STATE-OF-THE-ART

Delivery room interventions to prevent bronchopulmonary dysplasia in extremely preterm infants

EE Foglia1,2, EA Jensen1,2 and H Kirpalani1,2

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.

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 impairment11,12 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 channels20 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 < 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 at birth compared an initial strategy of early CPAP with immediate intubation and surfactant administration. The largest of these were COIN,27 SUPPORT28 and the Vermont Oxford Network delivery room management trial.29

In the COIN trial, Morley et al.27 randomized 610 infants from 25 to 286/7 weeks gestation to initial respiratory management of either initial CPAP therapy or mechanical ventilation. The SUPPORT trial enrolled 1316 infants between 24 and 276/7 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.28 randomized 648 infants between 26 and 296/7 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 H2O to 8 cm H2O). 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 35.30,31

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 ventilation 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>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Primary outcome</th>
<th>Comparison</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindner et al.</td>
<td>200536</td>
<td>Up to three SI (20 cm H2O × 15 s) vs IPPV</td>
<td>Intubation at 48 HOL: SI (61%) vs IPPV (70%), OR 0.68 (95% CI: 0.43–0.97)</td>
<td>No PEEP during intubation for the control group, different devices and interfaces used between groups</td>
</tr>
<tr>
<td>Harling et al.</td>
<td>200537</td>
<td>One SI (25–30 cm H2O × 15 s) via CPAP vs IPPV (2 s × 5 s)</td>
<td>Cytokine concentrations from BAL at 12 h of life: no significant differences between groups</td>
<td></td>
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<tr>
<td>Harling et al.</td>
<td>200538</td>
<td>Up to two SI (25–30 cm H2O × 15 s) via CPAP</td>
<td>Proximal primary outcomes. Heart rate and pulse oximetry in first 10 min of life; no significant differences between groups</td>
<td></td>
</tr>
<tr>
<td>Lista et al.</td>
<td>200739</td>
<td>201 infants 25–32 weeks GA</td>
<td>Mean FiO2 at 10 min after birth: SI (0.28, 95% CI: 0.25–0.31) vs control (0.47, 95% CI: 0.43–0.51)</td>
<td></td>
</tr>
<tr>
<td>Jiravisitkul et al.</td>
<td>201739</td>
<td>Up to two prophylactic SI (25 cm H2O × 15 s) via CPAP</td>
<td>No PEEP during intubation for the control group, different devices and interfaces used between groups</td>
<td></td>
</tr>
<tr>
<td>Lista et al.</td>
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</tbody>
</table>

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. 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.46

Te Pas et al. 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.47

The multisite SLI (Sustained Lung Inflation) trial randomized infants between 25 and 28 weeks gestation who were randomized to receive up to two 15-s SIs or nasal CPAP, with subsequent resuscitation according to Neonatal Resuscitation Program guidelines. 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.48

Jiravisitkul et al. 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 SpO2 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.49

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.50 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 (SpO2) 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 SpO2 transition in extremely preterm infants, which in turn complicates efforts to determine the optimal approach to FiO2 titration after birth.

Dawson et al. published nomograms of SpO2 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. recorded serial SpO2 measurements in 102 preterm infants (median GA 29 weeks) who were stabilized using CPAP without supplemental O2 after birth. Infants in that study achieved reference values of SpO2 faster than the preterm infants in the study by Dawson et al. (who received no respiratory support). In contrast, Mian et al. found that rise in SpO2 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 SpO2 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 FiO2.55-56 However, a meta-analysis comprising RCTs conducted in preterm infants (<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.57 More recently, Oei et al. performed a meta-analysis restricted to RCTs comparing low (<0.3) vs high (≥0.6) FiO2 for resuscitation in infants born <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).58

The meta-analysis by Oei et al. included results from the TO2RPIDO 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% FiO2 group (22% vs 6%, P = 0.01).54 In an observational study, Rabi et al. studied 2326 infants <27 weeks GA born in Canada before and after local practice changed from initiating resuscitation with 100% FiO2 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 FiO2 (adjusted odds ratio 1.36, 95% CI 1.11 to 1.66). Results from both of these studies should be interpreted cautiously, owing to limitations from stopping early (the TO2RPIDO 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 FiO2 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 FiO2 concentration (21% to 30%) but acknowledged the need for more evidence.59 The ongoing PreSOX trial 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 FiO2 during delivery room stabilization**

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>GA</th>
<th>Initial FiO2</th>
<th>FiO2 titrated based on HR not SpO2</th>
<th>Secondary outcomes</th>
<th>Primary outcome</th>
<th>Secondary outcomes</th>
<th>Abbreviations</th>
</tr>
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<tr>
<td>Lundstrøm et al., 2005</td>
<td>70 infants &lt; 33 weeks</td>
<td>23–34 weeks</td>
<td>21% vs 80%</td>
<td>Cerebral blood flow (measured by xenon clearance) at FiO2 titrated based on HR not SpO2</td>
<td>No significant difference in survival between groups</td>
<td>Cerebral blood flow was significantly lower in 80% FiO2 group compared to 21% FiO2 group</td>
<td>No significant difference in survival between groups</td>
<td>BAL, bronchoalveolar lavage; BAP, biological antioxidant potential; BPD, bronchopulmonary dysplasia; BPM, beats per minute; FiO2, fraction of inspired oxygen; GA, gestational age; HOL, hour(s) of life; MOL, minute(s) of life; PMA, postmenstrual age; SpO2, oxygen saturation (pulse oximetry); TH, total hydroperoxide.</td>
</tr>
<tr>
<td>Haling et al., 2005</td>
<td>52 infants &lt; 31 weeks</td>
<td>23–34 weeks</td>
<td>21% vs 100%</td>
<td>Cytokine concentrations in BAL collected at 12 HOL: no significant differences</td>
<td>No significant differences in cytokine concentrations</td>
<td>No significant differences in cytokine concentrations</td>
<td>No significant differences in cytokine concentrations</td>
<td>BAL, bronchoalveolar lavage; BAP, biological antioxidant potential; BPD, bronchopulmonary dysplasia; BPM, beats per minute; FiO2, fraction of inspired oxygen; GA, gestational age; HOL, hour(s) of life; MOL, minute(s) of life; PMA, postmenstrual age; SpO2, oxygen saturation (pulse oximetry); TH, total hydroperoxide.</td>
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<tr>
<td>Wang et al., 2008</td>
<td>41 infants &lt; 33 weeks</td>
<td>23–34 weeks</td>
<td>21% vs 100%</td>
<td>SpO2 values during stabilization.</td>
<td>No significant differences in SpO2 values</td>
<td>No significant differences in SpO2 values</td>
<td>No significant differences in SpO2 values</td>
<td>BAL, bronchoalveolar lavage; BAP, biological antioxidant potential; BPD, bronchopulmonary dysplasia; BPM, beats per minute; FiO2, fraction of inspired oxygen; GA, gestational age; HOL, hour(s) of life; MOL, minute(s) of life; PMA, postmenstrual age; SpO2, oxygen saturation (pulse oximetry); TH, total hydroperoxide.</td>
</tr>
<tr>
<td>Rabi et al., 2011</td>
<td>103 infants &lt; 33 weeks</td>
<td>23–34 weeks</td>
<td>21% vs 100%</td>
<td>Improved oxidative balance ratio (serum (BAP/TH)) at 24 weeks PMA: no significant differences</td>
<td>No significant differences in oxidative balance ratio</td>
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<td>BAL, bronchoalveolar lavage; BAP, biological antioxidant potential; BPD, bronchopulmonary dysplasia; BPM, beats per minute; FiO2, fraction of inspired oxygen; GA, gestational age; HOL, hour(s) of life; MOL, minute(s) of life; PMA, postmenstrual age; SpO2, oxygen saturation (pulse oximetry); TH, total hydroperoxide.</td>
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**SURFACANT ADMINISTRATION AFTER STANDARD ENDOTRACHEAL INTUBATION**

Beginning in the 1980s, several high-quality RCTs assessed the safety and timing of surfactant administration in preterm infants. Early RCTs demonstrated that administration of surfactant to preterm infants 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). Subsequent studies found that prophylactic administration of surfactant soon after birth also reduced pulmonary morbidity and improved BPD-free survival. 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.

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. 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).

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). 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. 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). 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.

To maximize the potential benefits of early surfactant administration without undergoing prolonged mechanical ventilation, Victorin et al. 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. 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. 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 SURFACANT 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. Of these strategies, surfactant instillation via thin catheter, often referred to as LISA or minimally invasive surfactant administration (LISA), has been the most widely studied.

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>GA</th>
<th>Initial FiO2</th>
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invasive surfactant therapy, is the most studied. Verder et al. 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).
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)\textsuperscript{75–78} and one compared LISA to ongoing nasal CPAP therapy.\textsuperscript{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).\textsuperscript{80} Two meta-analyses inclusive of this RCT were recently reported.\textsuperscript{81,82}

Isayama et al.\textsuperscript{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.\textsuperscript{85} 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.\textsuperscript{84}

OTHER STRATEGIES

Intratracheal budesonide

Yeh et al.\textsuperscript{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\textsubscript{2} requirement) at 36 weeks (42% vs 66%, P < 0.001).\textsuperscript{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.\textsuperscript{85} Notably, the effect size of this trial is rather large (NNT, 4.1; 95% CI 2.8 to 7.8).\textsuperscript{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 caffeine or placebo within the first 10 days of life.\textsuperscript{86} Infants randomized to caffeine experienced significantly less BPD than placebo infants, which was largely attributed to the fact that caffeine-treated

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**Box 1** Summary of Evidence for Perinatal Interventions to Prevent BPD

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Evidence</th>
<th>Results</th>
<th>Treatment effect</th>
<th>Number needed to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous positive airway pressure (CPAP) vs mechanical ventilation</td>
<td>Evidence: Cochrane meta-analysis of 3 large RCTs (n = 2358) reporting outcome of BPD or death at 36 weeks PMA\textsuperscript{12}</td>
<td>Results: Primary CPAP therapy compared with mechanical ventilation reduced the risk of BPD/death.</td>
<td>Relative risk 0.63 (95% CI: 0.42 to 0.93)</td>
<td>15 (95% CI: 8 to 70)</td>
</tr>
<tr>
<td>Sustained inflation vs intermittent positive pressure ventilation or CPAP</td>
<td>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\textsuperscript{80}</td>
<td>Results: Neither Si or IPPV was superior to reduce the risk of BPD/death.</td>
<td>Relative risk 0.92 (95% CI: 0.66 to 1.29)</td>
<td>—</td>
</tr>
<tr>
<td>Supplemental oxygen during delivery room resuscitation</td>
<td>Evidence: Meta-analysis of 10 RCTs (n = 677 infants &lt; 32 weeks gestation) comparing low (&lt;30%) with high (≥60%) initial FiO\textsubscript{2} for delivery room resuscitation reporting outcome of BPD\textsuperscript{55}</td>
<td>Results: Neither approach to supplemental FiO\textsubscript{2} was superior to reduce the risk of BPD</td>
<td>Relative risk 0.88 (95% CI: 0.76 to 1.02)</td>
<td>—</td>
</tr>
<tr>
<td>Early (&lt; 2 h of life) vs Late (≥2 h of life) administration among infants receiving invasive mechanical ventilation</td>
<td>Evidence: Cochrane meta-analysis of 3 RCTs (n = 3050) reporting the outcome of BPD or death at 36 weeks PMA\textsuperscript{64}</td>
<td>Results: Early compared with late surfactant reduced the risk of BPD/death.</td>
<td>Relative risk 0.83 (95% CI: 0.75 to 0.91)</td>
<td>16 (95% CI: 11 to 34)</td>
</tr>
<tr>
<td>Less-invasive surfactant administration (LISA) vs all control therapies</td>
<td>Evidence: Meta-analysis of 5 RCTs (n = 857) reporting the outcome of BPD or death at 36 weeks PMA (Figure 2)</td>
<td>Results: LISA compared with control therapy reduced the risk of BPD/death.</td>
<td>Relative risk 0.74 (95% CI 0.58 to 0.94).</td>
<td>15 (95% CI 8 to 70)</td>
</tr>
<tr>
<td>Less-invasive surfactant administration (LISA) vs INSURE</td>
<td>Evidence: Meta-analysis of 3 RCTs (n = 426) reporting the outcome of BPD or death at 36 weeks PMA (Figure 2)</td>
<td>Results: LISA compared with INSURE reduced the risk of BPD/death.</td>
<td>Relative risk 0.63 (95% CI 0.42 to 0.93)</td>
<td>12 (95% CI 6 to 66)</td>
</tr>
</tbody>
</table>

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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. A meta-analysis comprising both cohort studies and RCT demonstrated that early caffeine administration was 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. Two small RCTs demonstrated that caffeine administration within the first minutes of life is feasible and may improve short-term physiological outcomes. Either 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