

## Summary

Bronchopulmonary dysplasia (BPD) remains the most common severe adverse pulmonary outcome of preterm birth. Low gestational age and birth weight are the strongest risk factors for the development of BPD, but the pathogenesis is complex. The strategy for respiratory support immediately after birth and during the initial neonatal period may have a critical impact on the development of BPD. The preterm lung is highly susceptible to injury. An understanding of the physiology of the first breath, the initiation of breathing and respiratory adaptation after birth is essential for adequate resuscitation measures and a lung protective ventilation strategy. Excessive oxygen use in preterm infants can increase the risk of BPD. The recently developed nomograms for oxygen saturation levels during the neonatal transition phase have become part of the newly revised resuscitation guidelines. For term neonates, starting resuscitation with air, rather than 100% oxygen, is now advised. Preterm infants may require a higher initial inspiratory oxygen fraction than term infants; however, the ideal level remains to be defined. Primary intubation is no longer a prerequisite for preterm survival. Recent trials have demonstrated that even very preterm infants can be safely stabilised after delivery with continuous positive airway pressure and later be selectively treated with surfactant for respiratory distress syndrome. This initially less invasive strategy has the advantage of reducing the need for mechanical ventilation and, thereby, the risk of lung injury; however, to date, it has not been clearly shown to reduce the incidence of BPD. Combining an approach of noninvasive ventilator support with a strategy of minimally invasive surfactant administration is important, but questions remain about the optimal timing, mode of delivery and value of predictive tests for surfactant deficiency.

## Key points

- The risk and severity of bronchopulmonary dysplasia (BPD) is strongly associated with the earliest gestational ages (GAs). Apart from GA and birth weight, initiation of mechanical ventilation is the most important predictor for development of BPD.
- A noninvasive ventilation strategy with continuous positive airway pressure (CPAP) from birth in spontaneously breathing infants has a similar outcome as routine intubation in the delivery room.
- Prophylactic surfactant treatment has no advantage over early CPAP with selective surfactant administration.
- Surfactant can be safely administered during CPAP using the INSURE (intubation, surfactant and extubation) approach.

# Neonatal resuscitation and respiratory support in prevention of bronchopulmonary dysplasia

## Educational aims

- › To understand the physiology of respiratory support immediately after birth
- › To learn the current guidelines for neonatal resuscitation
- › To discuss noninvasive ventilation strategies in relation to development of bronchopulmonary dysplasia

Pulmonary disorders represent the most common diagnoses in infants admitted to neonatal units. The overall incidence of any form of acute lung disease in the newborn is ~3% [1–4]. The incidence of respiratory distress syndrome (RDS) increases with decreasing gestational age (GA) and birth weight [5]. More than 50% of infants with birth weights <1,500 g have signs of RDS, increasing to almost 90% in infants <750 g [6, 7]. Over the last few decades, neonatal care has changed considerably. The introduction of antenatal steroids, surfactant treatment, new ventilation strategies and improved nutrition are some of the major advances that have contributed to a significant reduction in mortality from neonatal lung disease. Antenatal corticosteroid treatment clearly reduces the incidence of RDS, as shown in randomised controlled trials (RCTs) [8, 9]. However, epidemiological data show that the overall incidence of RDS remains at ~1% [3, 4]. This may be explained by an increasing number of viable extremely premature infants.

Bronchopulmonary dysplasia (BPD) is a chronic and severe complication of preterm birth. It usually occurs in infants following significant RDS, but can also develop in preterm infants with only mild initial respiratory

distress. Interestingly, the incidence of BPD varies between populations and centres. In the USA, the National Institute of Child Health's Neonatal Research Network reported a 68% incidence of BPD among a population of infants born at 22–28 weeks GA [10]. In the Swedish national cohort of all infants born <27 weeks GA between 2004 and 2007, 73% had some degree of BPD [11]. The risk and severity of BPD is strongly associated with the earliest GAs, and GA, birth weight, and mechanical ventilation (MV) are the most important predictors of BPD [12].

In 1967, NORTHWAY *et al.* [13] were the first group to characterise BPD. The incidence of BPD may have changed very little over the past decades [14], but the clinical picture of BPD today differs from the original description of NORTHWAY *et al.* [13]. Instead of the classical progressive fibroproliferation and inflammation, the “new BPD” is predominantly defined by the disruption of distal lung growth [15].

The definition of BPD is based on a consensus conference of the US National Institutes of Health published in 2001 [16] and attempts to categorise the severity of the disease according to the level of respiratory support needed (table 1). A problem with this definition is the wide

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### Competing interests

None declared.

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**Table 1 Diagnostic criteria for bronchopulmonary dysplasia (BPD)**

	GA weeks	
	<32	>32
<b>Treatment with oxygen</b>	>21% for $\geq 28$ days	>21% for $\geq 28$ days
<b>Time-point of assessment</b>	36 weeks post-menstrual age or discharge	>28 but <56 days or discharge
<b>BPD</b>		
<b>Mild</b>	Breathing room air at 36 weeks post-menstrual age or discharge	Breathing room air at 56 days post-natal age or discharge
<b>Moderate</b>	Need for <30% oxygen at 36 weeks post-menstrual age or discharge	Need for <30% oxygen at 56 days post-natal age or discharge
<b>Severe</b>	Need for >30% oxygen, with or without PPV or continuous positive pressure at 36 weeks post-menstrual age or discharge	Need for >30% oxygen, with or without PPV or continuous positive pressure at 56 days post-natal age or discharge

GA: gestational age; PPV: positive pressure ventilation. Modified from [16] with permission from the publisher.

range of criteria for supplemental oxygen requirement and a physiological diagnosis of BPD, in which the need for supplemental oxygen is tested in a standardised way, has been suggested.

The cause of BPD is multifactorial. Many factors can modulate the pathogenesis of the disease, such as fetal infection or inflammation, antenatal steroids, oxidative stress, ventilator-induced lung injury, post-natal inflammation or infection, nutrition, abnormal growth factor signalling and genetic factors [15]. MV of the very preterm infant is a factor of great importance. The lung is generally not injured at birth, but can very easily be harmed by various means of respiratory support. Immature lungs suffer from an elevated surface tension resulting from surfactant deficiency, which leads to repeated alveolar collapse at the end of expiration. This results in atelectasis,

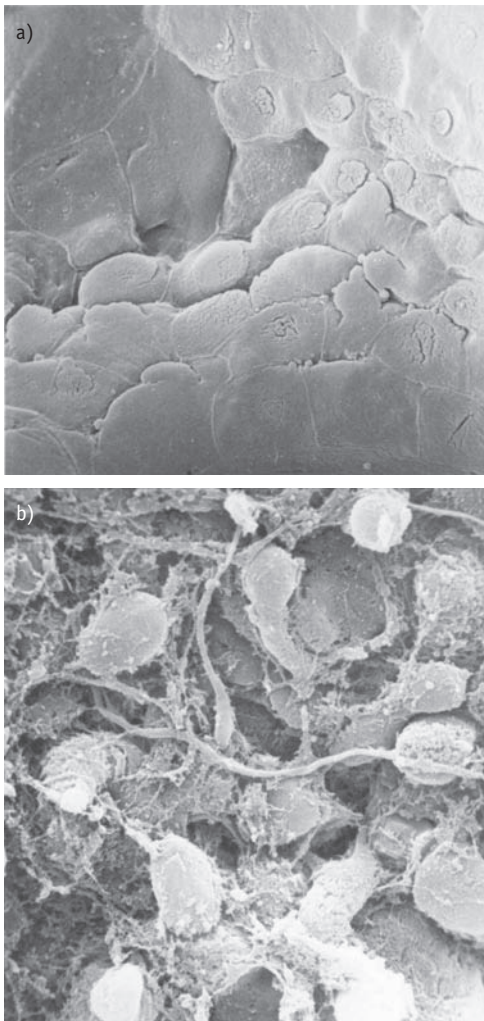


**Figure 1**  
Pre-term infant on nasal continuous positive airway pressure. Image: A-S. Gustafsson, RN.

uneven inflation and regional alveolar overdistension. If unrecognised, the immediate consequences will be epithelial injury and pulmonary oedema, which further interfere with surfactant function, giving rise to RDS (fig. 2a and b). Superimposed lung injury from MV and high concentrations of inspired oxygen trigger the release of pro-inflammatory cytokines, which further impair surfactant function and predispose to the development BPD [17].

## The physiology of the first breath

At birth, the newborn infant needs to rapidly clear its airways of fetal lung fluid to build up its functional residual capacity (FRC) and to generate an appropriate tidal volume ( $V_T$ ) in order to facilitate sufficient gas exchange. The term newborn achieves this lung fluid clearance through active and passive mechanisms. Pulmonary expansion is achieved by creating subatmospheric inspiratory pressures during the first diaphragmatic contractions [18, 19]. The inspired air remains in the lung through active glottis closure [20], while the surfactant lining of the alveolar space prevents repeated alveolar collapse on expiration. At the cellular level, luminal sodium channels are activated at birth, and sodium reabsorption through these channels promotes liquid clearance from the airways to the pulmonary interstitial space [21, 22]. As a consequence of both active and passive mechanisms, the term neonate generates an FRC of  $\sim 30$  mL per kg body weight and a  $V_T$  of



**Figure 2**  
 a) Smooth alveolar surface in surfactant-treated preterm rabbit lung. b) Disrupted alveolar surface in ventilated preterm rabbit without prior treatment of surfactant.

~5 mL per kg within minutes after birth. According to a comprehensive review of the physiology of the first breaths by TE PAS *et al.* [22], studies of the early breathing mechanisms were performed in human subjects up to the early 1980s: in 1960, KARLBERG [23] used plethysmography to measure the physiological changes that take place in the human lung during the first minutes after birth. Accordingly, OLVER and co-workers have performed cineradioscopy on newborn humans to illustrate pulmonary expansion and managed to capture the first radiographic images of pulmonary aeration in humans. Very recently, our understanding of the physiological changes during pulmonary aeration was enhanced by studies by HOOPER *et al.* [24]. Their studies of term and preterm animals [25, 26] confirmed the

observations by KARLBERG [23] and OLVER and have further added valuable information to our understanding of the dynamic changes in  $V_T$  and FRC formation.

While most of the aforementioned studies have investigated the pulmonary changes in term infants or animals, less is known about the mechanisms of lung aeration in the preterm infant. The preterm infant's respiratory system differs from that of the term infant in certain aspects: preterm infants have an immature surfactant system and their pulmonary architecture remains at an earlier, saccular developmental stage. Both factors predispose to alveolar instability after birth. Furthermore, the chest wall and larger airways are still cartilaginous, offering less resistance against atmospheric pressure, which may result in repeated airway collapse, reduction in  $V_T$  and loss of FRC. At the cellular level, the lungs of preterm infants have less effective sodium channels, which further delays lung fluid clearance [22]. The preterm infant's respiratory drive from the immature respiratory centres of the brain is poorly controlled, which leads to a less coordinated respiratory pattern [27]. These peculiarities of the immature respiratory system predispose to development of respiratory distress: airway clearance,  $V_T$  and FRC formation are hampered, and unaided spontaneous breathing is achieved only with difficulty. As physicians, we are challenged to assist the newborn as gently as possible during its transition to breathing air, albeit with a need to be effective in our efforts without causing harm. In a recent review, JOBE *et al.* [28] speculated on the caretaker's role and possible interference in the dynamic changes that take place during fetal-to-neonatal transition. The authors emphasise the small margin between helping the infant to expand its lungs sufficiently and causing harm by over distending the delicate pulmonary structures [28]. Recent work by SIEW *et al.* [26] has confirmed concept of gradual pulmonary aeration in the preterm animal model, as proposed by JOBE *et al.* [28]. In summary, physicians involved in aiding preterm infants to take their first breaths need to take multiple variables into account, such as the unknown pulmonary fluid volumes, the immaturity of structures that define lung volumes, the degree of surfactant deficiency, and pulmonary vascular changes, all of which interact and may thus interfere with the adaptation to breathing air [28].

## Current neonatal resuscitation guidelines on initial airway management

The American Heart Association (AHA) [29], European Resuscitation Council [30] and International Liaison Committee on Resuscitation (ILCOR) [31, 32] regularly publish evidence-based guidelines on neonatal resuscitation. According to these guidelines, three characteristics denote the newborn infant in need of resuscitation at birth: pre-term gestation, absence of crying or breathing, and poor muscle tone [29]. The assessment of colour is no longer an element of the guidelines [33]. Whenever possible, newborn infants with signs of distress should be monitored with pre-ductal pulse oximetry, *i.e.* measurements should be taken from the right wrist or hand. Pulse oximetry has the added advantage of further providing heart rate, the most sensitive parameter of successful adaptation. The intensity of the medical intervention should be guided by the changes in heart rate and the dynamics of peripheral oxygenation measurements. Nomograms for the natural progression of peripheral oxygenation are now an integral part of the resuscitation guidelines [29–32].

Sufficient airway management helps facilitate lung aeration and is the key to successful resuscitation. Respiratory support should be initiated by mask ventilation; immediate endotracheal intubation is reserved for the severely sick infant [29–32]. Use of a laryngeal mask airway is discussed for sufficiently developed infants ( $\geq 34$  weeks GA) [29–32]. A respiratory rate of 40–60 breaths per min is advised [29–32]. The AHA and ILCOR do not suggest so-called prolonged inflations, and the recommended inspiratory pressures should be 20–40 cmH<sub>2</sub>O [29–32].

Different resuscitation devices for respiratory support are used: the flow-inflating bag (FIB), the self-inflating bag (SIB) (ideally with an attached pressure manometer) or pressure-limited devices (So-called T-piece devices) [29–32]. T-piece devices, as opposed to FIBs and SIBs, have been shown to deliver defined positive inspiratory pressures and positive end-expiratory pressures more accurately than self-inflating bags [34, 35]. However, T-piece devices require a continuous gas flow and, therefore, offer only limited flexibility [36]. More research is needed to determine the ideal resuscitation device [28].

## Oxygen saturation targets in the delivery room

Much research has gone in to defining the ideal oxygen concentration for depressed neonates. Several meta-analyses have compared the use of air (inspiratory oxygen fraction ( $F_{i,O_2}$ ) 0.21) *versus* pure oxygen ( $F_{i,O_2}$  1.0) in the delivery room [37, 38]. An  $F_{i,O_2}$  of 0.21 improved survival rates following resuscitation, while pure oxygen significantly delayed the time to first breath and increased mortality of depressed term or near-term infants [37, 38]. Survival was also improved in the subgroup of preterm infants resuscitated with an  $F_{i,O_2}$  of 0.21; however, the data stems from a small number of patients only [37]. Consequently, the current guidelines prefer air as the primary gas in the resuscitation of term and near-term infants at birth [29–32]. For infants  $<32$  weeks GA, use of oxygen blenders is advised. Due to the paucity of data on the ideal gas mix for preterm infants, no clear-cut recommendations on a specific  $F_{i,O_2}$  are given.

Several RCTs including preterm infants  $<32$  weeks GA have sought to identify the ideal initial concentration of oxygen. WANG *et al.* [39] investigated a starting  $F_{i,O_2}$  of 0.21 for preterm neonates of  $<32$  weeks GA. Being resuscitated in air, these neonates did not reach the target arterial oxygen saturation measured by pulse oximetry ( $S_{p,O_2}$ ) of 85% by 5 min of life [39]. VENTO *et al.* [40] studied a comparable patient group and succeeded in reaching an  $S_{p,O_2}$  of 85% by 10 min of life when starting at an  $F_{i,O_2}$  of 0.30. The recently published Surfactant Positive Pressure and Oxygen Randomized Trial (SUPPORT) investigated two different  $S_{p,O_2}$ -target levels (85–89 *versus* 91–95%) of very low birth weight infants from birth to 36 weeks corrected GA [41]. There was a marginal increase in mortality amongst individuals from the lower  $S_{p,O_2}$  target group (28.3 *versus* 32.1%;  $p=0.04$ ), while severe retinopathy occurred less frequently amongst survivors from this group (8.6 *versus* 17.9%,  $p<0.001$ ) [41]. Very recently, STENSON *et al.* [42] reported on the Benefits of Oxygen Saturation Targeting (BOOST) II trial in the UK and Australia. This multicentre RCT investigated different  $S_{p,O_2}$  target ranges for infants  $<28$  weeks GA, either 91–95% or 85–89%, while breathing supplemental oxygen. The study was closed prematurely after an interim analysis showed a higher survival rate in infants assigned to the higher

$Sp_{O_2}$  target range. The authors warned against targeting maximal  $Sp_{O_2}$  levels of 85–89% in infants born <28 weeks GA. This is in accordance with results from the SUPPORT trial [41]. However, until further information including full longer-term data on survival and morbidity are available from all the aforementioned trials, the ideal target range for infants <28 weeks GA remains to be defined. Addressing this, SAUGSTAD and AUNE [37] concluded that a low- $Sp_{O_2}$  approach during the first week of life reduces severe retinopathy of prematurity (ROP) by 50%, and BPD and other pulmonary problems by 25%.

The need for unanimous oxygen treatment has been questioned and the normal ranges of peripherally measured oxygen concentrations following birth have only recently been defined. KAMLIN *et al.* [43] and MARIANI *et al.* [44] have described the natural progression of  $Sp_{O_2}$  levels after birth. Recently, DAWSON *et al.* [45] have provided nomograms of pre-ductal peripheral oxygenation for term and pre-term infants, according to gestational age [45].

## Surfactant treatment: when and how?

Surfactant treatment is defined as prophylactic when administered in the delivery room (DR), usually within 15 min from birth. To protect the immature, surfactant-deficient lung from injury and facilitate the establishment of FRC, it would be desirable to give surfactant prior to the first breath; however, this is rarely feasible in clinical practice. The term “rescue administration” is used to describe later, selective surfactant treatment of infants with progressive signs of RDS; however, the criteria for selective surfactant treatment vary greatly between studies. If the aim is to avoid intubation in the DR by stabilising spontaneously breathing infants on continuous positive airway pressure (CPAP), some infants will be able to continue on CPAP alone, but many, particularly the extremely preterm infants, will still need surfactant. Therefore, the question might rather be how early is early enough for surfactant treatment?

The available evidence suggests that prophylactic surfactant would be superior; however, the groundwork for this evidence is getting old. A Cochrane review of prophylactic *versus* selective surfactant use included eight studies, all performed between 1991 and 1997 [46]. In reviewing early *versus* delayed selective surfactant treatment, four studies performed between 1992

and 1998 were included in the Cochrane database [47]. Although the results showed a reduced risk of air leaks, mortality and BPD with both prophylactic and early surfactant, the data are difficult to apply to current care practice: antenatal steroid use was low, which should be kept in mind, as antenatal steroids will reduce the severity of RDS; some studies used synthetic surfactant, which we know is inferior to natural surfactant; and CPAP as the primary respiratory support was uncommon. Hence it is unclear whether these results hold true today.

Currently, surfactant needs to be administered as a tracheal instillation in order to be effective; this poses a dilemma in a noninvasive ventilator approach. Some different strategies for surfactant treatment during CPAP are available. The Scandinavian model, the so-called INSURE (intubation, surfactant and extubation) procedure, has now been used for almost two decades and has been proven to reduce the need for MV [48–53].

The INSURE procedure for spontaneously breathing infants was first reported by a Swedish neonatologist working in Kuwait [54], then further developed in conjunction with CPAP in Denmark, resulting in the first RCT in 1994 [47]. In this study, 68 infants with a GA of 25–35 weeks and moderate-to-severe RDS were randomly assigned to receive either nasal CPAP (nCPAP) and surfactant or nCPAP alone at an arterial to alveolar oxygenation index (a/A ratio) of 0.22, corresponding to an  $F_{i,O_2}$  of ~0.4. The results showed that a single dose of surfactant reduced the need for MV by half, from 85 to 43%. The effect was even more pronounced if surfactant was given as an early rescue treatment, at  $F_{i,O_2}$  0.3–0.35 (a/A 0.35), which was reported in a subsequent randomised study of 60 infants with GA <30 weeks [48]. Several studies have followed, all confirming a significantly reduced need for MV with the INSURE strategy, both compared to CPAP alone and to primary intubation and surfactant [49–52]. Although a second surfactant dose is more seldom needed after INSURE compared with surfactant followed by MV [50, 51], the overall use of surfactant increased in Stockholm, Sweden in the 5-year period after the introduction of INSURE in 1998 compared with the 5-year period before (from 42 to 65% in infants with RDS, 27–34 weeks GA) [50]. This is consistent with the Cochrane meta-analysis comparing early surfactant administration with brief MV to later, selective surfactant treatment followed by continued MV [55]. The meta-analysis showed

significantly reduced BPD rates and fewer air leaks after early surfactant and rapid extubation within 1 h, which was even further pronounced in a subanalysis using a low threshold for surfactant treatment of  $F_{i,O_2} < 0.45$ . The INSURE procedure is a means to provide surfactant for a selected population of surfactant-deficient infants. Making surfactant treatment available to more infants is therefore to be regarded as a desirable effect associated with INSURE and the key for reducing MV rates.

An alternative to the INSURE procedure is to treat spontaneously breathing infants on CPAP with surfactant by inserting a thin feeding catheter into the trachea. The technique is minimally invasive and performed without analgesia, but it still requires direct laryngoscopy. It is reported to be well tolerated in extremely preterm infants [56, 57], but more difficult in infants with more advanced GA (>28 weeks) [58]. This is in contrast to INSURE, for which a birth weight <750 g has been identified as an independent risk factor for failure [59]. A randomised multicentre trial of the catheter technique is under way in which surfactant is administered as very early rescue when the supplemental oxygen requirement reaches 30% and preliminary results indicate a significant reduction in CPAP failure.

## Early CPAP or DR intubation

For extremely pre-term infants <27 weeks GA, the rate of intubation in the DR remains high, reflecting either a need for initial resuscitation or an intention to give surfactant prophylactically, but may also be a care practice of DR intubation irrespective of the infant's status. In the Vermont Oxford Network, 81% of infants with birth weight <750 g were intubated in the DR and in Sweden, where there is a very strong tradition of early CPAP, 61% of infants <27 weeks GA were subjected to DR intubation [60]. Two recent randomised trials, CPAP or Intubation of Neonates at Birth (COIN) and SUPPORT [61, 62], showed that with early CPAP, stabilisation without intubation in the DR is feasible, but CPAP failure is frequent, particularly in the most immature infant (<26 weeks GA), where 46–83% required later intubation. Both trials had a design with late rescue surfactant treatment in the CPAP groups, at  $F_{i,O_2}$  levels of 0.6 and 0.5, respectively. There are no good predictors of early CPAP failure, but

selective surfactant treatment at lower  $F_{i,O_2}$  threshold appears to be beneficial and does not increase intubation rate compared with higher thresholds [63].

The following recent RCTs address the issue of DR management and surfactant administration from slightly different angles. COIN and SUPPORT compared primary DR intubation followed by MV to early CPAP with rescue surfactant.

### COIN Trial

The COIN trial enrolled 610 pre-term infants born at 25 and 0/7 to 28 and 6/7 weeks, and randomised spontaneously breathing infants at 5 min of age to receive either CPAP with a pressure of 8 cmH<sub>2</sub>O or intubation and MV [61]. Intubation criteria in the CPAP group were severe apnoea, acidosis or oxygen requirement of >60%. There was no protocol for surfactant treatment, which was administered according to local guidelines. In the CPAP group, 46% required intubation during the first 5 days.

At 28 days GA, the unadjusted odds ratio for death or BPD was in favour of the CPAP group, but the primary outcome of death or BPD at 36 weeks GA did not differ between the groups. The secondary outcomes revealed fewer days intubated and in need of MV in the CPAP group, and fewer infants in the CPAP group received surfactant (38 *versus* 77%;  $p < 0.001$ ). Moreover, the CPAP group exhibited a significantly higher rate of pneumothorax (9.1 *versus* 3.0%;  $p < 0.001$ ). The high CPAP pressure, low use of surfactant and late timing of surfactant treatment are factors that probably contributed to the high incidence of air leaks. When early rescue surfactant treatment at  $F_{i,O_2}$  0.4 was used in a retrospective report from the Netherlands regarding change of care practices from elective DR intubation to early CPAP, the incidence of pneumothorax was instead lower in the CPAP group [64]. The analysis of neonatal lung function at term, performed by a single centre from the multicentre COIN trial, revealed that patients started on early CPAP had a significantly lower respiratory rate, minute ventilation and elastic work of breathing, possibly due to a markedly higher pulmonary compliance ( $p < 0.01$ ), as compared with the early intubation group [65].

### SUPPORT

SUPPORT enrolled 1,316 infants born at 24 and 0/7 to 27 and 6/7 weeks, and randomised to

receive DR CPAP at 5 cmH<sub>2</sub>O or DR intubation with surfactant treatment within 1 h [62]. Intubation criteria for the CPAP group were haemodynamic instability, acidosis or oxygen requirement >50% to reach oxygen saturations of >88%. All infants in the CPAP group who were intubated within the first 48 h received surfactant.

In the CPAP group, 67% received surfactant and 83% were intubated for any reason. Rates of death or BPD were similar with the two strategies (48% in the CPAP group *versus* 51% in the intubation/surfactant group). CPAP infants had fewer days on MV, less use of post-natal corticosteroids for BPD, and were more likely to be alive and off MV by day 7 of life ( $p=0.01$ ).

### CURPAP Trial

The CURPAP trial aimed to evaluate early CPAP in combination with prophylactic *versus* later selective surfactant treatment followed by immediate extubation (*i.e.* prophylactic or selective INSURE). It enrolled 208 infants born at 25 and 0/7 to 28 and 6/7 weeks [65]. Infants were managed with CPAP from birth and randomised at 30 min of age to either prophylactic surfactant followed by immediate extubation back to CPAP or CPAP alone. In the latter group, surfactant was administered as early rescue if oxygen requirements were >40% to maintain saturations of 85–92%. The need for MV in the first 5 days of life was similar in both groups (31.4 *versus* 33.0%). Mortality, BPD and the incidence of air leaks did not differ.

The trials do not provide substantial evidence of superiority but clearly show that early CPAP is as efficient in the DR as routine intubation in extremely preterm infants. In addition, they indicate no advantage of prophylactic surfactant but suggest early rescue surfactant is important.

The recent preliminary report from the Vermont Oxford Network showed that after randomisation to one of three approaches (DR intubation with prophylactic surfactant and continued MV, or DR intubation with rapid extubation to CPAP, or early CPAP with rescue surfactant when  $F_{iO_2}$  exceeded 0.6), the outcome was similar. However, approximately half of the early CPAP infants required MV and received late rescue surfactant treatment, suggesting both that early CPAP is a means to avoid intubation in many infants and that early identification of those infants that will need surfactant remains elusive [66].

## Noninvasive ventilation and prevention of BPD

Noninvasive respiratory support options, such as CPAP, are means to avoid the harmful effects of positive pressure ventilation and possibly reduce the risk of developing BPD. Infants with mild RDS can often be managed on CPAP alone, without exogenous surfactant treatment [67, 68], but as shown above, very preterm infants are at risk for severe RDS, often require surfactant and their immature lungs are highly vulnerable to ventilator-induced injury.

In comparisons between centres, a practice of early CPAP is linked to a favourable outcome and that the rates of MV are strongly associated with pulmonary morbidity and BPD [12, 69, 70]. The RCTs available support the safety and efficacy of CPAP, even in extremely preterm infants, but fail to reliably show a reduction in BPD. Predicting which infants will fail CPAP, and deciding the optimal time and mode for surfactant administration are important aims for future studies.

In a situation of equipoise, the least invasive approach should be chosen. Thus, early CPAP could now be considered as the recommended ventilation support in preterm infants, leaving the burden of proving superiority to those still advocating primary intubation.

## Conclusion

The pre-term lung is highly susceptible to injury. A protective respiratory support strategy from birth is imperative as it has the potential of reducing not only the respiratory morbidity in the immediate neonatal period, but also influence some of the known triggers for the development of BPD, such as inflammation, oxidative stress and lung growth. Current evidence indicates that a strategy of delivery room CPAP in very preterm infants with signs of breathing is as safe as routine intubation. There appear to be no serious side effects and a tendency towards improved outcomes, at least in the short term. Prophylactic surfactant no longer gives any clear benefits over selective treatment, but surfactant should be given early in the course of RDS and a strategy for surfactant administration should be incorporated in a practice of early CPAP. Predicting which infants who will fail CPAP and decide the optimal time and mode for surfactant administration are important future goals for neonatologists and pulmonologists alike.



## Educational questions

One or several correct answers:

1. How is moderate BPD diagnosed in an infant born at 26 weeks gestation?
  - a) Characteristic chest radiograph.
  - b) Need for supplemental oxygen at 28 days of life.
  - c) Need for positive pressure ventilation at 36 weeks post-menstrual age.
  - d) Need for supplemental oxygen <30% at 36 weeks post-menstrual age or discharge.
  
2. With current evidence on short- and long-term outcome, should primary intubation be considered superior to early CPAP in the DR in an infant born at 26 weeks gestation?
  - a) Yes
  - b) No
  - c) Evidence today indicates both are equally safe.
  - d) CPAP has the short-term benefit of reducing the need for MV.
  
3. Why is surfactant treatment important in the respiratory management of very pre-term infants?
  - a) It may protect the immature lung from ventilator-induced injury.
  - b) With only CPAP, half or more of very pre-term infants will fail and require intubation.
  - c) Surfactant treatment significantly reduces mortality from RDS.
  - d) Surfactant treatment reduces the incidence of pneumothorax and other air leaks.

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Suggested reading: refs 10, 16, 22, 24, 27, 28, 40, 45 and 71.

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Suggested answers

1. b and d  
2. c and d  
3. a, b, c and d