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**Clinical Strategies
to Minimise BPD**

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Introduction

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Bronchopulmonary dysplasia (BPD) is one of the most prevalent chronic morbidities associated with premature birth. The pathogenesis of this condition remains largely unknown, as several factors are potentially harmful to the immature lung and, depending on the timing, extent, and duration of the exposure to these factors, different patterns of pulmonary damage may occur. Genetic factors are likely to play a significant role. Thus the development of therapeutic approaches for the prevention and treatment of BPD is very challenging. It is, therefore, key to increase our understanding of the pathogenesis of this condition before interventions can positively impact the clinical outcome of premature infants.

Since mechanical ventilation (MV) is a major factor in the development of lung injury, in the last decade the use of non-invasive ventilation techniques has been frequently advocated to reduce the incidence of BPD. The use of surfactant in combination with nasal continuous positive airways pressure (NCPAP) has been shown to reduce the need for MV and to have the potential to reduce the incidence of BPD. However, the rate of extubation failures with NCPAP is still relatively high, and improved non-invasive approaches aimed at reducing the time infants spend in MV are needed.

Nasal intermittent positive pressure ventilation (NIPPV) is being investigated as a possibly more effective approach than NCPAP in reducing extubation failures and thus the incidence of BPD. A recent randomised controlled trial (NIPPV trial) demonstrated that early treatment with poractant alfa 200 mg/kg followed by rapid extubation to NIPPV led to a reduction in the requirement for MV and the incidence of BPD among preterm infants at high risk. This therapeutic strategy represents a promising approach to minimise BPD in infants requiring surfactant treatment for neonatal respiratory distress syndrome.

Among pharmacological interventions for BPD prevention, recent interest has been raised by caffeine citrate. This is mainly due to the results of the Caffeine for Apnea of Prematurity trial, which investigated the long-term effects of caffeine citrate in premature infants undergoing caffeine treatment. The study showed a clear benefit of caffeine over placebo for the primary endpoint of death or disability at 18 months corrected age. Furthermore, a reduction in the incidence of BPD in the caffeine group was also observed. The mechanisms through which caffeine leads to these impressive benefits still need further investigation. However, the reduction in the incidence of BPD seems to be driven mainly by the significantly shorter intubation/positive pressure support period allowed by caffeine treatment.

There is continuous scientific effort in the field of BPD and this will ultimately lead to an increased number of therapeutic tools available to neonatologists, but new investigations are needed to fully understand the nature of this multifactorial disease.

Surfactant and non-invasive ventilation, partners in neonatal respiratory disease management

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The introduction of surfactant replacement therapy for the treatment of neonatal respiratory distress syndrome (NRDS) marked a major breakthrough in neonatology. Treatment with surfactants reduces both neonatal mortality and air leaks by approximately 50%.¹ The clinical benefit seen with surfactant treatment corresponds to an approximately 6% reduction in overall mortality in the first year of life, with no increase in pulmonary or neurodevelopmental problems at long-term follow-up.¹ However, there is still a requirement for improved strategies to treat NRDS in order to further reduce exposure to mechanical ventilation, since mechanical ventilation can lead to the development of chronic lung diseases such as bronchopulmonary dysplasia (BPD). Minimising the duration of time the infant is intubated is fundamental to reduce the incidence of ventilatory-mediated trauma, a common precursor of BPD.

Minimising the occurrence of BPD in preterm infants with NRDS

Surfactant plus invasive ventilation methods

Invasive ventilation is the most common form of respiratory support used to treat infants with NRDS. A survey of neonatal ventilation strategies in the United Kingdom (N=228 neonatal intensive care units [NICUs]) demonstrated that intermittent positive pressure ventilation (IPPV) is the method most frequently used for infants during the acute-phase of NRDS, and that synchronised intermittent mandatory ventilation (SIMV) is the preferred mode of treatment for infants with NRDS during the recovery or weaning phase [Table 1].² According to this survey, continuous positive airway pressure (CPAP) is used in only 2% of infants during the acute phase of NRDS [Table 1].² However, while prolonged invasive ventilation is linked to ventilatory-mediated trauma and the development of BPD, the type of invasive ventilation used appears to have no impact on the degree of BPD seen. Indeed, similar rates of BPD are observed in infants treated using high-frequency or conventional invasive ventilation.³

Table 1: Neonatal respiratory support strategies in the United Kingdom (N=228 NICUs*²).

Ventilation method	NRDS treatment acute phase	NRDS treatment weaning phase
IPPV	73%	N/A
HFO	2%	N/A
IMV	N/A	13%
A/C	4%	15%
SIMV	13%	73%
VG	5%	6%
CPAP	2%	N/A

*Response rate: 80%; data are the percentage of responders choosing each method.
A/C: assist-control; HFO: high frequency oscillation; IMV: intermittent mandatory ventilation;
VG: volume guarantee.

Surfactant plus non-invasive ventilation methods

It is known that the use of non-invasive ventilation methods reduces the risk of ventilatory-mediated trauma, which in turn reduces the overall incidence of BPD. Common non-invasive ventilation techniques include nasal CPAP (NCPAP), which relies on spontaneous breathing by the infant and does not have a back-up rate, and nasal IMV (NIMV), such as nasal IPPV (NIPPV), which has a back-up rate and allows spontaneous breaths to be augmented.

NCPAP plus surfactant

Before surfactants and antenatal steroids were used, NCPAP was the standard of care for preterm infants with NRDS and was associated with reductions in mortality in both low-weight and higher-birth weight preterm infants.^{4,5} Treatment with NCPAP was, however, associated with a higher incidence of pneumothorax.⁵

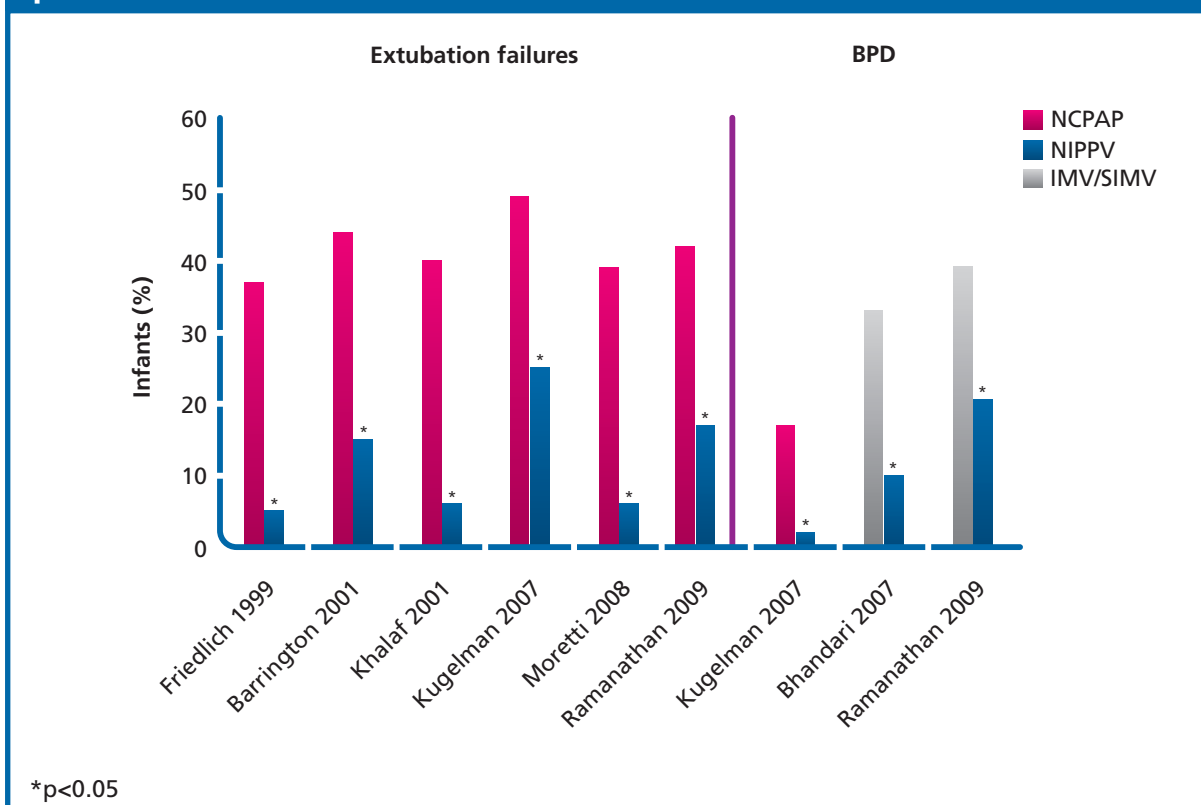
Since the introduction of surfactant and antenatal steroid treatments, much work has been conducted to investigate the optimal non-invasive ventilation method for use in combination with surfactant. A study by Morley *et al.* demonstrated that use of NCPAP in infants of 25–28 weeks' gestation is associated with high extubation failure rates, with 46% of infants requiring invasive ventilation.⁶ Additionally, NCPAP was associated with a higher incidence of pneumothorax versus invasive intubation, and no decrease in BPD or death was noted.⁶

Numerous other studies, in both low-weight and higher-birth weight preterm infants, have shown that surfactant plus NCPAP reduces the rate of extubation failures, and some have demonstrated a trend towards a lower incidence of BPD.^{7,8} Early use of surfactant followed by NCPAP decreases BPD versus late use of surfactant and NCPAP, highlighting the need for infants to receive early treatment.⁸ However, the rate of extubation failures on NCPAP remains relatively high, ranging from 20 to 80%, and the key to improve survival without complications lies in reducing the length of time infants require rescue invasive ventilation.

NIMV plus surfactant

Studies have been conducted to assess NIMV techniques as modes of extubation in preterm infants who had received surfactant therapy [Figure 1]. Studies demonstrated that NIMV techniques reduced extubation failure rates compared with NCPAP in preterm infants, irrespective of gestational age.^{9–15} Bhandari *et al.*¹³ showed that NIMV use was associated with a lower incidence of BPD in a small randomised controlled trial comparing NIMV versus IMV. Recently, a large study by Ramanathan *et al.* showed that the requirement for mechanical ventilation at 7 days of age and the incidence of BPD was significantly reduced in infants treated with surfactant followed by NIMV versus those in the SIMV arm.¹⁵

Figure 1: NIPPV techniques versus NCPAP as modes of extubation in preterm infants.^{9–15}



Furthermore, another study by Bhandari *et al.*¹⁶ demonstrated that early surfactant therapy followed by early NIPPV in low-birth weight (500–750 g) infants at greatest risk for BPD or death was associated with decreased BPD, BPD or death, neurodevelopmental impairment, and neurodevelopmental impairment or death when compared with NCPAP.¹⁶

Conclusions

Invasive mechanical ventilation is linked to ventilatory-associated trauma, a common precursor of BPD. Reducing the length of time infants with NRDS remain intubated through the use of non-invasive ventilation helps to minimise BPD. The use of surfactant and non-invasive NIMV (e.g. NIPPV) is an optimal treatment approach in the management of neonatal respiratory disease. NIPPV is more effective than NCPAP in reducing extubation failures and the incidence of BPD, in both low- and higher-birth weight preterm infants. Notably, early surfactant therapy followed by early NIPPV and administration of caffeine citrate prior to extubation, led to a reduction in BPD among low-birth weight preterm infants at greatest risk.

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Caffeine beyond treatment of apnoea of the premature

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Despite the paucity of efficacy and safety data available until recently, methylxanthines have been used as respiratory stimulants for preterm infants for more than 30 years.^{1,2} Caffeine is known to stimulate the central nervous system at all levels and is commonly used as a respiratory stimulant.^{3,4} Caffeine citrate was the sixth most common drug used in a United States study of 253,541 infants treated in neonatal intensive care units (NICUs) from 1996 to 2005, being administered to 13% of all admissions.⁵ Indeed, there was a shift away from usage of theophylline/aminophylline (15.4% of infants in 1996 to 3.9% in 2005) towards caffeine use (9.9% in 1996 to 16.6% in 2005).⁵ This change in treatment practice is supported by a meta-analysis of three studies showing that caffeine had fewer side effects resulting in risk reduction than theophylline/aminophylline (relative risk 0.17 [95% CI: 0.05–0.72]).⁶ Another study demonstrated that side effects were seen at lower serum drug levels for theophylline (20 mg/l compared with 50 mg/l for caffeine); there was no difference between drugs in treatment failure rate.⁷

The Caffeine for Apnoea of Prematurity (CAP) study

The CAP study examined the long-term effects of caffeine in premature infants, enrolling infants between 500 and 1250 g birth weight who were considered candidates for caffeine treatment by their attending neonatologist. Infants who were treated with caffeine versus placebo had increased survival rates without neurodevelopmental disability at 18–21 months.^{8,9}

A total of 2006 infants were randomised to receive either caffeine or placebo.^{8,9} Risk of death or neurosensory disability was measured at a corrected age of 18 months. Infants previously treated with a methylxanthine were excluded.

Overall, 1006 infants received 20 mg/kg caffeine citrate (loading dose) followed by once-daily treatment with 5–10 mg/kg (maintenance dose), and 1000 infants received placebo.^{8,9} Of the treated infants, 937 and 932 in the caffeine and placebo arms, respectively, had adequate data to assess the primary outcome. The primary outcome parameters were death, cerebral palsy or mental development index (MDI) <85 (Bayley scales of infant development), hearing impairment or blindness. Other outcomes assessed included height, weight and head circumference.

There were no significant differences between caffeine and placebo groups in demographic or clinical data, including birth weight, gestational age, gender, single births or steroid use.^{8,9} The use of caffeine over placebo offered a significant benefit in death or disability at a corrected age of 18 months [Figure 1].⁹ Furthermore, significantly fewer patients developed cerebral palsy or MDI<85 in the caffeine versus placebo groups [Table 1].⁹

Figure 1: Death/disability was significantly reduced in infants who received caffeine versus placebo.⁹

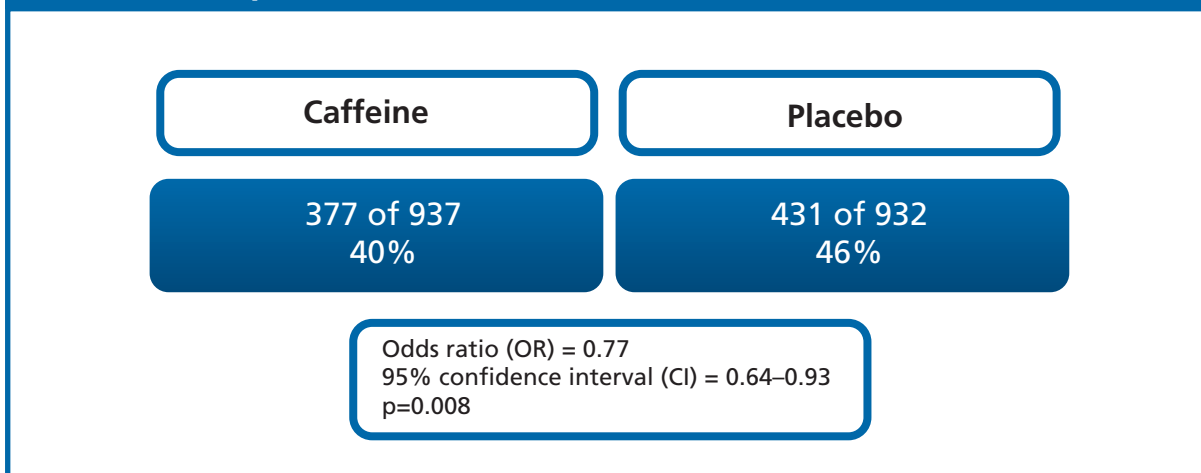


Table 1: Disability outcomes were reduced in infants who received caffeine versus placebo.⁹

	Caffeine (n=937)	Placebo (n=932)	OR	95% CI
Cerebral palsy	4.4%	7.3%	0.58	0.39–0.87
MDI<85	34.0%	38.0%	0.81	0.66–0.99
Deafness	1.9%	2.4%	0.77	0.40–1.45
Blindness	0.7%	0.9%	0.74	0.26–2.15

Additional outcomes also showed a benefit for caffeine versus placebo. The median postmenstrual age at the last use of respiratory support was significantly lower in the caffeine group than in the placebo group ($p < 0.0001$). This was true for intubation, any positive pressure support, and oxygen. Similarly, the proportion of infants with bronchopulmonary dysplasia (BPD) was significantly lower in patients who received caffeine versus placebo. In addition, a post hoc exploratory analysis recommended by the external safety monitoring committee found that a lower proportion of infants underwent surgery to correct a patent ductus arteriosus in the caffeine versus placebo group.^{8,9}

The effect of caffeine on death or disability depended on the type of positive pressure ventilation given, with those supported by an endotracheal tube deriving significant benefit in the caffeine versus placebo groups (OR 0.73 [95% CI: 0.6–0.9]). Caffeine use was associated with a significant reduction in the duration of mechanical ventilation if started early (up to 3 days of life, $p < 0.05$), but not if started after day 3.¹⁰

Further studies on caffeine treatment in premature infants

Taken together, the data from the CAP study support the use of caffeine for the treatment of premature infants <1250 g likely to develop symptomatic apnoea. Further evidence for caffeine treatment comes from a randomised controlled trial that compared the use of two doses of caffeine citrate to facilitate extubation in neonates who were born at less than 30 weeks' gestation.¹¹ Characteristics of the 234 randomised infants were similar between the higher- and lower-dose groups of 10 mg/kg versus 2.5 mg/kg daily maintenance dose (caffeine base) following a four times loading dose. A significant benefit was seen in the higher- versus lower-dose group in the proportion of infants who experienced extubation failure (15% versus 30%; $p<0.01$), and in the number of episodes of chart-documented apnoea within 7 days of the start of treatment (median 4 versus 7 per day; $p<0.01$). In the subgroup of infants who were born at less than 28 weeks' gestation, those in the higher-dose group required a significantly shorter duration of mechanical ventilation than those in the lower-dose group (mean 14 days versus 22 days, respectively; $p<0.01$). However, there was no significant difference between groups in the proportion of infants with BPD at 36 weeks' postmenstrual age (34% versus 48% in higher- versus lower-dose groups, respectively; $p=0.06$) or major disability at 12 months (6/87 versus 14/86 in the higher- versus lower-dose groups; OR 0.42 [95% CI: 0.17–1.05]). There were no significant differences in adverse effects between groups with the exception of time to regain birth weight, which was significantly shorter in infants receiving the lower caffeine citrate dose (15 days versus 13 days in higher- versus lower-dose groups, respectively; $p<0.01$).

An ongoing consideration with caffeine treatment is whether monitoring of the plasma concentrations of the drug is required to ensure standardised dosing. An observational study of 101 preterm neonates suggested that therapeutic drug monitoring is not necessary for those treated with caffeine for apnoea of prematurity.¹² In this study, 230 measurements were taken in infants with a gestational age of 23–32 weeks and the caffeine citrate dose used was 2.5–10.9 mg/kg. The plasma levels achieved were 3.0–23.8 mg/l, with only 3.1% of patients developing levels in excess of 20 mg/l. The majority of patients with impaired renal (91.3%) or hepatic (100%) function also attained a plasma level between 5.1 and 20 mg/l.

Conclusions

Caffeine citrate is an effective treatment for apnoea of prematurity and has been thoroughly investigated in infants with low birth weight (<1250 g). Caffeine is the only drug shown to reduce the incidence of cerebral palsy, and its use in premature infants with respiratory distress is associated with a significantly reduced duration of mechanical ventilation, particularly if treatment is started early. Studies also indicate a reduced risk of duct ligation and BPD when caffeine is used, compared with placebo. A higher caffeine citrate dose (10 mg/kg daily) may be considered if insufficient clinical effect is achieved, although data on the long-term effects of increased dosing are currently lacking.

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Lung development and inflammation – insights into the pathogenesis of BPD

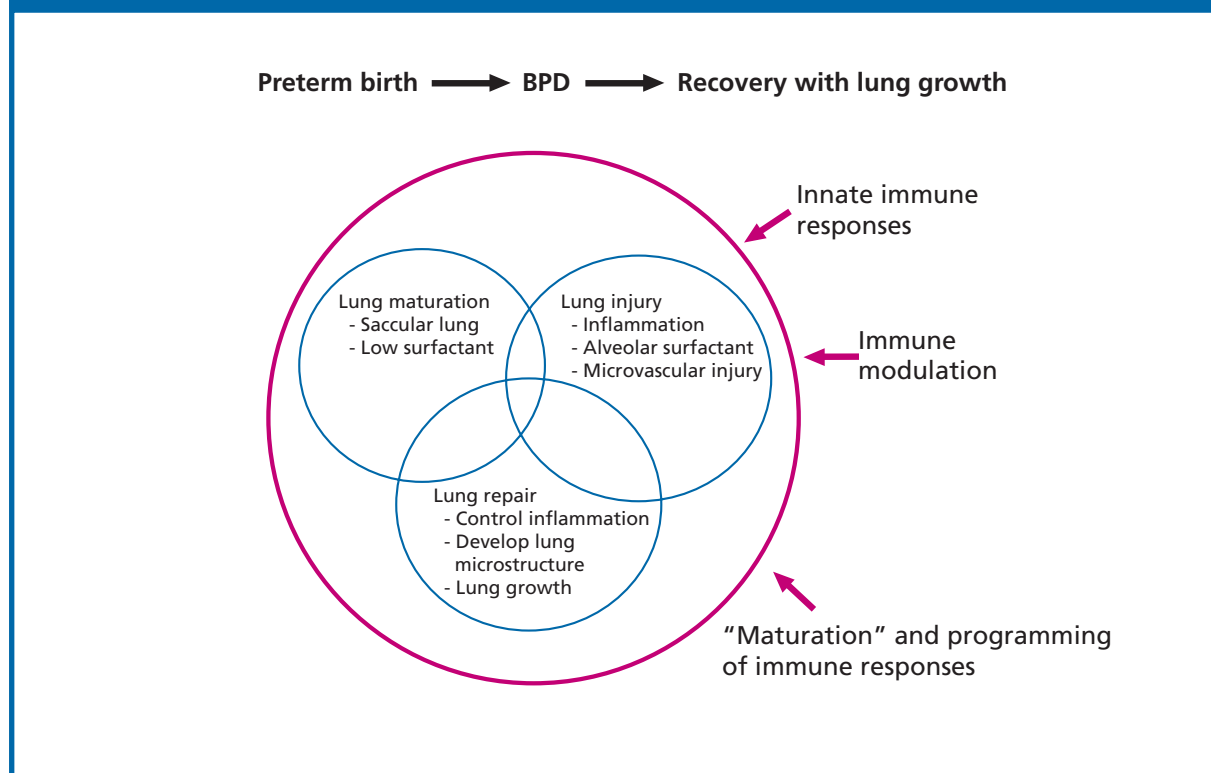
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Bronchopulmonary dysplasia (BPD) is a multifactorial condition and the scientific evidence about the pathophysiology from different clinical studies and animal models is often conflicting.

The main underlying causes of BPD in premature infants are underdeveloped lungs, lung injury and abnormal lung repair. Different infants may be primarily affected by immaturity, injury or failure of healing, but inflammation and innate immune responses have a central role in each of these scenarios [Figure 1].

Figure 1: Interrelationship between causative factors and immune responses in BPD.



Lung inflammation and maturation

Lung maturation occurs relatively late in fetal development and will not be complete in infants born prematurely. Distal saccular development occurs at a fetal age of 24 to 36 weeks of gestation and BPD may affect subsequent alveolarisation and development of the lung.

Fetal exposure to chorioamnionitis has been linked to the subsequent development of BPD, however, the precise causal link between chorioamnionitis and BPD is unclear. The association is confounded by the fact that a diagnosis of chorioamnionitis indicates only that the infant has been exposed to a proinflammatory stimulus. There is no information on the nature of that stimulus. However, lessons can be learned from animal models, where the presence of proinflammatory molecules within the amniotic fluid has been associated with inflammation in the lung of the fetus. In studies by Kramer *et al.*, intra-amniotic injection of bacterial endotoxin in sheep was associated with an increased inflammatory and injury response as measured by increases in apoptosis, proliferation, and proinflammatory cells and cytokines (interleukin [IL]-1 β , IL-6 and IL-8).^{1,2} Furthermore, this treatment induced the maturation of fetal lung monocytes to alveolar macrophages,³ and this early maturation of immune responses within the lung may exacerbate chronic lung disease.

Lung inflammation and injury

Mechanical ventilation is a major factor in lung injury, as it may amplify and prolong tissue damage. This is exemplified by data demonstrating that infants exposed to chorioamnionitis and ventilated for more than 7 days have a strikingly increased risk of BPD.⁴ Therefore, the outcome for the infant may depend on both the fetal exposure to inflammation and the treatment received by the child after birth.

Injury caused by ventilation: delivery room management is key

Delivery room management has a pivotal role in minimising lung damage to a premature infant, as ventilation can lead to overdistension and injury of the lung. At birth the lung is filled with fluid, and the infant has a tracheal volume of approximately 3 ml. Therefore, providing 5 ml tidal volume to the infant leads to overdistension of the airways [Figure 2]. At 2 minutes after birth the infant may have a 4 ml functional residual capacity in the upper lung, with a tidal volume of 5 ml reaching 20% of the parenchyma. The resulting volume of 25 ml/kg may lead to focal overdistension. At 10 minutes after birth the functional residual capacity has reached approximately 5 ml in the airways and 15 ml in the parenchyma. Therefore, in this model, delivering a tidal volume of 5 ml to 100% of the parenchyma from 10 minutes after birth onwards results in non-injurious ventilation. Unfortunately, however, overdistension may have already occurred in the first 10 minutes after delivery.

Figure 2: A model of overdistension of the lung within the first 10 minutes after delivery.





	Birth	20 breaths	2 min	10 min
				
PEEP	0 ml	3 ml airway FRC	3 ml airway FRC + 4 ml FRC in UL	5 ml airway FRC + 15 ml FRC in parenchymal
V_T	0 ml	+5 ml to airways	5 ml to 20% of parenchyma = 25 ml/kg	5 ml to 100% of parenchyma = 5 ml/kg
Outcome	Airless lung	Overdistend airway	Focal overdistension	Non-injurious ventilation

Figure is based on a 1 kg preterm infant, intubated at delivery and volume ventilated with PEEP 5 ml and V_T 5 ml/kg.
PEEP: positive end-expiratory pressure; FRC: functional residual capacity; UL: upper lung; V_T : tidal volume.

Transitory overdistension such as that described above may cause clinically significant damage to the lung. The airways of preterm infants contain relatively little collagen and elastin, and are therefore easily distorted and damaged during the initiation of ventilation. In ventilated animals elastin became diffusely located within 24 hours, rather than focally localised in areas of alveolar septation as seen in control animals.⁵ Changes in elastin localisation may therefore interfere with subsequent ventilation and alveolarisation.

Injury caused by ventilation: lessons from animal models

Studies in sheep have shown that as little as 15 minutes of initial ventilation can cause lung injury that is amplified by subsequent ventilatory support. To evaluate the injury response, preterm lambs were ventilated with a large tidal volume for 15 minutes to simulate delivery room resuscitation, followed by surfactant and maintenance ventilatory support for 2 hours 45 minutes.⁶ The 15 minutes of fetal ventilation caused increases in inflammatory cells and expression of the proinflammatory cytokines IL-1 β , IL-6, IL-8 and macrophage chemotactic protein-1 (MCP-1) in newborn lambs versus controls.⁶

Continued ventilation led to amplification of responses with further increases in neutrophils, IL-6 and IL-8 versus non-ventilated controls. Similarly, 5 days of ventilation increased levels of neutrophils, IL-6, IL-8 and MCP-1 in airway aspirates of preterm baboons at 28 days.⁷ In the sheep model, the overexpression of MCP-1 was primarily localised in the airways, with less seen in the parenchyma.⁸ Heat shock protein-70 (HSP-70), another inflammatory marker expressed by epithelial cells, was recovered in the bronchoalveolar lavage of preterm animals. Cells were sloughed from the airway epithelium during the 15 minutes of ventilation, and lung injury was ongoing.⁸ Furthermore, if the animal continued to be ventilated, expression of HSP-70 was observed in the smooth muscle, suggesting that the continued ventilation resulted in muscle damage.⁸

Conclusions

BPD is a multifactorial condition and the scientific evidence from different clinical studies and animal models can be difficult to interpret. However, it is clear that lung immaturity, inflammation and injury are key elements that can lead to the subsequent development of BPD. This has important implications for the management of infants since initial injury may occur in the delivery room and subsequently be amplified by continued ventilation. Furthermore, an increased understanding of the precise role of inflammatory mediators in the initiation and exacerbation of lung damage may facilitate future treatment advances.

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Question and Answer Session

Question

In the trial where you investigated early NIPPV, what criteria did the infants have to fulfil before being extubated and what extubation parameters were used?

Answer

R. Ramanathan: All infants randomised to the NIPPV arm had to be extubated within 2 to 6 hours of being intubated for respiratory distress. Infants meeting the minimum extubation criteria were extubated to NIPPV.

Question

Did you use nasal prongs or a nasopharyngeal tube for NIPPV?

Answer

R. Ramanathan: We used both in this trial. The aim was to be as pragmatic as possible to enable the results to be applied to the general practice in many NICUs.

Question

Can you use NIPPV for infants with apnoea?

Answer

R. Ramanathan: In this trial we gave caffeine treatment to all infants and also used a back-up rate. Apnoea is one of the most common reasons for failure of NCPAP, but by adding a back-up rate we were able to avoid reintubation in a higher proportion of babies.

Question

The CAP trial recruited infants whom the clinicians considered to need caffeine treatment. Would you recommend that all preterm infants should be treated with caffeine?

Answer

C. Poets: Infants included in this trial were born at less than 1250 g. These infants should only receive a few days' mechanical ventilation if possible, and are likely to develop apnoea. Therefore I would consider most, if not all, such infants within my practice to be candidates for caffeine treatment.

Question

In your practice, which infants receiving mechanical ventilation are candidates for caffeine? How long after extubation would you stop caffeine if their breathing appears to be regular?

Answer

C. Poets: We begin caffeine in infants of less than 29 weeks' gestation if they still require ventilation on day 3. We use an apnoea scoring system in our practice, but data on how to best assess when an infant no longer requires caffeine are urgently needed.

Question

How can we avoid causing volume trauma to the airways and lung in the delivery room?

Answer

A. Jobe: We know that injury occurs if the lung is allowed to expand and collapse, so CPAP is probably helpful. We should try to allow the infant to transition more slowly if possible.

Question

What is your view on postnatal steroids?

Answer

A. Jobe: Steroid use can be beneficial to some infants receiving mechanical ventilation beyond about 8 days of age and at high risk of BPD. However, there are data to support a lower dose and shorter duration of steroid use, which may be less toxic.