Initial Respiratory Support of Preterm Infants
The Role of CPAP, the INSURE Method, and Noninvasive Ventilation

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KEYWORDS

- Respiratory support
- Preterm infants
- CPAP
- Noninvasive ventilation

KEY POINTS

- Respiratory support of preterm infants is increasingly being achieved through noninvasive methods.
- Nasal continuous positive airway pressure (CPAP) is safe and is at least as effective as management via conventional mechanical ventilation.
- Nasal CPAP is associated with a decreased risk of developing chronic lung disease compared with conventional mechanical ventilation.
- An intubate, surfactant, and extubation (INSURE) strategy has been successfully applied both early and late in the course of respiratory distress syndrome.
- Techniques for administering exogenous surfactant while providing noninvasive respiratory support require further investigation.

INTRODUCTION

This article explores the potential benefits and risks for the various approaches to the initial respiratory management of preterm infants. The authors focus on the evidence for the increasingly used strategies of initial respiratory support of preterm infants with continuous positive airway pressure (CPAP) beginning in the delivery room (DR) or very early in the hospital course and blended strategies involving the early administration of surfactant replacement followed by immediate extubation and stabilization on CPAP. Where possible, the evidence referenced in this review comes from individual randomized controlled trials (RCTs) or meta-analyses of those trials.
HISTORICAL PERSPECTIVE

Based on the combined weight of multiple RCTs and their subsequent meta-analyses performed in the 1990s, surfactant was given as part of the initial resuscitation and management of preterm infants either at risk for or with evidence of respiratory distress syndrome (RDS). Available evidence led neonatologists to develop strong convictions that among infants who were intubated for respiratory distress, early surfactant administration was associated with decreased risk of pneumothorax (typical relative risk [RR] 0.63 [95% confidence interval (CI) 0.59–0.82]; typical risk difference [RD] -0.05 [95% CI -0.08 to -0.03]); decreased chronic lung disease (CLD) (typical RR 0.70 [95% CI 0.55–0.88]; typical RD -0.03 [95% CI -0.05 to -0.01]); and decreased mortality (typical RR 0.87 [95% CI 0.77–0.99]; typical RD -0.03 [95% CI -0.06 to -0.00]).

Intubation and surfactant administration immediately following birth was thought to be effective and lifesaving in infants thought to be at risk for RDS. On the weight of such sentiment, the proportion of infants receiving surfactant within 2 hours of life became a therapeutic goal, a standard endorsed by the National Quality Forum for infants born less than or equal to 29 weeks’ gestation.

However, as the adage goes, things change. Investigators began to more broadly examine the possibility of less-invasive respiratory support with the possibility of alternate approaches that potentially avoid deleterious outcomes of the accepted standards of care. An understanding that the physiology and the severity of illness of RDS were tied closely with the ability to establish a functional residual capacity (FRC) led to treatment involving the administration of continuous distending pressure in lieu of surfactant replacement. Both CPAP and surfactant replacement were seen as leading to the same final goal of establishing and maintaining FRC. As such, the spectrum of respiratory support given to preterm neonates continues to evolve and become increasingly complex.

DRAWBACKS OF THE CONVENTIONAL APPROACH

Despite the well-documented benefits of surfactant replacement therapy, there are several negative aspects related to the way surfactant is administered and the subsequent respiratory management that follows. The act of placing an endotracheal tube (ETT) is invasive and may be traumatic. Laryngoscopy and intratracheal intubation is often unsuccessful and may cause hypoxemia, bradycardia, increased cranial pressure, systemic and pulmonary hypertension, and airway trauma. In part to avoid these complications, the American Academy of Pediatrics has suggested that sedation be offered to all nonemergent intubations; however, this too may be associated with undesirable side effects, such as respiratory depression that could potentially interfere with spontaneous respiration. Surfactant replacement itself is associated with changes in cerebral blood flow, although the impact of these changes is not fully understood. Most relevant to this article, avoidance of mechanical ventilation use altogether may be the best way to avoid or reduce the risk of CLD from volutrauma and barotrauma. Additionally, animal data suggest that mechanical ventilation is associated with inflammatory lung injury. As such, reduction of mechanical ventilation by means of noninvasive ventilation has become the most accepted method by which to reduce ventilator-associated lung injury and CLD.

In 1987, a game-changing report by Avery and colleagues suggested that one center’s less-invasive approach, namely stabilization with nasal CPAP from birth in preterm infants with respiratory distress, was associated with a decreased risk of CLD when compared with 7 other centers that relied on conventional mechanical ventilator management. In 2001, Van Marter and colleagues noted similar protective
findings of CPAP against the development of CLD when compared with conventional ventilator stabilization. Surfactant administration and antenatal corticosteroids are thought to be synergistic, and this report was notable in that it occurred in a period that had high rates of maternal antenatal steroids and surfactant administration. Although observational in design, these studies demonstrated that CPAP may be associated with improved outcomes over surfactant administration even in infants who had the benefits of antenatal steroids and created a need for RCTs to address whether or not preterm infants at risk for surfactant deficiency could be safely managed on CPAP alone.

Linder and colleagues published a retrospective cohort study following the outcomes of extremely low birth weight (ELBW) infants at a single center during a period when the local DR policy changed from one of immediate intubation of any infant at risk to transitional support with a bag and mask and stabilization on CPAP, saving intubation only for infants who did not transition to spontaneous breathing. They noted that by providing an individualized intubation strategy, even in ELBW infants, 25% of these smallest infants were never intubated.

CPAP INTERFACES

CPAP has been successfully administered through a variety of methods. Although first administered for the treatment of RDS via ETT, and later via only one naris through a modified ETT or single nasal prong, other superior interfaces have been developed and adopted. The most common interfaces in use today typically involve a nose mask or, more commonly, short bilateral nasal prongs. Distending pressure is generated either by simply placing the distal end of a CPAP circuit under a known depth of water (bubble CPAP), connecting it to a ventilator (ventilator CPAP), or to a variable-flow nasal continuous positive airway pressure (nCPAP) device (infant flow driver). Each method has its theoretic advantages and proponents. One RCT comparing variable-flow with constant-flow CPAP and one RCT comparing variable-flow to bubble CPAP to a variable-flow device failed to show any significant difference in rates of extubation failure.

CPAP BENEFITS

It is thought that CPAP assists the breathing of preterm infants in several ways. CPAP stents open the airways of preterm infants, which are characterized by their poor muscle tone and compliant structure. This effect reduces obstructive events that may translate to less apnea and less atelectasis. Animal models have demonstrated that CPAP causes a mechanical strain that is associated with accelerated lung protein accretion, lung growth, elastic recoil, and ultimately improved remodeling of lung parenchyma.

If CPAP is successfully applied and intubation is avoided, less trauma to the airway will occur as a result of laryngoscopy, intubation, and from an ETT that is left in place chronically. Early CPAP alone will prevent progression to respiratory failure in many spontaneously breathing preterm infants and in combination with antenatal steroids, the number of infants without clinical symptoms of RDS is further decreased.

CPAP DRAWBACKS

Pragmatically there are few problems with CPAP, mostly directly related to the CPAP interface. Given that the goal of CPAP is to provide continuous distending pressure that extends from the interface through the nasopharynx and the proximal airway
and transmitted to the distal airways and alveoli, a tight seal must be maintained throughout. Leakage and the resultant pressure loss may occur at many points: from the CPAP system itself, out the mouth, or at the nasal interface. Chin straps may be used to ensure that the mouth stays shut and may reduce mouth leak.\textsuperscript{18} It is vital that caregivers at the bedside ensure that there is a tight seal in the nares. Efforts to maintain the required tight seal, incorrect positioning, or poorly sized nasal prongs can cause serious injury to the inside of the nose and the columella. Constant caregiver vigilance toward developmentally appropriate positioning is vital for the success of nasal CPAP.

**CPAP IN THE DR**

Following the promising results of these early observational studies, several RCTs have been performed to address the question of whether the conventional approach of intubation and subsequent mechanical ventilation versus nasal CPAP is the superior approach for initial stabilization of the preterm infant at risk for developing RDS. The details of these studies are discussed later.

In 2004, Finer and colleagues\textsuperscript{19} reported the results of their feasibility study that examined whether initiating mask CPAP using a T-piece resuscitator in the DR and continuing CPAP therapy via nasal CPAP once in the neonatal intensive care unit (NICU), without intubation for surfactant, was possible in a population of 104 ELBW infants. Despite the intention to avoid intubation in the DR for the purpose of surfactant administration, 27 infants randomized to the DR CPAP arm were intubated as part of their initial resuscitation. After admission to the NICU, all nonintubated infants were placed on CPAP and were to be intubated for surfactant administration only after they met a prespecified definition of hypoxia or respiratory distress. Of the infants initially randomized to stabilization on CPAP, 16 more were subsequently intubated in the NICU by the seventh day of life. Overall, 80% of the studied infants required intubation within the first 7 days of life. This early study was illustrative for several reasons. It showed that trials of CPAP in the DR are feasible and that greater than 90% of the infants in the study received the DR intervention to which they were randomized. It also demonstrated that there are at least 3 circumstances that ultimately lead to intubation: prophylactically for the purpose of surfactant administration (independent of respiratory status), as part of the initial DR resuscitation, and finally as later rescue for infants initially stabilized on CPAP.

Ammari and colleagues\textsuperscript{20} made similar observations. They followed a cohort of consecutively born infants with a birthweight less than or equal to 1250 g and noted that they could be divided into 3 groups (termed ventilator-started, CPAP-failure, and CPAP-success) based on their initial respiratory support modality and whether CPAP was able to be continued at 72 hours of age. They noted that CPAP in the DR was progressively less successful in more preterm, smaller infants; about a third of the infants born 23 to 25 weeks’ gestation or weighing less than 700 g needed to be intubated as part of their initial resuscitation and about 40% of these infants failed CPAP and required increased support by 72 hours of life.

These observations are important to keep in mind when evaluating the studies of initial respiratory support of preterm infants with CPAP beginning in the DR and the blended strategies of surfactant replacement with subsequent stabilization on CPAP. To understand the results and outcomes of the various trials discussed later, it is important to view their eligibility criteria through the prism that separates out the infants based on whether or not they needed intubation as initial respiratory support. The trials discussed later are characterized accordingly as those that enrolled
only infants who had successfully transitioned but had mild to moderate respiratory insufficiency (infants successfully transitioned [ie, not requiring intubation as part of initial resuscitation]) and those that enrolled all infants at high risk for respiratory distress regardless of their initial stabilization.

EARLY CPAP VERSUS STANDARD CARE (INTUBATION IN DR AND MECHANICAL VENTILATION)

There are 3 large trials that examine the strategy of initial stabilization on nasal CPAP versus conventional management of intubation and surfactant administration in preterm infants (Table 1).

The CPAP Or nasal INtubation at birth (COIN) trial was a large RCT that compared CPAP versus early intubation among 610 preterm infants born between 25 + 0 and 28 + 6 weeks’ gestation. Only infants who exhibited some degree of respiratory distress but were spontaneously breathing at 5 minutes of life were eligible. In essence, the most well and most ill infants were excluded; infants were ineligible if they required intubation by 5 minutes of life or if they did not require any type of respiratory support or supplemental oxygen. Among the infants randomized to receive CPAP, single or binasal prongs delivered 8 cm of H2O pressure. Infants randomized to the nCPAP group were intubated if they had severe apnea, hypoxia (fraction of inspired oxygen [FIO2] >0.6), or severe respiratory acidosis. The protocol did not specify that the infants randomized to intubation be given surfactant and there were no discrete extubation criteria. There was no difference between the CPAP group and the intubation group in the primary outcome, death, or oxygen treatment at 36 weeks’ postmenstrual age (unadjusted odds ratio [OR] 0.80 [95% CI 0.58–1.12]). As expected, the CPAP group used significantly less surfactant and spent less time on mechanical ventilation. The CPAP group required less postnatal steroids for CLD. Of concern, the group of infants stabilized on CPAP also had significantly more pneumothoraces (9.1% vs 3.0%). This difference is especially notable given that among the intubated infants, only 77% received surfactant (typically as part of a less successful late-rescue strategy), which has been documented to reduce the incidence of all air leaks.

The Surfactant Positive Pressure and Oxygen Randomized Trial (SUPPORT) was a large trial sponsored by the National Institute of Child Health and Human Development that compared stabilization on CPAP with early surfactant therapy following intubation and mechanical ventilation according to the Neonatal Resuscitation Program’s guidelines. This comparison was one part of a 2 × 2 factorial design that also assigned infants 1 of 2 oxygenation saturation target ranges. The SUPPORT trial enrolled 1316 infants between 24 + 0 and 27 + 6 weeks’ gestation. In contrast to the COIN trial, infants were randomized before delivery to eliminate the entry requirement that infants need to be spontaneously breathing. This trial also benefitted by having clear criteria to address both the intubation of infants initially stabilized on CPAP and the extubation of infants initially stabilized following surfactant administration and mechanically ventilated. CPAP was initiated early, in the DR if required, at 5 cm H2O and could be provided with any CPAP device. The investigators reported no difference in the primary outcome of mortality or CLD (OR 0.95 [95% CI 0.85–1.05]). In keeping with the findings of the COIN trial, infants randomized to CPAP in the delivery room received less surfactant, spent less time on mechanical ventilation, and received less postnatal steroids. The increased rate of pneumothorax observed in the COIN trial was not noted, perhaps because of a lower initial CPAP pressure or possibly because of a lower threshold for designating CPAP failure. Antenatal steroid
<table>
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<th>Author, Year</th>
<th>n</th>
<th>Gest Age</th>
<th>Comparison</th>
<th>Status in DR</th>
<th>Primary Outcome</th>
<th>Results of Primary Outcome</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Morley et al, 2008</td>
<td>610</td>
<td>25–28 + 6</td>
<td>CPAP in DR vs STD care</td>
<td>Mild-mod resp distress</td>
<td>CLD @ 36 wk or</td>
<td>OR 0.80 (95% CI 0.58–1.12)</td>
<td>CPAP group spent less time on mechanical vent, less postnatal steroids</td>
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<td>Spontaneously breathing</td>
<td>mortality</td>
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<td>9.1% vs 3.0% PTX rate in CPAP group vs STD care</td>
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<td></td>
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<td>Only 77% of intubated infants received surfactant</td>
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<td>CPAP failure threshold high (FIO2 &gt; 0.6)</td>
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<td>Initial CPAP at 8 cm H2O</td>
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<tr>
<td>Finer et al, 2010</td>
<td>1316</td>
<td>24–27 + 6</td>
<td>CPAP in DR vs STD care</td>
<td>All comers independent of</td>
<td>CLD @ 36 wk or</td>
<td>OR 0.95 (95% CI 0.85–1.05)</td>
<td>High antenatal steroids rates</td>
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<td>respiratory status</td>
<td>mortality</td>
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<td>CPAP group spent less time on ventilator, received less postnatal steroids</td>
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<td>One part of a 2 x 2 factorial design also investigation 2 oxygenation saturation target ranges</td>
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<td>Dunn et al, 2011</td>
<td>648</td>
<td>26–29 + 6</td>
<td>CPAP in DR vs STD care</td>
<td>All comers independent of</td>
<td>CLD @ 36 wk or</td>
<td>RR 0.83 (95% CI 0.64–1.09)</td>
<td>High antenatal steroids rates</td>
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<td>respiratory status</td>
<td>mortality</td>
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<td>48% in CPAP group were never intubated</td>
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<td>Third comparison group received INSURE</td>
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Abbreviations: CI, confidence interval; CLD, chronic lung disease; CPAP, continuous positive airway pressure; DR, delivery room; FIO2, fraction of inspired oxygen; Gest, gestational; INSURE, intubate, surfactant, and extubation; mod, moderate; OR, odds ratio; PTX, pneumothorax; resp, respiratory; RR, relative risk; STD, standard.
administration in both groups was high (>96%). However, these high antenatal steroid rates are much higher than what is typically achievable, drawing concern that the results might not be generalizable to real-world scenarios in which the benefits of antenatal steroids were not administered.24 Despite these limitations, the investigators of the SUPPORT trial concluded that CPAP in the DR could be considered as an alternate path for consideration in the management of even quite preterm ELBW infants.

The Vermont Oxford Network Delivery Room Management trial (VON DRM) also compared early stabilization on CPAP versus intubation, prophylactic surfactant, and mechanical ventilation.25 However, a third arm of infants was also included that was intubated, given prophylactic surfactant, and rapidly extubated to CPAP (details of this third arm are discussed later.) The VON DRM trial included 648 infants born between 26 + 0 and 29 + 6 weeks’ gestation. Enrollment was stopped early because of declining enrollment rates before the goal sample size was reached. Similar to the SUPPORT trial, the VON DRM featured randomization before delivery and excluded no infants based on their need for immediate intubation secondary to inadequate initial respiratory drive. Accordingly, the antenatal steroid administration rate in this trial was also very high. There was no difference between the primary outcome of mortality or CLD at 36 weeks’ postmenstrual age between the CPAP group and those treated with conventional management (RR 0.83 [95% CI 0.64–1.09]). Additionally, there were no statistically significant differences in mortality or other complications of prematurity.

The findings from these 3 studies are remarkably consistent. Although entry criteria and indications for intubation and surfactant administration were different, no single trial was able to demonstrate a statistically significant difference in the risk of death or CLD when infants were managed initially with CPAP. A recent Cochrane systematic review of prophylactic versus selective use of surfactant by Rojas-Reyes and colleagues26 contained a subgroup that specified that CPAP be used to stabilize infants in the selective-surfactant-use arm. This report included the SUPPORT trial and the comparison arm detailed in the VON DRM trial comparing prophylactic surfactant and subsequent standard care with DR CPAP. The COIN trial was not included because infants at risk in the standard-care arm did not routinely receive prophylactic surfactant. A meta-analysis of these two studies demonstrated a compelling trend toward an increase in the risk of neonatal mortality or CLD associated with the use prophylactic surfactant when compared with early stabilization on CPAP with selective use of surfactant (n = 1744) (typical RR 1.12 [95% CI 1.02–1.24], typical RD 0.06 [95% CI 0.01–0.10]). The investigators concluded that routine stabilization on CPAP was associated with less risk of CLD or death when compared with prophylactic surfactant administration.

A COMBINED STRATEGY: INTUBATE, SURFACTANT, AND EXTUBATION

From the results of the COIN, SUPPORT, and VON DRM trials as well as the Rojas-Reyes meta-analysis, it is clear that initial stabilization on CPAP and provision of rescue surfactant only when necessary is at least as beneficial and quite possibly preferred over the standard therapy of intubation of all infants at risk in the DR and subsequent support with mechanical ventilation. However, the optimal respiratory care of newborns with RDS may involve yet another choice. Because mechanical ventilation before surfactant administration has been associated with decreased dynamic compliance, bronchiolar injury, and less therapeutic benefit,27–29 an approach that combines the benefits of surfactant administration and the benefits of early CPAP but without the drawbacks associated with mechanical ventilation has great intellectual appeal. Described by Verder and colleagues30 in 1992 at a Danish
hospital that routinely stabilized infants on CPAP, this novel approach has been named INSURE (intubate, surfactant, extubate). Linked to the core concept of INSURE are the observations that a single dose of surfactant was enough to reverse RDS in most cases and that administering surfactant treatment to infants earlier in the course of their disease is more desirable.

In Verder and colleague’s initial trial, the infants had severe distress on CPAP and were treated with surfactant at a mean age of 19 hours of life. This same Scandinavian group went on to perform 2 additional unblinded studies in the 1990s, enrolling infants born at less than 30 weeks’ gestation and stabilized on CPAP. When the infants exhibited signs of RDS, they were randomized to intubation, surfactant administration, and rapid extubation to CPAP or to continued CPAP with rescue surfactant only if needed as evidenced by clinical deterioration. The results were encouraging; the investigators noted a decreased need for repeat dosing of surfactant, oxygen requirement, and subsequent mechanical ventilation in the earlier-treated infants.

The INSURE method has been reported in several different contexts and compared with existing respiratory support strategies. The INSURE method has been evaluated in the DR or shortly after birth (within 1 hour) as the method of initial stabilization and has also been used later in the course of illness to treat established RDS in spontaneously breathing preterm infants already on nasal CPAP. For the purpose of this discussion, the authors refer to INSURE used as the initial stabilization in the DR or during the initial hour of life as early INSURE and refer to INSURE used later in the course of established RDS as late INSURE. Both early and late INSURE strategies have been compared with the conventional standard approach of intubation, surfactant administration, and continued mechanical ventilation and compared with continued nasal CPAP.

**EARLY INSURE VERSUS EARLY CPAP AS INITIAL STABILIZATION**

Given that previous studies supported the concept that in preterm infants at risk of RDS prophylactic surfactant was more effective than rescue surfactant, An International Randomized Controlled Trial to Evaluate the Efficacy of Combining Prophylactic Surfactant and Early Nasal Continuous Positive Airway Pressure in Very Preterm Infants (CURPAP) trial was designed to evaluate early CPAP in the DR and early rescue surfactant for CPAP failures versus brief initial intubation, surfactant administration, and extubation to CPAP by 1 hour of life (INSURE) (Table 2). CPAP failure was defined as requiring a FIO2 greater than 0.4, severe apnea requiring bag and mask intervention twice per hour, pH less than 7.2, or PCO2 greater than 65 mm Hg. Infants that were intubated for insufficient initial respiratory drive or as part of resuscitation were excluded, similar to the COIN exclusion criteria. Unlike the COIN trial, infants intubated and given surfactant initially were extubated back to CPAP at 1 hour of life (INSURE) if satisfactory respiratory drive was present. Two hundred eight infants born between 25 + 0 and 28 + 6 weeks’ gestation were enrolled. Unfortunately, this trial did not clarify which approach was superior. Thirty-one percent of infants in the INSURE group needed mechanical ventilation in the first 5 days compared with 33% in the CPAP group (RR 0.95 [95% CI 0.64–1.41]). Almost half (49%) of the infants in the CPAP group ultimately needed rescue surfactant. No statistically significant differences in the primary outcome, need for mechanical ventilation during the first 5 days of life, were reported (RR 0.95 [95% CI 0.64–1.41]). Additionally, no significant differences in mortality, steroid use, or any measure of CLD were reported. Of note, the incidence of pneumothorax was similar between the two groups and much lower than that reported in the COIN trial. Postulated reasons for the lack of effect include that the INSURE group received preintubation sedation, high antenatal
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<th>Author, Year</th>
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<th>Gest Age</th>
<th>Comparison</th>
<th>Status at Enrollment</th>
<th>Primary Outcome</th>
<th>Results of Primary Outcome</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Sandri et al, 2010</td>
<td>208</td>
<td>25–28 + 6</td>
<td>Early CPAP (and rescue surfactant if needed) vs INSURE</td>
<td>Spontaneous breathing (intubated infants excluded)</td>
<td>Mechanical ventilation within the first 5 d of life</td>
<td>RR 0.95 (95% CI 0.64–1.41)</td>
<td>No difference in mortality, CLD, or any other outcomes. 50% of infants 25–28 wk managed without intubation.</td>
</tr>
<tr>
<td>Dunn et al, 2011</td>
<td>648</td>
<td>26–29 + 6</td>
<td>Early CPAP vs INSURE</td>
<td>All comers independent of respiratory status</td>
<td></td>
<td>45% of infants in CPAP group intubated. 51% of infants in INSURE group intubated. No difference in mortality, CLD, or other outcomes.</td>
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<tr>
<td>Rojas et al, 2009</td>
<td>279</td>
<td>27–31 + 6</td>
<td>Early CPAP vs INSURE</td>
<td>Spontaneously breathing on CPAP between 15–60 min of life</td>
<td>Subsequent mechanical ventilation</td>
<td>RR 0.69 (0.49–0.97)</td>
<td>Less pneumothorax in INSURE group. Trend toward less CLD (RR 0.84 [95% CI 0.66–1.05]). Slightly larger, more mature infants.</td>
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**Abbreviations:** CI, confidence interval; CLD, chronic lung disease; CPAP, continuous positive airway pressure; Gest, gestational; INSURE, intubate, surfactant, and extubation; RR, relative risk.
steroid rates, and earlier rescue surfactant administration. The CURPAP trial median rescue surfactant administration time was 4.0 hours compared with 6.6 hours in the COIN trial. The investigators did demonstrate that using these strategies, greater than 50% of infants between 25 and 28 weeks' gestation could be managed without intubation.

The multicenter VON DRM trial discussed in the previous section on stabilization on nCPAP also included an INSURE arm in which infants were intubated, given prophylactic surfactant, and rapidly extubated to CPAP.25 Termed ISX in this study (for intubation, surfactant, extubation), these infants were compared with infants who were intubated, given prophylactic surfactant, and maintained on mechanical ventilation. (Comparison of early stabilization on CPAP vs intubation, prophylactic surfactant, and mechanical ventilation is discussed earlier.) Infants between 26 + 0 and 29 + 6 weeks' gestation were included in this study. Unlike the COIN and CURPAP studies, this trial did not exclude infants based on their need for immediate intubation secondary to inadequate initial respiratory drive during initial resuscitation. Similar to the SUPPORT trial, antenatal steroid administration was nearly universal. The INSURE (ISX) group was intubated 5 to 15 minutes after birth, administered surfactant, and extubated to CPAP 15 to 30 minutes later if their FiO2 was less than 0.6 without severe respiratory distress or apnea. The early CPAP arm had CPAP applied within 15 minutes of birth and was rescued (intubated for surfactant administration) only for severe apnea, Pco2 greater than 65 mm Hg, or FiO2 greater than 0.4. In keeping with the findings of the CURPAP trial, almost half (51% in the INSURE group and 45% in the CPAP group) required intubation during the first week of life, and the rates of pneumothoraces in both groups were much lower than those in the COIN trial. However, this study also failed to demonstrate any difference in the primary outcome of death or CLD at 36 weeks' postmenstrual age between the 3 groups.

Rojas and colleagues performed a trial that examined the INSURE method in slightly larger infants. Rojas and colleagues34 enrolled 279 infants from 8 centers in Columbia. Infants between 27 + 0 and 31 + 6 weeks' gestation (mean 29 weeks and 1300 g) were eligible if they had evidence of RDS and were spontaneously breathing on nasal CPAP between 15 and 60 minutes of life. The infants were randomized to continued nasal CPAP or to brief intubation, surfactant administration, and extubation to CPAP (INSURE). The primary outcome was the need for subsequent mechanical ventilation using predefined criteria. All of the infants in the INSURE group were successfully extubated to CPAP. The need for intubation and mechanical ventilation was lower in the INSURE group compared with the CPAP group (26% vs 39%). Pneumothorax was noted less frequently in the INSURE group compared with the CPAP group (2% vs 9%). The percentage of patients receiving surfactant after the first hour of life was also significantly less in the INSURE group compared with the CPAP group (12% vs 26%). Importantly, the incidence of CLD at 36 weeks' postmenstrual age was high in both groups: 49% in the INSURE group compared with 59% in the CPAP group (RR: 0.84 [95% CI 0.66–1.05]).

**EARLY INSURE VERSUS STANDARD CARE (INTUBATION IN DR AND MECHANICAL VENTILATION)**

Little data are available that directly compare the INSURE method to the more conventional approach of intubation, prophylactic surfactant administration, and continued mechanical ventilation (Table 3). This lack of data may be partly caused by the observation that centers implementing INSURE strategies are heavily invested in CPAP as
### Table 3
**Early INSURE versus standard care (intubation in DR and mechanical ventilation)**

<table>
<thead>
<tr>
<th>Author, Year</th>
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<th>Gest Age</th>
<th>Comparison</th>
<th>Primary Outcome</th>
<th>Results of Primary Outcome</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Tooley et al, 2003</td>
<td>42</td>
<td>25–28 + 6</td>
<td>INSURE vs intubation in DR and mechanical ventilation</td>
<td>Need for mechanical ventilation at 1 h of life</td>
<td>Mechanical ventilation at 1 h of life: CPAP group 62% Standard group 100% ($P = .0034$)</td>
<td>All infants intubated in DR, received surfactant, and caffeine None of STD group intubated by 6 h of life 47% of INSURE infants never needed mechanical ventilation No difference in CLD or mortality</td>
</tr>
<tr>
<td>Dunn et al, 2011</td>
<td>1316</td>
<td>24–27 + 6</td>
<td>INSURE vs intubation in DR and mechanical ventilation</td>
<td>CLD @ 36 wk or mortality</td>
<td>RR 0.78 (95% CI 0.59–1.03)</td>
<td>High antenatal steroids rates INSURE group extubated by 6 h of life Third arm of this study on CPAP</td>
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</table>

*Abbreviations:* CI, confidence interval; CLD, chronic lung disease; CPAP, continuous positive airway pressure; DR, delivery room; Gest, gestational; INSURE, intubate, surfactant, and extubation; RR, relative risk; STD, standard.
primary stabilization and have lost equipoise toward continued management on mechanical ventilation.

Tooley and Dyke performed a pilot RCT that enrolled 42 infants born between 25 + 0 and 28 + 6 weeks’ gestation. All infants in the study were electively intubated at delivery, received one dose of prophylactic surfactant, and a loading dose of caffeine. Infants randomized to the standard therapy arm were managed on conventional ventilation and weaned toward extubation using a predefined guideline. These infants were also routinely given morphine as an analgesic. Infants randomized to an INSURE strategy were extubated to CPAP following surfactant administration within 1 hour of birth. Strict criteria for increasing CPAP support and CPAP failure (FiO₂ > 0.70, pH < 7.2, hypoxia, and significant apnea) were followed. However, the treatment of CPAP failures with rescue surfactant or repeat dosing surfactant for the standard group was not part of the study protocol. The primary outcome in this study was the need for continued mechanical ventilation after 1 hour from birth for the INSURE group versus 6 hours of life for the standard care group. Of the infants who were extubated to CPAP by 1 hour of life, 47% never required reintubation. None of the infants in the standard therapy group were extubated within 6 hours from birth. This study was limited by its small sample size and failed to show any difference in outcomes of interest (CLD at 36 weeks or mortality); however, it did confirm that a significant number of preterm infants treated with the INSURE strategy can be successfully extubated and avoid continued ventilation.

The 3-armed VON DRM trial contained the comparison of intubation, prophylactic surfactant, and mechanical ventilation (standard care) versus an early INSURE strategy. This trial is described in detail earlier. The INSURE (ISX) group was intubated 5 to 15 minutes after birth, administered surfactant, and extubated to CPAP 15 to 30 minutes later if their FiO₂ was less than 0.6 without severe respiratory distress or apnea. The standard-care group was eligible for extubation at 6 hours of age and had prespecified criteria for surfactant redosing; however, subsequent ventilator management, including the decision to extubate to CPAP, was left to the discretion of the clinical team. This trial ended enrollment before reaching the goal sample size and was not able to differentiate the superior strategy. The RR of CLD or death was 0.78 (95% CI 0.59–1.03) for the INSURE group compared with the group receiving the standard traditional approach of intubation, surfactant administration, and continued mechanical ventilation.

The REVE (REduction of VEntilation) trial is a French RCT that is currently unpublished but has been presented in abstract form. It compared early CPAP use after prophylactic surfactant administration (INSURE) with prophylactic surfactant followed by mechanical ventilation in 133 infants born at 25 to 27 weeks’ gestation with mild respiratory distress. All infants received caffeine, and antenatal steroid use was very high. The full results are not available; however, the investigators concluded that the INSURE method of intubation with early surfactant administration followed by CPAP mostly benefits infants who are 25 to 26 weeks’ gestational age.

**LATE INSURE**

The earliest studies of the INSURE method did not test INSURE as part of the initial stabilization of high-risk infants but rather as rescue treatment for spontaneously breathing infants managed on CPAP with already established RDS. Verder and colleagues studies demonstrated that infants who were rescued with the INSURE strategy were less likely to need continued mechanical ventilation and that this effect was more pronounced if the treatment was applied earlier in the course of the disease,
before the oxygen requirement increases to approximately FiO2 0.4.\textsuperscript{31,32} Several studies have followed comparing the INSURE procedure used later (>1 hours of life) as part of a rescue strategy for spontaneously breathing preterm infants with RDS on CPAP, to both the standard management of late rescue surfactant therapy and continued mechanical ventilation or to continued management on nasal CPAP without INSURE intervention. These studies are discussed later.

**LATE INSURE VERSUS STANDARD CARE (RESCUE SURFACTANT AND MECHANICAL VENTILATION)**

There are relatively few published reports comparing the use of the INSURE method later (>1 hour of life) in the course of established RDS to the standard approach of intubation, surfactant administration, and subsequent mechanical ventilation (Table 4). Each is discussed in detail next.

The VON has presented the results of a multicenter study randomizing 267 larger spontaneously breathing preterm infants (birth weight 1501–2500 g) with established RDS between 2 and 24 hours of life to either early intubation, surfactant treatment, and rapid extubation (INSURE) or standard respiratory management, including intubation and surfactant treatment based on predefined clinical indications.\textsuperscript{37} This study has been presented in abstract form. A nonsignificant trend toward favoring the INSURE strategy for the primary outcome measure of the need for mechanical ventilation in the first week of life (RR 0.78 [95% CI 0.59–1.03]) was observed, a finding in keeping with Verder’s work.

A report from a single center in Italy by Dani and colleagues\textsuperscript{38} enrolled 27 infants born at less than 30 weeks’ gestation with established RDS. Infants were eligible if they were on CPAP and were breathing spontaneously, displayed evidence of respiratory distress, and had an FiO2 requirement of greater than 0.3. All enrolled patients were intubated for surfactant treatment, although infants in the INSURE arm received surfactant earlier than those randomized to standard management (mean 2.7 hours vs 3.5 hours, $P = .18$). Infants randomized to an INSURE strategy were extubated shortly after surfactant administration. At 7 days of life, none of the patients in the INSURE group were on a ventilator compared with 43% of those infants randomized to continued mechanical ventilation ($P = .026$). A second dose of surfactant was needed less frequently in the INSURE group compared with the infants randomized to surfactant followed by mechanical ventilation. Additionally, the duration on mechanical ventilation, on CPAP, and on any supplemental oxygen was statistically significantly shorter among infants treated with the INSURE early extubation strategy.

**LATE INSURE VERSUS CONTINUED CPAP**

As previously noted, the first RCT of the INSURE method was Verder and colleagues\textsuperscript{32} 1994 study performed in Scandinavia (Table 5). They enrolled 73 preterm infants (25–35 weeks’ gestational age) with moderate to severe distress on CPAP to either INSURE or to continued CPAP. Eligible infants already on CPAP with established RDS had to be at least 2 hours of age. The median time of randomization was 12 hours. The INSURE treatment was considered to have failed if extubation was not possible within 1 hour of the surfactant instillation or if rescue reintubation was required within 5 days. Indications for rescue intubation, mechanical ventilation, and surfactant were available to both groups via standardized guidelines and based on an oxygen-tension ratio of less than 0.15 or severe apnea. As previously noted, the need for subsequent mechanical ventilation was reduced with the INSURE
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>n</th>
<th>Population</th>
<th>Comparison</th>
<th>Status at Enrollment</th>
<th>Primary Outcome</th>
<th>Results of Primary Outcome</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soll et al, 37 2003</td>
<td>267</td>
<td>Birth weight 1501–2500 g</td>
<td>Late INSURE vs STD care</td>
<td>2–24 h old with established RDS</td>
<td>Need for mechanical ventilation in first week of life</td>
<td>RR 0.78 (95% CI 0.59–1.03)</td>
<td>Larger infants Not published, presented in abstract form</td>
</tr>
<tr>
<td>Dani et al, 38 2004</td>
<td>27</td>
<td>&lt;30 wk gestation</td>
<td>Late INSURE vs STD care</td>
<td>Breathing spontaneously on CPAP, with evidence of RDS</td>
<td>Need for mechanical ventilation in first week of life</td>
<td>INSURE 0% Standard care 43% ($P = .026$)</td>
<td>INSURE infants received surfactant sooner (2.7 vs 3.5 h of life) Duration of mechanical ventilation, CPAP, O$_2$ use less among INSURE infants</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; CPAP, continuous positive airway pressure; INSURE, intubate, surfactant, and extubation; RDS, respiratory distress syndrome; RR, relative risk; STD, standard.
### Table 5
Late INSURE versus continued CPAP

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>n</th>
<th>Gest Age</th>
<th>Comparison</th>
<th>Status at Enrollment</th>
<th>Primary Outcome</th>
<th>Results of Primary Outcome</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verder et al, 1994</td>
<td>73</td>
<td>25–35</td>
<td>Late INSURE vs continued CPAP</td>
<td>At least 2 h old with a/A gradient &lt;0.22</td>
<td>Need for mechanical ventilation</td>
<td>Late INSURE 43% Continued CPAP 85% ($P = .003$)</td>
<td>No difference in rate of CLD or mortality Median time of randomization ~12 h</td>
</tr>
<tr>
<td>Reininger et al, 2005</td>
<td>105</td>
<td>29–35</td>
<td>Late INSURE vs continued CPAP</td>
<td>At least 30 min old on CPAP with O$_2$ requirement</td>
<td>Need for mechanical ventilation</td>
<td>Late INSURE 50% Continued CPAP 70% ($P = .04$)</td>
<td>Median enrollment at 6.5 h (range: 1.6–49 h) Larger, more mature infants Blinded study involving sham treatment No differences in CLD or mortality</td>
</tr>
</tbody>
</table>

*Abbreviations: a/A, alveolar-arterial; CLD, chronic lung disease; CPAP, continuous positive airway pressure; Gest, gestational; INSURE, intubate, surfactant, and extubation.*
treatment (85% vs 43%, \( P = .003 \)). No significant differences in the rate of pneumothorax, mortality, or CLD were reported.

One additional study, reported by Reininger and colleagues,\(^{39}\) examined the INSURE strategy used later (>1 hour of life) compared with continued CPAP in 105 larger infants (29 and 35 weeks’ gestational age). Infants were eligible if they had established RDS, were stabilized on CPAP with an oxygen requirement, and were at least 30 minutes old. Infants were randomized typically at 6.5 hours; however, they ranged in age between 1.6 and 49.0 hours. Unlike many of the other studies of the INSURE method, this trial was blinded. Blinding was facilitated using privacy screens placed around the infants. A study team not involved in that infant’s daily care administered surfactant to infants randomized to the INSURE strategy and these infants were extubated to CPAP while still behind the privacy screen. Infants randomized to continued CPAP were not intubated nor received any placebo but were cared for in the interim behind the privacy screen for approximately 15 minutes. Uniform criteria for rescue mechanical ventilation and surfactant administration were used to manage both groups. Similar to Verder and colleagues’ study, infants treated with the INSURE method were less likely to need subsequent mechanical ventilation (70% in CPAP-only group vs 50% in INSURE group), were less likely to need subsequent surfactant, and had lower oxygen needs. There were no significant differences in the rate of pneumothorax, CLD, or mortality.

**OTHER STUDIES FEATURING INSURE**

The Texas Neonatal Research Group performed a multicenter trial that enrolled 132 larger (birth weight >1250 g) preterm (<36 weeks’ gestation) infants with RDS between 4 and 24 hours of life.\(^{40}\) Unlike the previously discussed studies, infants were not required to be routinely stabilized on CPAP before the intervention, although approximately two-thirds in each group were managed in this fashion. Infants randomized to the INSURE arm were intubated and extubated unless the \( F_{IO_2} \) was higher than before intubation. These infants were also not required to be extubated to CPAP following the INSURE treatment. Infants randomized to the standard arm had no prespecified treatment but could receive rescue surfactant and/or CPAP per the hospitals’ routine guidelines. INSURE-treated infants were less likely to require subsequent mechanical ventilation for worsening respiratory disease (RR 0.60 [95% CI 0.37–0.99]) but actually had a higher median duration of mechanical ventilation (2.2 vs 0 hours) because only 29 out of 67 control infants required mechanical ventilation. There were no differences in any other outcome of interest (duration of CPAP, duration of supplemental oxygen, pneumothorax, or mortality). CLD was not reported, but discharge on home oxygen was not different between the groups. The investigators concluded that the INSURE method among these larger preterm infants (>1250 g) with mild to moderate RDS is not recommended. However, the omission of CPAP for functional residual capacity (FRC) stabilization before randomization or in the standard care arm makes this study difficult to interpret.

A Cochrane systematic review has been performed containing RCTs comparing early surfactant administration with less than 1 hour of mechanical ventilation followed by extubation (INSURE) versus selective surfactant administration, continued mechanical ventilation, and extubation from low respiratory support.\(^{41}\) The investigators included studies that gave surfactant either to spontaneously breathing infants with signs of RDS (who received surfactant for established RDS but before requiring intubation for frank respiratory failure) and infants at a high risk for RDS (who received prophylactic surfactant administration within 15–60 minutes after birth). Nine of the
previously mentioned studies met selection criteria and were included in the review (6 as early treatment and 3 as prophylaxis). In the meta-analysis of the 6 studies that included early INSURE strategies, there were significant reductions in the need for oxygen use at 28 days of life (typical RR 0.43 [95% CI 0.20–0.92]), mechanical ventilation (typical RR 0.67 [95% CI 0.57–0.79]) and fewer air leak syndromes (typical RR 0.52 [95% CI 0.28–0.96]) but no differences in either CLD, mortality, or the combined outcome of CLD or mortality compared with the standard conventional strategy of selective surfactant administration and continued mechanical ventilation in infants with RDS. The protection against air-leak was more pronounced in a subanalysis using a low threshold for surfactant replacement of FIO2 less than 0.45. The meta-analysis of the 3 studies featuring a prophylactic INSURE strategy with intubation of patients at a high risk for RDS immediately after birth for the purpose of surfactant administration followed by rapid extubation to nasal CPAP compared with initial stabilization on CPAP and selective surfactant administration demonstrated no significant advantage or difference between the two strategies.

Although the INSURE method seems to reliably reduce the burden of mechanical ventilation in preterm infants with RDS, some infants still fail, requiring reintubation and mechanical ventilation. Dani and colleagues have identified independent risk factors for INSURE failure. Among preterm neonates born less than 30 weeks’ gestation, having a birth weight less than 750 g or severe hypoxia (a/A gradient <0.44 on initial blood gas) has been demonstrated to be an independent risk factor for INSURE failure.

NASAL INTERMITTENT POSITIVE PRESSURE VENTILATION

Several studies have been performed examining the role of nasal intermittent positive pressure ventilation (NIPPV) as part of the initial stabilization of preterm infants. Although clinicians are increasingly trying to manage preterm infants without mechanical ventilation, the reality is that many preterm infants with RDS managed primarily on CPAP or extubated early to CPAP will fail, requiring intubation and stabilization on mechanical ventilation. NIPPV use in preterm infants is an attempt to improve these failure rates. NIPPV is a method of noninvasive respiratory support in which intermittent ventilator-generated inflations via the nasal CPAP interface are used to augment CPAP.

Bhandari and colleagues conducted an RCT that enrolled 41 infants less than 32 weeks’ gestational age that were intubated and given surfactant for RDS. Infants were randomized to either continued management on conventional ventilation or extubation to NIPPV within 90 minutes of the surfactant administration. No differences in duration of endotracheal mechanical ventilation or oxygen use were observed; however, there was a significant reduction (from 52% to 25%, \( P = .03 \)) in the combined outcome of CLD or death observed in the group that was extubated to NIPPV.

Two studies have been performed comparing NIPPV to CPAP as initial treatment of RDS to prevent intubation. Bisceglia and colleagues randomized 88 preterm infants with RDS to either continued CPAP or NIPPV. The investigators reported improved \( P CO_2 \) levels and shorter duration of mechanical ventilation when it was indicated in the NIPPV group, but no difference was noted in the need for endotracheal ventilation. The investigators did not report mortality or CLD outcomes. A second study, reported by Kugelman and colleagues, randomized 84 infants born less than 35 weeks’ gestation with clinical RDS to either NIPPV or CPAP. Infants from either arm were eligible for intubation, rescue surfactant administration, and mechanical ventilation using uniform criteria. In this trial, infants initially stabilized using NIPPV were less
likely to be intubated (25% vs 49%, \( P = .04 \)) and less likely to have CLD (2% vs 17%, \( P = .03 \)).

One study has been performed comparing post-INSURE extubation to nCPAP versus NIPPV. Ramanathan and colleagues\(^4\) performed an RCT enrolling 110 spontaneously breathing preterm infants born between 26 + 0 and 29 + 6 weeks’ gestation that were administered surfactant at 60 minutes of life. In this report, infants intubated either in the DR or soon after admission as well as spontaneously breathing infants stabilized initially on CPAP were eligible for inclusion in the study. Infants randomized to extubation with CPAP remained on CPAP until at least 72 hours of life or until they no longer had an \( O_2 \) requirement. Infants randomized to extubation on NIPPV were weaned according to a standard guideline; however, infants were maintained on NIPPV for at least 24 hours following extubation. Both groups were reintubated for the same indications (severe apnea, \( FIO_2 >0.6, pH <7.25, PCO_2 >65 \) mm Hg). Days spent on endotracheal mechanical ventilation were shorter in the group randomized to NIPPV compared with CPAP (median 1 vs 7 days, \( P = .006 \)). CLD was observed in 39% of the infants in the CPAP group compared with 21% in the NIPPV group (OR 2.4 [95% CI 1.02–5.6]). No differences were observed in mortality rates or in the combined outcome of mortality and CLD.

**MIST AND OTHER METHODS OF SURFACTANT REPLACEMENT**

The benefits seen with the INSURE method are likely secondary to surfactant replacement among infants who are surfactant deficient, thereby establishing an adequate FRC. However, to facilitate this treatment, intubation and some brief period of positive pressure endotracheal ventilation is required. As previously noted, both intubation and mechanical ventilation can be associated with adverse outcomes. An alternative to the INSURE procedure has been developed and has been referred to by some as minimally invasive surfactant therapy (MIST). The MIST procedure consists of instilling surfactant to the trachea via a thin catheter to spontaneously breathing infants stabilized on CPAP. Several observational studies have demonstrated that the technique is feasible and, in contrast to INSURE, seems well tolerated in the smallest infants.\(^4\),\(^9\)

One large multicenter RCT randomized 220 infants born between 26 to 28 weeks’ gestation with a birthweight less than 1.5 kg to the MIST procedure if their \( FIO_2 \) was greater than 0.3 versus continuation on CPAP. This report is called the Avoidance of Mechanical Ventilation trial. Failure of either group was defined as the need for mechanical ventilation, \( PCO_2 \) greater than 65 mm Hg, or \( FIO_2 \) greater than 0.6. The study demonstrated that this approach is technically feasible; in 95% of the cases, surfactant replacement was performed on the first attempt. The group treated with MIST had less need for mechanical ventilation (absolute risk reduction \(-0.18 [95\% CI -0.30 to -0.050]\)) and a decreased need for \( O_2 \) at 28 days of life (30% vs 45%, \( P = .032 \)) compared with the CPAP-only group. There were no differences in mortality reported. No studies comparing the INSURE method versus the MIST method are available.

The MIST procedure, like the INSURE procedure, still requires the need for laryngoscopy. Other alternatives to direct laryngeal instillation of surfactant have been attempted and are under investigation. Several trials have been performed attempting to administer nebulized surfactant to spontaneously breathing preterm infants with RDS stabilized on CPAP as rescue or as prophylaxis; although some of these trials have demonstrated small clinical improvements, the earliest reports used less effective surfactant preparations and they have not demonstrated meaningful efficacy.\(^5\)–\(^3\)

Other methods of surfactant deposition include directly into the nasopharynx
immediately following delivery of the head\textsuperscript{54} or via a laryngeal mask airway.\textsuperscript{55} These approaches have great appeal but also have not been proven to be effective in large RCTs.

**OPTIMIZATION OF THERAPY**

Independent of the strategy to stabilize preterm infants with or at risk for RDS, several adjunctive therapies have been associated with improved outcome. Antenatal steroid administration has a well-documented diminution of the risk of RDS and is likely synergistic when used with surfactant replacement, such as the INSURE method.\textsuperscript{31} This effect may also translate into a decreased risk in the development of CLD.\textsuperscript{56} Caffeine prophylaxis has been proven to decrease apnea, decrease extubation failure, decrease time on mechanical ventilation, and decrease the risk of CLD development.\textsuperscript{57} Opiate medications are recommended as part of premedication for elective intubation for the INSURE procedure. However, these medications are associated with unfavorable side effects in preterm infants struggling to breathe, such as respiratory depression and chest wall rigidity. Naloxone, an opiate antagonist, has been used to reverse the effects of opiates; however, shorter-acting opiates, such as remifentanil, are being evaluated for use in newborns.\textsuperscript{58}

Accurate identification of infants at the highest risk for RDS or for the development of CLD would be helpful. One test being developed is based on sampling gastric aspirates from newborns for the quantity of lamellar bodies (a storage form of surfactant).\textsuperscript{59} This technique has practical appeal because the size of the lamellar bodies is similar to the size of platelets, allowing for the use of readily available automated blood counters. Clinical studies are underway to further refine this method.

**SUMMARY**

Despite the lack of definitive evidence of a single superior strategy, a groundswell is taking place toward noninvasive respiratory support. Several well-designed trials suggest that strategies, including application of CPAP in the DR or early in the course of RDS in preterm infants, are as safe and at least as effective as the standard approach of intubation in the DR. Although prophylactic surfactant does not offer any definite benefit over selective treatment, it should be given as early as possible in the course of RDS, when it looks as if mechanical ventilation will be likely. Those probabilities will vary from nursery to nursery and will depend on the comfort level and experience of nurses with CPAP. Efforts to decrease the use of mechanical ventilation via the combination of maternal antenatal steroid administration and early INSURE strategies are associated with decreased morbidities associated with RDS and are likely an important part of a coordinated plan to reduce the risk of CLD. Newly developed techniques for administering exogenous surfactant and providing noninvasive respiratory support require further investigation. More trials comparing different techniques of respiratory support are justified and should include an evaluation of long-term respiratory and neurodevelopmental outcomes.

**REFERENCES**


