Preventing Continuous Positive Airway Pressure Failure

Evidence-Based and Physiologically Sound Practices from Delivery Room to the Neonatal Intensive Care Unit

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KEYWORDS

• Continuous positive airway pressure • Bronchopulmonary dysplasia
• Ventilatory-induced lung injury • Sustained lung inflation • INSURE
• Randomized controlled trial • Mechanical ventilation • Infant flow driver

KEY POINTS

- The incidence of bronchopulmonary dysplasia, and the competing outcomes death or bronchopulmonary dysplasia, is decreased with early initiation of nCPAP.
- The best available evidence supports the premise that efforts to minimize CPAP failure start in the delivery room.
- Various modes and interfaces to deliver CPAP exist; although there may be considerable differences in the ability of these various CPAP devices to prevent failure, little data from RCT exist to support this.

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- Compared with infant flow driver, bubble CPAP may decrease the risk of postextubation failure in infants less than 30 weeks' gestation who are ventilated ≤14 days.
- Available data demonstrate that the INSURE approach is not superior to use of CPAP without prophylactic surfactant in preventing CPAP failure.
- Sustained lung inflation may increase the rate of CPAP success, but may not decrease the incidence of BPD if positive pressure ventilation is needed.

WHY PREVENT CONTINUOUS POSITIVE AIRWAY PRESSURE FAILURE?

The need to identify safe and effective interventions to prevent bronchopulmonary dysplasia (BPD) has reached a critical point. In the simplest terms, BPD is the most common morbidity affecting a cohort of patients whose survival is increasing at the greatest rate. Data collected by the Neonatal Research Network recently on more than 34,000 infants born at 22 to 28 weeks gestation between 1993 and 2012 demonstrated significant increases in survival among infants born at 23, 24, and 25 weeks' gestational age (GA).[1] Importantly, these tiny babies are at the highest risk of developing BPD, with an incidence of 60% to 80%. In this same cohort of patients, it seems that practice changes over this period did little to improve the incidence of BPD.

An alternative to identifying additional interventions to prevent BPD is improving the interventions clinicians already make to support the highest risk neonates. More than 85% of the 34,000 infants in the Neonatal Research Network cohort were exposed to mechanical ventilation during their neonatal intensive care unit (NICU) stay.[1] Recent clinical data continue to support a direct relationship between exposure to mechanical ventilation and an increased risk of developing BPD.[2–6] As the survival of the tiniest babies increases, it is important to determine if a better modality of invasive mechanical ventilation exists to minimize these exposures and prevent BPD. High-frequency ventilation does not reduce the incidence of BPD in the smallest, high-risk babies.[7] Volume-targeted ventilation still remains promising, but randomized trials remain small and unconvincing.[8] Newer approaches, including neurally adjusted ventilator assist, have not yet been adequately studied.[9] These data may point to the reality that the developing human lung at 22 to 26 weeks' gestation is uniquely susceptible to injury caused by invasive mechanical ventilation. If this is true, reducing the burden of BPD will come only with limiting the exposure to invasive mechanical ventilation.

Data from randomized controlled trials (RCTs) demonstrate that routine use of continuous positive airway pressure (CPAP) significantly reduces the combined outcome of BPD (assessed at 36 weeks' gestation) or death in at-risk preterm infants, with an number needed to treat of 17.7.[10] Two other similar meta-analyses have been performed, each including slightly different combinations of trials whose comparison groups go beyond strictly CPAP versus prophylactic surfactant.[11,12] In all of these meta-analyses, the signal for benefit always points toward CPAP. Unfortunately, the routine use of CPAP does not provide a larger treatment effect; the numbers needed to treat determined across these three analyses were 17.7,[10] 25,[11] and 35.[12] It is reasonable to ask why the treatment effect is not larger, and can more be done to enhance the benefit of CPAP.

If CPAP prevents BPD by limiting the exposure to mechanical ventilation, efforts to prevent CPAP failure would likely lead to increased protective effects. In the preterm infant at highest risk for developing BPD, CPAP failure is common. Data from three large RCTs evaluating routine CPAP versus routine intubation show that 45% to 50% of high-risk babies fail CPAP within the first week of life (**Table 1**). Data from

Table 1
Incidence of CPAP failure in large RCTs evaluating CPAP alone as primary mode of respiratory support

Trial	Year	Subjects Enrolled	GA	ACS, % (Any)	CPAP Failure, % (5–7 d)
COIN[13]	2008	610	25 0/7–28 6/7	94	46
SUPPORT[19]	2010	1316	24 0/7–27 6/7	>95	51.2
CURPAP[20]	2010	208	25 0/7–28 6/7	>95	33
Dunn[18]	2011	648	26 0/7–29 6/7	>98	45.1

Abbreviations: ACS, antenatal corticosteroids; GA, gestational age.

observational studies and RCT demonstrate that rates of CPAP failure are highest for the smallest babies, approaching 60% at 25 to 26 weeks' GA.[13–16] These data inform practice in one of two ways: either efforts to minimize CPAP failure in this group of infants will result in less BPD and improved outcomes; or, despite best efforts, CPAP failure in this group of patients will remain unacceptably high and the ability to detect who will fail must be improved to provided supportive therapy (eg, mechanical ventilation and/or surfactant) as soon as possible.

HOW TO PREVENT CONTINUOUS POSITIVE AIRWAY PRESSURE FAILURE: EVIDENCE-BASED INTERVENTIONS, FROM THE DELIVERY ROOM TO THE NEONATAL INTENSIVE CARE UNIT

Does Receipt of Antenatal Corticosteroids Decrease the Risk of Continuous Positive Airway Pressure Failure?

Antenatal corticosteroids (ACS) are considered "one of the most important antenatal therapies available to improve newborn outcomes," and are now recommended for threatened delivery at 24 0/7 weeks to 33 6/7.[17] It is reasonable to hypothesize that rates of CPAP failure would be higher among neonates that did not receive ACS. Among neonates enrolled in RCTs evaluating CPAP versus routine intubation, receipt of ACS was high (>90%, see **Table 1**).[13,18–20] These data suggest that even with the benefit of ACS, rates of CPAP failure remain high (~60%). So, the question remains: in the unfortunate circumstance that a baby at high risk of developing BPD (23–28 weeks) did not receive the benefit of ACS, should there be a lower threshold to intervene and provide exogenous surfactant?

Randomized studies performed in the 1980s and 1990s demonstrated that in large (>28 weeks' GA) intubated infants with respiratory distress syndrome (RDS), who often had not received ACS, early and even prophylactic surfactant treatment decreased mortality and air leak.[21,22] It is likely that a protective signal exists for earlier treatment of RDS in more immature infants 24 to 28 weeks' GA who did not receive ACS, but an RCT will never likely provide these answers.

*Therefore, we recommend that a trial of CPAP should be attempted for all neonates born at less than 28 weeks' GA, but the threshold for intervention (*ie, *intubation and exogenous surfactant) should be considered early in the course of RDS if ACS were not administered. Quality of evidence: low, based on the lack of data in patient population of interest (24–28 weeks' GA). Strength of recommendation: weak, based on the lack of clear data guiding practice.*

Does Routine Use of Sustained Lung Inflation Prevent Continuous Positive Airway Pressure Failure?

At delivery, term infants provide a sustained pressure (30–35 cm H_2O) over a long inspiratory time (4–5 seconds) to clear lung fluid and establish functional residual

capacity (FRC).[23] Assisting preterm infants in the delivery room by providing positive pressure at 20 to 25 cm H_2O for 5 to 20 seconds via a nasopharyngeal tube or face-mask has been proposed as a method to establish FRC.[23] Smaller RCTs demonstrate that use of sustained lung inflation (SLI) decreases the need for mechanical ventilation at 72 hours, without increasing the risk of air leak.[24–27] A much larger trial powered to determine if use of SLI is safe and decreases the incidence of BPD or death in neonates born at 23 to 26 weeks' GA is ongoing.[28]

Therefore, we recommend SLI should be considered for all neonates born at less than 28 weeks' GA. Quality of evidence: moderate, based on consistent findings across multiple smaller RCTs. Strength of recommendation: strong recommendation, based on potential benefit and lack of data demonstrating harm.

Does the Modality of Assisted Ventilation Used in the Delivery (Resuscitation) Room Affect Continuous Positive Airway Pressure Failure?

Assisted ventilation in the delivery room is provided using one of three devices: (1) self-inflating bag, (2) flow-inflating bag, and (3) T-piece resuscitator. The theoretic advantages of the T-piece resuscitator include delivering a consistent end expiratory pressure while precisely delivering the desired peak inspiratory pressure. Whether use of the T-piece in the resuscitation suite prevents CPAP failure in the babies at highest risk of CPAP failure (<26 weeks' GA) is unknown. However, in babies greater than or equal to 26 weeks' GA, use of a T-piece resulted in less intubation in the delivery room when compared with use of a self-inflating bag. Importantly, use of the T-piece did not increase the need for chest compressions or air leak.[29]

Therefore, we recommend that when available, a T-piece resuscitator should be used to resuscitate neonates born at less than 28 weeks' GA. Quality of evidence: low, based on the lack of data in the population of interest (24–28 weeks' GA). Strength of recommendation: weak, based on the lack of clear data guiding practice balanced by the absence of evidence of harm.

Does Intubation, Surfactant, Extubation Improve Continuous Positive Airway Pressure Success?

Isayama and colleagues[30] recently published a systematic analysis comparing the intubation, surfactant, extubation (INSURE) approach with nasal CPAP. There were no statistically significant differences between the nasal CPAP and INSURE groups. However, the relative risks seemed to favor the INSURE group with a nonsignificant (12%) reduction in chronic lung disease and/or death (moderate-quality evidence), a 14% decrease in chronic lung disease (moderate-quality evidence), and a 50% decrease in air-leak (very-low-quality evidence).

We recommend that nasal CPAP should be offered to all preterm neonates with RDS; however, there is no benefit to routine surfactant administration followed by rapid extubation (INSURE) unless the likelihood of CPAP failure is very high. When the likelihood of CPAP failure is greatly increased, surfactant should be administered followed by rapid extubation. Quality of evidence: moderate. Strength of recommendation for using CPAP without prophylactic surfactant: strong.

Recently, there has been renewed interest in the INSURE approach using surfactant administration through a thin plastic catheter (minimally [or less] invasive surfactant therapy and less invasive surfactant administration [LISA]) (**Table 2**). Isayama and colleagues[31] recently published a meta-analysis comparing seven ventilation strategies (including LISA and INSURE). The primary outcome was death or BPD at 36 weeks' postmenstrual age. Compared with all other ventilatory strategies, LISA had the lowest risk of the primary outcome. However, this outcome was not robust for death when

Table 2
Need for CMV and incidence of BPD in preterm infants with RDS treated with INSURE approach using surfactant administration through a thin plastic catheter versus ETT

Study	N (Gestation, wk)	Need for CMV, % Catheter vs ETT	Incidence of BPD Catheter vs ETT, %	Entry Criteria for Catheter
Gopel et al,[80] 2015	2206 (26–28)	41 vs 62 (P<.001)	12 vs 18 (P = .001)	Cohort study not specified
Kanmaz et al,[81] 2013	200 (<32)	40 vs 49 (P = NS)	10.3 vs 20.2 Moderate-severe (P = .009)	F_{IO_2} >0.4 and CPAP
Gopel et al,[82] 2011	220 (26–28)	33 vs 73 (P<.0001)	8 vs 13 (P = .268)	F_{IO_2} >0.3 and CPAP
Kribs et al,[83] 2015	211 (23–26.8)	74.8 vs 99 (P<.001)	67.3 vs 58.7 Survival without BPD (P = NS)	F_{IO_2} >0.3 and CPAP in first 2 h
Mohammadizadeh et al,[84] 2015	38 (<34)	15.8 vs 10.5 (P = NS)	P = NS	CPAP and need for surfactant
Bao et al,[85] 2015	90 (27–32)	17.0 vs 23.3 (P = NS)	P = NS	F_{IO_2} = 0.30–0.35 and CPAP
Mirnia et al,[86] 2013	136 (27–32)	19 vs 22 (P = NS)	7.5 vs 7.1 (P = NS)	F_{IO_2} >0.3 and CPAP

Abbreviations: CMV, conventional mechanical ventilation; ETT, endotracheal tube; F_{IO_2}, fraction of inspired oxygen; NS, nonsignificant.

limited to higher quality studies. Rigo and colleagues[32] recently published a systematic analysis of four trials comparing surfactant administration through a thin plastic catheter versus INSURE. Compared with INSURE, less invasive surfactant therapy decreased of death/BPD or CPAP failure.

We do not recommend administration of surfactant using a thin plastic catheter (LISA). Quality of evidence for LISA: low, given the small number of patients randomized to this intervention. Strength of recommendation: strong, based on lack of large RCTs comparing LISA with other modes of surfactant administration.

Does Bubble Continuous Positive Airway Pressure Improve Rates of Continuous Positive Airway Pressure Success?

CPAP delivery devices are broadly grouped into continuous-flow and variable-flow systems. With continuous-flow devices this is achieved by using water-seal bubble CPAP (Fisher and Paykel Healthcare, Auckland, New Zealand; Babi-Plus, A Plus Medical, Hollister, CA; home-made) systems or via flow opposition, where the patient's expiratory flow opposes a constant flow from nasal prongs (conventional ventilator provided neonatal CPAP). Variable-flow devices that include the infant flow driver (IFD; infant flow nasal CPAP system, Care Fusion, Yorba Linda, CA), Benveniste gas jet valve CPAP (Dameca, Copenhagen, Denmark), Aladdin, and Arabella systems (Hamilton Medical AG, Reno, NV) use flow opposition with fluidic flow reversal during expiration, where gas is entrained during inspiration to maintain stable pressure and expiratory flow is diverted via a separate fluidic flip-flop.

Randomized Trials Comparing Continuous Positive Airway Pressure Devices

Randomized controlled trials performed at birth

Mazzella and colleagues[33] compared IFD CPAP with bi-nasal prongs and bubble CPAP through a single nasopharyngeal tube in preterm infants with RDS at less

than 12 hours of age. They reported a significant beneficial effect on oxygen requirement and respiratory rate with IFD CPAP, compared with bubble CPAP, and a trend toward a decreased need for mechanical ventilation. Tagare and colleagues[34] compared the efficacy and safety of bubble CPAP with ventilator-derived CPAP in preterm neonates with RDS. A higher percentage of infants was successfully treated with bubble CPAP (83% vs 63%; $P = .03$), suggesting superiority of bubble CPAP. Mazmanyan and colleagues[35] randomized preterm infants to bubble CPAP or IFD CPAP after stabilization at birth in a resource-poor setting. They reported bubble CPAP equivalent to IFD CPAP in the total number of days CPAP was required.

Randomized trials of continuous positive airway pressure after extubation

Stefanescu and colleagues[36] examined extremely low birth weight infants and compared IFD CPAP with ventilator-derived CPAP using INCA prongs and found no difference in the extubation success rate between the two groups. In a subsequent trial, Gupta and colleagues[37] randomized preterm infants 24 to 29 weeks' gestation or 600 to 1500 g at birth to receive bubble CPAP or IFD CPAP following the first attempt at extubation. Infants were stratified according to duration of initial ventilation ($\leq$14 days or >14 days). Although there was no statistically significant difference in the extubation failure rate (16.9% on bubble CPAP, 27.5% on IFD CPAP) for the entire study group, the median duration of CPAP support was 50% shorter in the infants on bubble CPAP, median 2 days (95% confidence interval, 1–3 days) on bubble CPAP versus 4 days (95% confidence interval, 2–6 days) on IFD CPAP ($P = 0$ .03). In infants ventilated for less than or equal to 14 days, the extubation failure rate was significantly lower with bubble CPAP (14.1%; 9 of 64) compared with IFD CPAP (28.6%; 18 of 63) ($P = .046$). This well-designed clinical trial suggests the superiority of postextubation bubble CPAP over IFD CPAP in preterm babies less than 30 weeks, who are initially ventilated for less than 14 days.

Therefore, we recommend the use of bubble CPAP over variable-flow CPAP devices for postextubation respiratory support, especially in infants ventilated for less than or equal to 2 weeks. Quality of evidence: low, for device preference when used to treat RDS after birth; moderate, for use of bubble CPAP following postextubation. Strength of recommendation: weak, based on only a slight difference between continuous- or variable-flow CPAP devices when used after birth but a trend in favor of bubble CPAP for postextubation support, especially in infants ventilated for less than 2 weeks.

Does the Interface Used to Deliver Continuous Positive Airway Pressure Affect Continuous Positive Airway Pressure Failure?

The ideal interface would reliably deliver consistent distending pressure while being comfortable to the infant and easy to use. Several options are available, including short binasal prongs, nasopharyngeal prongs, masks, and the RAM cannula. No adequately powered trial has directly compared all interfaces. Several have examined nasal mask versus nasal prongs to prevent CPAP failure, with one demonstrating less CPAP failure in infants less than 31 weeks with the use of nasal mask.[38] However, another found no difference in CPAP failure between mask and binasal prongs.[39] The variability in these results may be caused by different definitions of CPAP failure and difference in maximum noninvasive support provided (CPAP level, noninvasive positive-pressure ventilation).

RAM cannula has been used to deliver CPAP in neonates.[40] It provides positive distending pressure through longer nasal cannula prongs made from softer material.[41] Unfortunately, there are no clinical studies directly comparing RAM with other nasal interfaces for preventing CPAP failure. However, there are several preclinical studies

using lung model systems that attempt to determine whether RAM cannula can reliably deliver mean airway pressure or peak inspiratory pressures. One demonstrated that when used as recommended with a 60% to 80% nasal occlusion, even with a closed mouth, the RAM cannula delivered on average 60% less mean airway pressure to the lungs than the set pressure.[42] Another showed RAM cannula resulted in significantly higher resistance and dramatically lower peak inspiratory pressures to the lungs than short binasal prongs.[43] The direct clinical relevance of these findings is unknown and deserves further study.

Therefore, we recommend use of either nasal mask or short binasal prongs for early CPAP administration. We recommend against the use of RAM cannula during the critical period determining CPAP success. Quality of evidence: low, based on the small number of patients studied. Strength of recommendation: strong, based on lack of clinical data directly comparing RAM cannula with CPAP.

Does Prone or Lateral Body Positioning Improve Continuous Positive Airway Pressure Success?

Prone positioning improves oxygenation in mechanically ventilated neonates,[44] infants, and children with acute respiratory distress.[45] Results in neonates on CPAP are conflicting, with several demonstrating improvements in oxygenation, respiratory rate, and end-expiratory lung volume with prone and lateral positioning.[46–48] However, another found no difference in vital signs or oxygen saturations regardless of position.[49] None of the studies found evidence of harm or adverse effect associated with prone or lateral positioning.

We recommend the prone and lateral positions for infants with the goal of increasing CPAP success. Quality of evidence: low, based on lack of trials evaluating position to prevent initial CPAP failure. Strength of recommendation: moderate, based on potential benefit and lack of demonstrated harm.

Does Timing of Caffeine Administration Affect Continuous Positive Airway Pressure Failure?

Importantly, the Caffeine for Apnea of Prematurity trial demonstrated that caffeine use was associated with a significant reduction in the duration of mechanical ventilation.[50] An enhanced protective effect on BPD and the duration of mechanical ventilation is observed when caffeine therapy is initiated early (before 2–3 days of life vs later than 2–3 days of life).[51–54] It is possible that these observations may be explained by later initiation of caffeine in infants with greater illness severity.[55] Additional prospective studies are needed to identify ideal timing of caffeine dosing.

Therefore, we recommend that caffeine should be administered to neonates both at and less than 28 weeks' GA, and there may be additional benefit of administering caffeine early in the first 24 to 72 hours of life. Quality of evidence: high, based on data from RCTs and large observational studies. Strength of recommendation: strong, based the consistent finding of benefit and the absence of evidence of harm.

WHEN NO EVIDENCE EXISTS, CAN ONE SUPPORT "BEST PRACTICE"?

Does Aggressive Airway Clearance Prevent Continuous Positive Airway Pressure Failure?

Effective delivery of noninvasive positive distending pressure cannot occur in the presence of obstructed nasal passages or oropharynx. Little evidence guides practice regarding how frequently one should preform nasal and oral suctioning. Although maintaining airway patency is paramount, aggressive suctioning can lead to edema, trauma, and bleeding, thus exacerbating plugging. In addition to the loss of positive

distending pressure during suctioning, other more serious complications can occur including bradycardia, laryngospasm, and arrhythmias. In practice, indications and frequency of suctioning is variable.[56] Instructions on nontraumatic suctioning have been published.[57] Units with long experience in successful application of CPAP in the most premature infants recommend suctioning every 3 to 4 hours.[58]

Therefore, we recommend that nasal and oropharyngeal suctioning should be performed every 3 to 4 hours, and more frequently with signs of obstruction (apnea, desaturation, acute increase in work of breathing). Attention must be paid to avoiding excessive suctioning and causing trauma. Quality of evidence: low. Strength of recommendation: strong, based on physiologic benefit and the low likelihood of harm.

Can Quality Improvement Projects Improve Continuous Positive Airway Pressure Success Rates?

Multiple obstacles stand in the way of implementing early, aggressive, and successful CPAP in high-risk neonates. It takes time to technically train the multidisciplinary team (eg, nursing, respiratory therapist, neonatal nurse practitioner.) in correct CPAP application, administration, and maintenance. It requires education and consensus of the attending physicians, trainees at multiple levels, and nurse practitioners who are making decisions regarding what defines CPAP failure, and when invasive mechanical ventilation should be used. Not surprisingly, time and experience with CPAP has been shown to increase CPAP success and decrease rates of BPD.[59]

Several groups have implemented quality improvement studies demonstrating short-term success increasing CPAP use and decreasing rates of intubation.[60–63] Some,[60,61] but not all,[62,63] have decreased unit BPD rates during the study period. Importantly, sustained practice improvement and decreased rates of BPD have been demonstrated.[64] These findings support that targeted multidisciplinary quality improvement efforts can help improve CPAP success.

We recommend that any institution dedicated to adopting a strategy of early CPAP develop a multidisciplinary team to champion this cause, whether it is through a formal quality improvement project or as an annual unit goal. Quality of evidence: low, based on small number of studies. Strength of recommendation: strong, based on potential benefit.

IF BABIES MUST FAIL, CAN ONE PREDICT WHO WILL FAIL, AND INTERVENE EARLY?

Are There Antenatal Characteristics that Reliably Predict Continuous Positive Airway Pressure Failure?

Studies of antenatal identifiers of CPAP failure report discordant results. Many establish early GA and lower birth weight as predictive as CPAP failure.[16,65,66] Lack of ACS and male sex have correlated with CPAP failure in some studies.[66–68] However, others have shown aspects of medical history, including GA and birth weight, are not predictive of CPAP failure.[15,69]

None of these studies identified factors with adequate sensitivity or positive pressure ventilation in predicting CPAP failure. Thus, we recommend against using antenatal characteristics to exclude infants from a trial of CPAP. Quality of evidence: moderate, based on lack of convincing evidence. Strength of recommendation: strong, based on potential benefit of CPAP success.

Are There any Clinical Variables or Diagnostic Tests that Predict Continuous Positive Airway Pressure Failure?

Multiple studies have attempted to define clinical features of a neonate's initial NICU course that predict CPAP failure. Several groups have shown early higher fraction of

inspired oxygen (F_{IO_2}) correlates with CPAP failure.[15,65,69] However, this relationship is confounded by including F_{IO_2} requirement in the definition of CPAP failure. The same can be said for the relationship between higher levels of CPAP and ultimate CPAP failure.[69] Importantly, one trial identified that infants who succeeded CPAP were started earlier (4.3 minutes vs 29 minutes), emphasizing the importance of early FRC establishment.[61] Multiple studies have performed sophisticated analyses to identify early clinical findings that predict CPAP failure (**Table 3**). Although no clinical variable is foolproof, thematic links begin to emerge. These studies would suggest that CPAP failure is more common in the most premature neonates, those with severe RDS on initial chest radiograph (CXR), and those requiring high levels of supplemental oxygen. Although none of these associations is surprising, these factors must be in the clinician's mind when attempting to determine if a neonate is "failing" CPAP. Other groups have recommended composite scoring and combining variables to help predict CPAP failure, such as birth weight less than 800 g, male sex, and F_{IO_2} greater than 0.25 at 1 or 2 hours,[14] the product of F_{IO_2} and CPAP level being greater than or equal to 1.28,[68] or creating a clinical score with features including GA, lack of antenatal corticosteroids, prolonged premature rupture of membranes, and the product of F_{IO_2} and CPAP level,[68] has also been considered.

Surfactant activity and/or production tests

A screening test able to identify surfactant deficiency would allow clinicians to target surfactant administrations to select patients at high risk of CPAP failure secondary to RDS. Surfactant activity level has been evaluated to predict CPAP failure using the surfactant adsorption test. The surfactant adsorption test is done on amniotic fluid and has demonstrated correlation with lamellar body counts and lung ultrasound scores. In a pilot study, infants failing CPAP have lower surfactant adsorption test levels than those who succeeded.[70]

The rapid bedside stable microbubble test evaluates if surfactant is present in tracheal, gastric, and amniotic fluid samples. This test has been used to stratify infants into high or low risk for CPAP failure.[71–74] Other tests of surfactant production include

Table 3
Clinical predictors of CPAP failure

Study	Infants Studied	Clinical Characteristics as Predictors of CPAP Failure	Odds Ratio (95% CI)
Ammari et al,[16] 2005	261 infants ≤1250 g	Severe RDS on initial CXR	6.42 (2.75–15.0)
		PPV at delivery	2.37 (1.02–5.52)
		A-a DO_2 >180 mm Hg	6.42 (2.75–15.0)
Pillai et al,[68] 2011	62 infants ≤1500 g	Product of CPAP and F_{IO_2} ≥1.28	3.9 (1.0–15.5)
		PPROM	5.3 (1.2–24.5)
		GA <28 wk	6.5 (1.5–28.3)
Dargaville et al,[14] 2013	66 infants 25–28 wk GA	F_{IO_2} by 2 h	1.19 (1.06–1.33)
		Caesarean delivery	14.77 (1.47–148.55)
Tagliaferro et al,[66] 2015	235 infants ≤1000 g	GA ≤26 wk	6.19 (2.79–13.73)
		A-a DO_2 >180 mm Hg	2.18 (1.06–4.47)
		pH ≤7.27	2.69 (1.27–5.69)
		Severe RDS on initial radiograph	10.81 (3.5–33.3)

Abbreviations: A-a DO_2, alveolar-arterial oxygen difference; CI, confidence interval; CXR, chest radiograph; F_{IO_2}, fraction of inspired oxygen; PPROM, prolonged premature rupture of membranes; PPV, positive pressure ventilation.

the click test, the shake test, and lamellar body counts, but have not been evaluating ability to predict CPAP failure.[75–78]

Chest radiographs

Severe RDS on a CXR obtained in the first hours of life has been identified as a predictive variable for CPAP failure in multiple studies.[14,16] A repeat study corroborated this finding in extremely low birth weight infants, finding that early radiologic evidence of severe RDS was a strong predictor of CPAP failure with a positive predictive value of 0.81. However, its utility as a screening tool is somewhat limited because the sensitivity of severe RDS on a CXR to predict CPAP failure was only 32%.[66] Because obtaining CXR is already a common part of clinical practice for these infants, incorporating a thoughtful interpretation of this modality to clinical decision making seems feasible and prudent to use it in decision making.

Lung ultrasound

Furthermore, a lung ultrasound score obtained in the first hours of life evaluating the patterns of aeration in different lung quadrants correlated well with CPAP level and oxygenation indices, such as alveolar-arterial gradient, oxygenation index, and arterial to alveolar ratio in infants 27 to 41 weeks.[79] Whether this information can be used to predict CPAP failure is unknown. Several of these diagnostic tools require further study before recommendation could be made for broad implementation.

We recommend against using a single antenatal risk factor or clinical finding to predict CPAP failure and implement surfactant treatment. At this point and pending further study, predicting CPAP failure depends on an individual's unique clinical characteristics. Quality of evidence: weak, based on lack of large studies and standardized criteria for defining CPAP failure. Strength of recommendation: strong, based on current available information. We also recommend that if an extremely premature neonate (<26 weeks GA) has a CXR with evidence of severe RDS, they be monitored closely and considered for early intubation and surfactant administration. Quality of evidence: moderate, based on support from multiple retrospective trials. Strength of recommendation: strong, based on ease of practice.

SUMMARY

Multiple studies support using CPAP as first-line therapy for many preterm infants requiring respiratory support. However, rates of CPAP failure remain high among neonates at highest risk for developing lung injury. Multiple interventions, from the delivery room to the NICU, stand to minimize the risk of CPAP failure. Future studies will determine whether SLI will decrease CPAP failure, and criteria used to predict CPAP failure require further refinement.

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