Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1995; **73**: F81–F86.
47 Harling AE, Beresford MW, Vince GS, Bates M, Yoxall CW. Does the use of 50% oxygen at birth in preterm infants reduce lung injury? *Arch Dis Child Fetal Neonatal Ed* 2005; **90**: F401–F405.
48 Wang CL, Anderson C, Leone TA, Rich W, Govindaswami B, Finer NN. Resuscitation of preterm neonates by using room air or 100% oxygen. *Pediatrics* 2008; **121**: 1083–1089.
49 Vento M, Moro M, Escrig R, Arruza L, Villar G, Izquierdo I *et al.* Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease. *Pediatrics* 2009; **124**: e439–e449.
50 Rabi Y, Singhal N, Nettel-Aguirre A. Room-air versus oxygen administration for resuscitation of preterm infants: the ROAR study. *Pediatrics* 2011; **128**: e374–e381.
51 Armanian AM, Badiee Z. Resuscitation of preterm newborns with low concentration oxygen versus high concentration oxygen. *J Res Pharm Pract* 2012; **1**: 25–29.
52 Kapadia VS, Chalak LF, Sparks JE, Allen JR, Savani RC, Wyckoff MH. Resuscitation of preterm neonates with limited versus high oxygen strategy. *Pediatrics* 2013; **132**: e1488–e1496.
53 Rook D, Schierbeek H, Vento M, Vlaardingerbroek H, van der Eijk AC, Longini M *et al.* Resuscitation of preterm infants with different inspired oxygen fractions. *J Pediatr* 2014; **164**: 1322–1326.
54 Oei JL, Saugstad OD, Lui K, Wright IM, Smyth JP, Craven P *et al.* Targeted oxygen in the resuscitation of preterm infants, a randomized clinical trial. *Pediatrics* 2017; **139**: e20161452.
55 Saugstad OD, Aune D, Aguar M, Kapadia V, Finer N, Vento M. Systematic review and meta-analysis of optimal initial fraction of oxygen levels in the delivery room at ≤ 32 weeks. *Acta Paediatr* 2014; **103**: 744–751.
56 Oei JL, Vento M, Rabi Y, Wright I, Finer N, Rich W *et al.* Higher or lower oxygen for delivery room resuscitation of preterm infants below 28 completed weeks gestation: a meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2017; **102**: F24–F30.
57 Rabi Y, Lodha A, Soraisham A, Singhal N, Barrington K, Shah PS. Outcomes of preterm infants following the introduction of room air resuscitation. *Resuscitation* 2015; **96**: 252–259.
58 Guyatt GH, Briel M, Glasziou P, Bassler D, Montori VM. Problems of stopping trials early. *BMJ* 2012; **344**: e3863.
59 Perlman JM, Wyllie J, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R *et al.* Part 7: Neonatal resuscitation: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation* 2015; **132**: S204–S241.
60 Study of room air versus 60% oxygen for resuscitation of premature infants (PRESOX). Clinicaltrials.gov Identifier NCT01773746. Available at: https://clinicaltrials.gov/ct2/show/NCT01773746?term = presox&rank = 1. Accessed 31 March 2017.
61 Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 2000; **2**: CD000511.
62 Soll RF. Prophylactic synthetic surfactant for preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 2000; **2**: CD001079.
63 Soll RF. Synthetic surfactant for respiratory distress syndrome in preterm infants. *Cochrane Database Syst Rev* 2000; **2**: CD001149.
64 Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. *Cochrane Database Syst Rev* 2012; **11**: CD001456.
65 Ardell S, Pfister RH, Soll R. Animal derived surfactant extract versus protein free synthetic surfactant for the prevention and treatment of respiratory distress syndrome. *Cochrane Database Syst Rev* 2015; **5**: CD000144.
66 Singh N, Halliday HL, Stevens TP, Suresh G, Soll R, Rojas-Reyes MX. Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants. *Cochrane Database Syst Rev* 2015; **12**: CD010249.
67 Moya F, Sinha S, Gadzinowski J, D'Agostino R, Segal R, Guardia C *et al.* One-year follow-up of very preterm infants who received lucinactant for prevention of respiratory distress syndrome: results from 2 multicenter randomized, controlled trials. *Pediatrics* 2007; **119**: e1361–e1370.
68 Sinha SK, Lacaze-Masmonteil T, Valls i Soler A, Wiswell TE, Gadzinowski J, Hajdu J *et al.* A multicenter, randomized, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome. *Pediatrics* 2005; **115**: 1030–1038.
69 Victorin LH, Deverajan LV, Curstedt T, Robertson B. Surfactant replacement in spontaneously breathing babies with hyaline membrane disease - a pilot study. *Biol Neonate* 1990; **58**: 121–126.
70 Stevens TP, Harrington EW, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Syst Rev* 2007; **4**: CD003063.
71 Isayama T, Chai-Adisaksopha C, McDonald SD. Noninvasive ventilation with vs without early surfactant to prevent chronic lung disease in preterm infants: a systematic review and meta-analysis. *JAMA Pediatr* 2015; **169**: 731–739.
72 More K, Sakhuja P, Shah PS. Minimally invasive surfactant administration in preterm infants: a meta-narrative review. *JAMA Pediatr* 2014; **168**: 901–908.
73 Verder H, Robertson B, Greisen G, Ebbesen F, Albertsen P, Lundstrøm K *et al.* Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. Danish-Swedish multicenter study group. *N Engl J Med* 1994; **331**: 1051–1055.
74 Göpel W, Kribs A, Härtel C, Avenarius S, Teig N, Groneck P *et al.* Less invasive surfactant administration is associated with improved pulmonary outcomes in spontaneously breathing preterm infants. *Acta Paediatr* 2015; **104**: 241–246.
75 Mirnia K, Heidarzadeh M, Hosseini MB, Sadeghnia A, Balila M, Ghojazadeh M. Comparison outcome of surfactant administration via tracheal catheterization during spontaneous breathing with insure. *Med J Islamic World Acad Sci* 2013; **21**: 143–148.
76 Kanmaz HG, Erdeve O, Canpolat FE, Mutlu B, Dilmen U. Surfactant administration via thin catheter during spontaneous breathing: randomized controlled trial. *Pediatrics* 2013; **131**: e502–e509.
77 Kribs A, Roll C, Göpel W, Wieg C, Groneck P, Laux R *et al.* Nonintubated surfactant application vs conventional therapy in extremely preterm infants: a randomized clinical trial. *JAMA Pediatr* 2015; **169**: 723–730.
78 Bao Y, Zhang G, Wu M, Ma L, Zhu J. A pilot study of less invasive surfactant administration in very preterm infants in a chinese tertiary center. *BMC Pediatr* 2015; **15**: 342.
79 Göpel W, Kribs A, Ziegler A, Laux R, Hoehn T, Wieg C *et al.* Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. *Lancet* 2011; **378**: 1627–1634.
80 Mohammadizadeh M, Ardestani AG, Sadeghnia AR. Early administration of surfactant via a thin intratracheal catheter in preterm infants with respiratory distress syndrome: feasibility and outcome. *J Res Pharm Pract* 2015; **4**: 31–36.
81 Rigo V, Lefebvre C, Broux I. Surfactant instillation in spontaneously breathing preterm infants: a systematic review and meta-analysis. *Eur J Pediatr* 2016; **175**: 1933–1942.

82 Aldana-Aguirre JC, Pinto M, Featherstone RM, Kumar M. Less invasive surfactant administration versus intubation for surfactant delivery in preterm infants with respiratory distress syndrome: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2017; **102**: F17–F23.
83 Isayama T, Iwami H, McDonald S, Beyene J. Association of noninvasive ventilation strategies with mortality and bronchopulmonary dysplasia among preterm infants: a systematic review and meta-analysis. *JAMA* 2016; **316**: 611–624.
84 Dargaville PA, Kamlin CO, De Paoli AG, Carlin JB, Orsini F, Soll RF *et al.* The OPTIMIST-A trial: evaluation of minimally-invasive surfactant therapy in preterm infants 25-28 weeks gestation. *BMC Pediatr* 2014; **14**: 213.
85 Yeh TF, Chen CM, Wu SY, Husan Z, Li TC, Hsieh WS *et al.* Intratracheal administration of budesonide/surfactant to prevent bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2016; **193**: 86–95.
86 Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A *et al.* Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006; **354**: 2112–2121.
87 Kribs A, Hummler H. Ancillary therapies to enhance success of non-invasive modes of respiratory support - approaches to delivery room use of surfactant and caffeine? *Semin Fetal Neonatal Med* 2016; **21**: 212–218.
88 Kua KP, Lee SW. Systematic review and meta-analysis of clinical outcomes of early caffeine therapy in preterm neonates. *Br J Clin Pharmacol* 2017; **83**: 180–191.
89 Dekker J, Hooper SB, van Vonderen JJ, Witlox R, Lopriore E, te Pas AB. Caffeine to improve breathing effort of preterm infants at birth; a randomized controlled trial. *Pediatr Res* 2017 (epub ahead of print 17 May 2017; doi:10.1038/pr.2017.45).
90 Sauberan J, Akotia D, Rich W, Durham J, Finer N, Katheria A. A pilot randomized controlled trial of early versus routine caffeine in extremely premature infants. *Am J Perinatol* 2015; **32**: 879–886.
91 Tataranno ML, Oei JL, Perrone S, Wright IM, Smyth JP, Lui K *et al.* Resuscitating preterm infants with 100% oxygen is associated with higher oxidative stress than room air. *Acta Paediatr* 2015; **104**: 759–765.