Management of respiratory distress syndrome

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Abstract
Respiratory distress syndrome is the most common pathology of preterm infants managed in neonatal intensive care units worldwide. Advances in neonatal intensive care, prenatal interventions, especially corticosteroid therapy, and postnatal respiratory support have considerably increased the survival of extremely premature infants. Despite these advances, epithelial lung injury and inflammation secondary to surfactant deficiency and as a consequence of mechanical ventilation ultimately leading to bronchopulmonary dysplasia has not significantly reduced. Animal studies have confirmed that the pathological cascade of inflammation is initiated within the first few breaths of life, more so in a surfactant-deficient lung. Hence early management is aimed at minimizing lung injury, starting in the delivery suite. Although a number of different modalities of ventilation are available for ongoing support, the principle is to administer controlled ventilation, avoiding overinflation, and to give just enough end expiratory pressure to prevent collapse of surfactant-deficient alveoli. Non-invasive ventilation is an invaluable tool both in the treatment of mild-to-moderate RDS and the prevention of post-extubation respiratory failure. Supportive treatment contributes equally to the outcome.

Keywords CPAP; neonatal delivery room management; neonatal respiratory distress syndrome; neonatal resuscitation; neonatal ventilation; preterm infant; RDS; surfactant

Introduction
Respiratory distress syndrome (RDS) is the commonest single condition managed in neonatal intensive care units. It is the commonest pathology of preterm infants born at less than 32 weeks’ gestation, and the disease and its complications still account for substantial mortality and long-term morbidity.

Initial disease severity is associated with lower gestational age, perinatal asphyxia, male gender, hypothermia, absence of maternal pre-delivery corticosteroid treatment and, probably, delivery by caesarian section. The role of perinatal infection in relation to disease severity is still to be elucidated. Without exogenous surfactant treatment, symptoms develop shortly after birth and usually increase in severity over the first 2 days of life. Without ventilatory support, infants present with grunting, cyanosis, tachypnoea and subcostal and intercostal recession, and less frequently with apnoea and circulatory collapse. Recovery usually starts after 48–72 h and is associated with a diuresis which coincides with clearance of excess lung fluid, decreasing oxygen and ventilatory requirements and improvement in functional residual capacity (FRC). Lung compliance improves later.

Aetiology and pathophysiology
The initial pathology of RDS is due to physiological and anatomical immaturity of the neonatal lung. Both synthesis and secretion of surfactant are deficient and the lungs are incompletely alveolarized and vascularized. Effective lung function requires not only surfactant, but also an efficient system for gas exchange, development of the diaphragm and chest wall rigidity, along with a mature respiratory drive. A complex secondary pathological cascade of tissue damage and inflammation follows the first breaths, leading to the characteristic clinical syndrome which may either resolve or progressively evolve into bronchopulmonary dysplasia (BPD).

Pulmonary functions
Lung volume: FRC is the volume of lung gas at normal tidal expiration. This is the volume available for gas exchange and is determined by the balance of expanding and collapsing forces from lung and chest wall. In RDS alveolar gas volume may be further displaced by vascular congestion, interstitial oedema and proteinaceous exudate. Improvement in FRC is clinically reflected by a decrease in oxygen requirement, and may be facilitated by application of positive airways pressure (or negative intrathoracic pressure), the presence of surfactant and clearance of oedema and exudates.

Lung compliance is the change in lung volume with the application of a unit change in airway pressure. As the chest walls of premature infants are pliable, the lungs are the major determinants of thoracic elasticity. High surface tension associated with surfactant deficiency increases the pressure increment needed to expand the surface area of the gas–liquid interface between expiration and inspiration. This is the major determinant of poor lung compliance in RDS. Hyaline membrane formation and interstitial oedema may be secondary factors.

Role of surfactant in pulmonary function and blood flow: surfactant forms a thin film at the gas–liquid interface within the terminal sacculles or alveoli and reduces surface tension. Reduced surface tension facilitates expansion of the terminal airways and reduces collapse at end-expiration during the first breaths of life, thus allowing the establishment of an FRC. Establishment of an FRC may be impaired both by surfactant deficiency and by the preterm infant’s impaired ability to clear fetal lung fluid. Once FRC is established, reduced surface tension improves lung compliance and reduces the work of breathing with each tidal breath.

Improvements in gas exchange, particularly oxygenation, result in pulmonary vasodilation and a significant fall in pulmonary arteriolar pressure, facilitating pulmonary blood flow. The pressure change reverses the pulmonary-to-systemic pressure relationship, usually leading to a bi-directional or left-to-right shunt until the duct closes.
Infants born prematurely are likely both to be surfactant deficient and to have a limited ability to clear lung fluid. Thus, they fail to establish an optimal FRC and also have decreased lung compliance. This may lead to hypoxia and acidosis, pulmonary vasoconstriction, pulmonary hypertension and decreased pulmonary blood flow. This in turn may lead to right-to-left shunting, endothelial and epithelial cell injury, pulmonary oedema and right heart failure.

The synthesis and release of surfactant are pH, temperature and perfusion dependent. Hypoxia, asphyxia, pulmonary ischaemia and cold stress are strong inhibitors of surfactant production. High oxygen concentrations and overdistension of alveoli result in a further reduction in surfactant production.

**Management**

Postnatal management of the preterm infant may be regarded as supportive care while the immature physiology and anatomy adapt to the postnatal environment independent of the placental circulation. Intact survival demands that for the respiratory and associated cardiovascular systems, this transition to tissue oxygen delivery and carbon dioxide elimination has to take place very rapidly. In general, with increasing gestational age, particularly at gestations greater than 32 weeks, most premature infants are capable of making the transition with minimal help. Below 32 weeks’ gestation the increased propensity to develop more severe RDS frequently requires some means of respiratory support. While many alternative or complementary respiratory supports exist, the evidence base for their comparative effectiveness individually and for clinical strategies underlying their deployment is limited. Similarly there is concern over potential but uncertain long term respiratory and neurological sequelae of the various treatment strategies and modalities, particularly should they be applied over zealously. Advances in neonatal intensive care and the widespread use of antenatal steroids, surfactant and ventilatory support have considerably increased the survival of extremely premature infants. Despite these advances, the consequence of surfactant deficiency and its management (epithelial lung injury and inflammation ultimately leading to BPD) has not significantly reduced.

Discussion of antenatal prevention of prematurity and RDS is beyond the scope of this review. Evidence in experimental animals for the initiation of the pathological cascade of RDS within the first few breaths of life and a general observation that most clinical interventions are more effective the earlier they are applied suggest that efforts to support respiration while minimizing injury need to focus on very early management. The relative contributions to the evolution of lung injury of such innate factors as molecular genetics, vertically transmitted infection and prenatally disordered lung development – as opposed to postnatal respiratory support strategies – is still unclear. However, pragmatically, there is now increasing emphasis on minimizing ventilation-induced lung injury (VILI) and its consequence, chronic lung disease (CLD), starting in the delivery suite.

**Delivery room management**

A preterm delivery under 30 weeks’ gestation requires skilled personnel trained in the resuscitation and stabilization of premature infants. Currently, the evidence for best practice for supporting preterm neonates in the delivery room remains weak. Intubation: it is known that premature lungs are surfactant deficient, so a rational approach is to replace deficient surfactant and inflate lungs with just enough distending pressure to achieve adequate gas exchange. Surfactant delivery currently requires endotracheal intubation. There is evidence that early surfactant administration is more effective than later administration. While it remains controversial for which preterm group elective endotracheal intubation for the sole purpose of administering early surfactant has advantages, it has been suggested that infants below 27 weeks’ gestation are most likely to benefit from this approach (see Surfactant section below). In premature infants whose clinical condition requires emergency intubation or in whom elective intubation has been chosen, it is good practice to administer exogenous surfactant as early as possible. The advantage of giving surfactant early is to help establish an FRC before lung damage starts, to reduce barotrauma and vascular injury from mechanical ventilation and to prevent damage-related protein leak.

**Oxygen and resuscitation**

Oxygen and resuscitation: oxygen is a potentially toxic gas which can cause direct damage to respiratory epithelium. There is good evidence that 100% oxygen is harmful to most neonates and potentially more so in extremely preterm infants, in whom hyperoxia results in a 20% decrease in cerebral blood flow and a much worse alveolar–arterial oxygen gradient. On the other hand, hypoxia can be detrimental too.

Pulse oximetry at resuscitation can be a useful way of providing immediate feedback on both oxygen saturation and heart rate, although evidence of long-term benefit of its use during delivery suite resuscitation is lacking. In contrast, pulse oximetry may help to wean inspired oxygen and prevent hyperoxic peaks. It is important to be aware of the relatively low fetal intrauterine arterial oxygen concentration of 30–40% and to avoid an obsession with rapidly achieving the high arterial oxygen saturations characteristic of adults. Care should be taken to avoid rapid swings in oxygen saturation. In the absence of evidence to the contrary it is suggested that inspired oxygen concentrations should start with air and be slowly increased to achieve saturations around 90% over no less than 5 min duration. It is no longer acceptable not to have air/oxygen mixed gas available for neonatal resuscitation in delivery suites.

**Continuous positive airway pressure (CPAP) and resuscitation:** there is increasing awareness from animal studies and observational studies in human infants that positive pressure ventilation is capable of inducing lung injury and triggering an inflammatory cascade within minutes of birth, especially in a surfactant-deficient lung.

CPAP support has re-emerged as a potentially ‘gentler’ and less invasive modality to stabilize preterm neonates in the delivery room. This modality appears to be beneficial for infants born with a good heart rate but who are slow to establish an FRC and effective spontaneous respiration. CPAP support with a pressure of at least 5–6 cm H2O helps stabilize expanded or recruited alveoli and also works in synergy with endogenous surfactant by conserving the surfactant on the alveolar surface.
rate of death or BPD in preterm infants born between 25 and 28 weeks’ gestation. The results of this study were inconclusive, showing no reduction in the primary outcome measure of death or BPD in the early CPAP group. In this group there was an increase in pneumothoraces but a decreased use of surfactant, fewer days on ventilation and a lower incidence of oxygen requirement or death at 28 days. This study did demonstrate that nCPAP initiated in the delivery suite in infants of 25–28 weeks’ gestation is an effective strategy, but the evidence to recommend routine use in this group over elective intubation, ventilation and surfactant administration is weak.

Positive pressure ventilation: If positive pressure breaths are required during resuscitation, either by mask or endotracheal tube, peak inspiratory pressure limiting or monitoring devices should be used to help avoid excessive tidal volumes.9,11 Uncontrolled pressure inflations may result in lung damage, capable of triggering an exaggerated inflammatory reaction and of reducing the effectiveness of both endogenous and exogenous surfactant.3 ‘Controlled ventilation’ that avoids overinflation (volutrauma) is essential. It is desirable to administer just enough peak end expiratory pressure (PEEP) to prevent collapse of surfactant-deficient alveoli (as the amount of pressure required is greater to open atelectatic alveoli than it is to ventilate already open alveoli) and to prevent generation of shear forces that can disrupt respiratory epithelium.4

Thermal control: hypothermia in preterm infants decreases endogenous surfactant production, increases the incidence and severity of RDS and is associated with decreased survival. Avoiding early hypothermia is essential secondary management of RDS.15 Measures should include avoidance of draughts and nearby cold surfaces (e.g. windows), elevation of the short-term environmental temperature, use of radiant heat sources and use of an occlusive plastic bag to reduce heat loss by evaporation – this is more effective than attempting to dry the infant. There should be appropriate thermal control during transfer to the neonatal unit and the route from delivery suite to neonatal unit should preferably be short.15

Exogenous surfactant therapy
Since exogenous surfactant’s first use in the 1980s by Fujiwara for the management of neonatal RDS, many randomized controlled trials have been undertaken; making surfactant the most extensively studied pharmacological agent in neonatal medicine. These studies have helped determine the type (natural versus synthetic), optimal dosage, timing (prophylactic versus early rescue) and method of administration of surfactant to maximize its usefulness. Its clinical efficacy is immediately suggested by sometimes dramatic improvements in gas exchange. Meta-analyses of surfactant trials demonstrate a 40% reduction in odds of neonatal mortality and a 30–50% reduction in odds of pulmonary air leaks.12

Types of surfactant: human surfactant is a complex and poorly understood mixture of surface tension reducing and spreading components. Exogenous surfactant used therapeutically may be primarily derived from animal sources (natural) or chemically constituted (synthetic). Both natural and synthetic surfactants are effective in the management of neonatal RDS (Table 1). Despite some theoretical advantages of artificial surfactants (lack of viral risk and of immunogenicity, and better availability of the phospholipid component for recycling by the type II alveolar cells), meta-analysis of randomized controlled trials comparing different types of surfactants have favoured natural surfactants in reducing neonatal mortality (RR 0.86, NNT 50) and pulmonary air leaks (RR 0.63, NNT 25). Natural surfactants are the treatment of choice not only for their rapid onset of action, but also for their sustained effect in maintaining lower mean oxygen requirements for the first 72 h following their first administration.9

Timing of surfactant administration: surfactant should be administered as early as possible. There is a considerable body of evidence to support prophylactic use of surfactant (Table 2). Despite convincing evidence, many clinicians are still hesitant to use prophylactic surfactant as the standard care for infants at high risk of RDS, on the grounds that intubation and surfactant administration is an invasive, expensive and potentially unnecessary procedure.

<table>
<thead>
<tr>
<th>Types of surfactants (adapted from Sweet et al9)</th>
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<tbody>
<tr>
<td><strong>Generic name</strong></td>
</tr>
<tr>
<td>Natural surfactants</td>
</tr>
<tr>
<td>Calfactant</td>
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<tr>
<td>Bovactant</td>
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<tr>
<td>BLES</td>
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<tr>
<td>Surfactant TA</td>
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<tr>
<td>Beractant</td>
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<tr>
<td>Poractant α</td>
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<tr>
<td>Synthetic surfactants</td>
</tr>
<tr>
<td>Colfosceril palmitate</td>
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<tr>
<td>Pumactant</td>
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<tr>
<td>Lucinactant</td>
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Table 1
However, it is currently recommended that all preterm infants born under 27 weeks’ gestation should be electively intubated and given surfactant at birth, especially where prenatal steroids have not been administered.5 Surfactant should in addition be considered for infants under 30 weeks’ gestation who require intubation in the delivery room. A dose of 100–200 mg/kg of phospholipid is recommended. The higher dose may allow time for the endogenous surfactant pool to recycle and replenish, whilst the exogenous surfactant continues to reduce surface tension. Exogenous surfactant should be given as a bolus to assist in rapid and equal distribution through both lungs. A repeat dose of surfactant is recommended if there is an ongoing oxygen requirement on mechanical ventilation 12 h after the initial dose. There is an uncertain evidence base for earlier or additional doses.

Oxygen therapy
In mild RDS, increasing the inspired oxygen concentration may suffice to elevate arterial oxygen concentrations. Much of the oxygen desaturation in RDS is caused by failure to establish and maintain an adequate FRC and associated atelectasis, so this approach has severe limitations and will usually need to be supplemented by pressure support if the oxygen requirement exceeds 30% or there is significant costal or intercostal recession. Oxygen therapy has no impact on the hypercapnia and respiratory acidosis of RDS.

Further/ongoing management
There is now a wide range of available pressure support modalities including:
- CPAP (using a variety of techniques to generate airway pressure)
- nasal positive pressure ventilation (BIPAP)
- intermittent positive pressure ventilation (IPPV)
- intermittent mandatory ventilation (IMV)
- patient triggered ventilation (PTV)

### Timing of surfactant administration (adapted from Soll and Morley24 and Enhorning et al25)

<table>
<thead>
<tr>
<th>Timing</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td><strong>Prophylactic</strong></td>
<td>Avoid barotrauma and vascular injury</td>
<td>A number of infants are subjected to unnecessary treatments</td>
</tr>
<tr>
<td>(treatment within minutes after birth, regardless of respiratory status)</td>
<td>Reduction in mortality (RR 0.61, NNT 20) and air leaks (RR 0.62, NNT 50)</td>
<td>Side effects of endotracheal intubation (hypoxia and trauma)</td>
</tr>
<tr>
<td>NNT in &lt;30 weeks 17</td>
<td>Aid in re-absorption of lung fluid</td>
<td></td>
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<tr>
<td></td>
<td>Homogeneous distribution</td>
<td></td>
</tr>
<tr>
<td><strong>Early rescue</strong></td>
<td>Reduction in mortality (RR 0.87) and air leaks (RR 0.7)</td>
<td>Careful clinical monitoring required</td>
</tr>
<tr>
<td>(administration of surfactant to symptomatic infants before 2 h of life)</td>
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Table 2

- volume limited ventilation
- volume guarantee ventilation (VGV)
- pressure support ventilation (PSV)
- high frequency oscillatory ventilation (HFOV) (using a variety of techniques to generate the high frequency energy within the airway).

Each of these modalities may be deployed in a variety of ways during both acute and weaning phases of RDS. Evidence from large randomized multicentre clinical trials for superiority of one modality over another is largely missing. Such trials are notoriously difficult to design due to the many variables influencing medium- and long-term respiratory outcomes. It is beyond the scope of this review to discuss each modality in detail, but there are generally accepted principles for pressure support interventions for RDS and a hierarchy of interventions for increasing disease severity, with many variations of application between different centres and clinicians depending on personal experience and preferences.

Non-invasive ventilation
Continuous positive airway support
CPAP is a technique of respiratory support useful in infants with respiratory distress who are spontaneously breathing, and is widely used both in the early acute and late weaning/recovery phases of RDS. The continuous distending pressure applied to the lung improves oxygenation by decreasing atelectasis, helping establish an FRC and eliminating fetal lung fluid, controlling excessive pulmonary blood flow and pulmonary plethora in the presence of a patent ductus arteriosus (PDA) and left-to-right shunt, and improving ventilation–perfusion matching.6,16 It may also reduce airways resistance by supporting the non-surfactant dependent upper airways. The effect of CPAP on lung compliance is variable from infant to infant and time to time in the same infant, depending on disease severity and the pressure used. At higher pressures, the work of breathing against the positive pressure may increase and so the impact of CPAP on carbon dioxide elimination is variable. CPAP is also useful in reducing apnoea of prematurity which commonly coexists with RDS.

Potential disadvantages of CPAP tend to be common to most methods of respiratory pressure support and include increased risk of pneumothorax and decreased pulmonary perfusion. Effectiveness may also be limited by technical difficulties in maintaining an adequate airway pressure. Effective use of CPAP requires considerable nursing and medical skill. Excessive hypercapnia due to increased airways pressure, and insufficiently improved oxygenation (required FIO2 more than 40%) generally herald the need to progress to tidal or high frequency oscillatory pressure support.

Cochrane reviews of trials of the early use of CPAP in the pre-surfactant era failed to demonstrate clear clinical benefit over intubation and ventilation. More recent trials comparing early use of CPAP with early positive pressure ventilation have demonstrated that many infants can be satisfactorily supported on CPAP alone, although evidence of resultant decrease in BPD or mortality is disappointingly absent.14

It is suggested that early intubation for the administration of surfactant followed by immediate extubation and CPAP may have benefits over early use of CPAP alone or early intubation,
surfactant administration and ongoing positive pressure ventilation. Evidence from trials is still awaited.6,11

In the weaning/recovery phase of RDS, CPAP is invaluable after extubation from positive pressure ventilation by reducing the need for re-intubation due to respiratory failure.9,17

**Nasal positive pressure ventilation (BiPAP/SiPAP)**

Nasal ventilation (NV) through prongs is a non-invasive way of delivering positive pressure throughout the respiratory cycle (like CPAP) with additional phasic increases in airway pressure that can be synchronized with the infant’s respiratory effort. NV could be used as a non-invasive alternative to CPAP both in early RDS and post-extubation. This modality could potentially be more effective than CPAP by decreasing the work of breathing and thus hypercapnia, and in reducing apnoea. One trial has shown that use of NV produced fewer failed extubations than use of CPAP in infants weighing less than 1251 g. The use of NV in the acute phase of RDS lacks an evidence base at present.18

**Invasive ventilation**

Indications for invasive ventilation include failure of non-invasive ventilation (see above) or a policy of initial intubation and ventilation for the high-risk preterm infant.

**Intermittent positive pressure ventilation**

IPPV delivered by constant flow, time-cycled, pressure limited ventilators is the most frequently used and familiar modality of neonatal ventilation. A constant flow of gas through the circuit allows the infant to take their own spontaneous breaths. Adjustable inspiratory and expiratory valves control the pressures within the circuit for the two phases of the ventilatory cycle. Depending on lung compliance, gas flows through the T-piece into the infant’s lungs during the inspiratory phase; during the lower pressure expiratory phase, elastic recoil of lung and chest wall allows gas to leave the lungs. It is usual to maintain a PEEP of between 4 and 6 cm H2O – the equivalent of CPAP – to avoid alveolar de-recruitment during expiration.

Higher PEEP may be desirable in the presence of large left-to-right ductal shunts, pulmonary haemorrhage or severe RDS and high oxygen requirement. Lower PEEP may be advantageous if there is radiographic evidence of air trapping and this sometimes helps carbon dioxide elimination. Higher inspiratory pressures improve lung inflation and oxygenation but carry the risk of lung damage and pulmonary air leak. Tidal volume and therefore carbon dioxide elimination is generally proportional to the difference between inspiratory and expiratory pressures.

Many modern neonatal ventilators allow not only the monitoring of proximal airway pressure, but also flow within the T-piece. This has many potential advantages, including an ability to target desired tidal or minute volumes by adjusting inspiratory and expiratory pressures and times, to display pressure–volume loops and assess dynamic lung compliance, to detect gas leaks from around the endotracheal tube and to detect spontaneous respiratory effort and synchronize the ventilator to the infant. Most neonatal ventilators allow manipulation of the pressure–time waveform either through varying the circuit flow rate or controlling the release of the inspiratory valve. It is unclear what constitutes an optimal pressure waveform – a squarer waveform is likely to be more effective both in terms of oxygenation and carbon dioxide elimination for given pressures and rates, but may increase pulmonary shear forces and lung damage.

Time-cycling is generally achieved through adjustable electronic timer control of the opening and closing of the inspiratory valve, to deliver variable inspiratory and expiratory times and the resultant ventilator rate. Shorter inspiratory times (0.2–0.35 s) are generally favoured for better carbon dioxide elimination with very stiff lungs. Longer inspiratory times may improve oxygenation but carry the risk of air trapping. Longer expiratory times allow extra spontaneous breaths during weaning but in general lead to poorer oxygenation and carbon dioxide elimination. Conversely, within limits, shorter expiratory times and thus faster ventilator rates improve both oxygenation and carbon dioxide elimination.

There is little definitive outcome-related evidence for varying styles of IPPV ventilator settings, although current practice favours faster rates (shorter expiratory times), which may reduce the incidence of pulmonary air leak7,19 and help achieve entrainment of the infant’s spontaneous respiratory effort leading to improved ventilator synchrony (see below).

**Patient-triggered ventilation**

It is customary to ventilate preterm infants without muscle relaxant medications (see below). The unselected use of muscle relaxants has been associated with the need for higher ventilatory pressures, longer ventilation and increased BPD. As a result, most infants will breathe spontaneously while ventilated. When the spontaneous breathing pattern is totally dissociated from that of the mechanical ventilator, the efforts of infant and ventilator may intermittently conflict. This is liable to lead to a need for higher ventilator settings, a higher incidence of pulmonary air leak and worse BPD. Patient-triggered ventilation attempts to introduce a degree of synchrony between infant and ventilator.20 All modern neonatal trigger ventilators detect infant ventilatory effort through spontaneous inspiratory flow through the T-piece and attempt to synchronize mechanical inflation with the infant’s own effort. There are several modes of ventilation which use PTV principle, including synchronized intermittent mandatory ventilation (SIMV), assist/control (A/C), pressure support ventilation (PSV) and flow cycling. The modes differ in respect to the available trigger time window during the ventilatory cycle, the presence of back-up ventilator breaths when spontaneous respiration is not detected, the level of pressure support provided for spontaneous breaths, and whether the inspiratory and/or expiratory phases of ventilation are triggered.16

Short-term benefits of PTV have been well recorded, and there is some evidence for shorter periods of ventilation requirement but there is a lack of clear evidence for reduction in BPD, probably due to methodological difficulties and underpowering of trials.

**Volume-targeted ventilation**

Conventionally, the volume of gas delivered with each ventilator breath is clinician controlled by adjusting inspiratory pressure and time. The volume is monitored directly on the ventilator by integrating flow and time. Much of the lung damage represented by BPD is thought to be mediated through excessive volume delivery – volutrauma. Arguably it might be advantageous to allow the ventilator to deliver pre-set volumes rather than pre-set pressures. This would allow the ventilator to respond to rapid
changes in lung compliance without clinician intervention and is potentially a self-weaning modality of ventilation, possibly facilitating faster weaning from mechanical ventilation. Although there is early promising work, the relative advantages of this form of ventilation over conventional techniques remains unproven.

**High-frequency oscillatory ventilation**

HFOV utilizes different physical principles from conventional tidal IPPV to achieve gas exchange. Very small tidal volumes are delivered at rapid rates, while alveolar recruitment is achieved by the application of a continuous distending pressure similar but usually higher than conventional CPAP. This has proven to be an effective mode of ventilation in infants who have severe carbon dioxide retention or pulmonary hypertension. Because the airway pressure excursion at alveolar level is very small, it has been thought that this style of ventilation might cause less lung damage.

Strategies for applying HFOV have polarized between ‘low volume’ where the mean airways pressure is minimized and therefore required inspired oxygen concentrations are liable to be high, and ‘high volume’ where sufficient distending pressure is applied to achieve near full alveolar recruitment and low inspired oxygen concentrations. High volume strategies are considered to offer the best hope for minimizing lung damage as oxygen toxicity is also avoided. Lower pressures and volumes may be more appropriate in the presence of air leak or cardiovascular compromise.

Treatment strategies are further polarized between use of the modality as rescue treatment for infants failing conventional ventilatory management at moderate pressures and first-line treatment with the objective of avoiding early lung damage associated with conventional ventilation.

The diverse trials of early use of HFOV with varying designs and case mixes have reported diverse outcome. On balance, early HFOV has been shown to be an effective ventilation modality for RDS but there is no good evidence for a reduction in CLD. Clinical experience of ‘rescue’ treatment is that many infants with RDS who are unstable with escalating oxygen requirements on conventional ventilation do well on transfer to HFOV, providing that any associated cardiovascular compromise is addressed. A Cochrane review of rescue HFOV use showed reduction in new pulmonary air leaks (NNT 6), but increased risk of intraventricular haemorrhage in preterm infants.

**Permissive hypercapnia**

Whatever style of ventilation, it has been argued that allowing carbon dioxide to run at supra-physiological levels will reduce ventilatory requirements and thus CLD. Randomized controlled trials have shown that permissive hypercapnia decreases the duration of mechanical ventilation and reduces the hypocapnia-associated decreased cerebral blood flow. Unfortunately, there is no evidence of reduction in incidence of CLD. The relative safety, acceptable range of hypercapnia and long-term neurodevelopmental outcome are not yet known and require further studies.

**Sedation and muscle relaxants**

Endotracheal ventilation of unsedated patients of any age is likely to be unpleasant and it is now considered good practice for all intubated ventilated infants to receive some sedation, at least until extubation is contemplated and respiratory drive needs to be optimized.

Muscle relaxants are widely used in other intensive care scenarios, but preterm infants often have relatively weak respiratory muscular effort and there is evidence that routine unselected use of paralysing agents is associated with delayed ventilatory weaning and extubation. In addition, even weak respiratory effort may help support respiration while on a ventilator as evidenced by the acute need for higher inspiratory pressures in some infants on starting muscle relaxant therapy. However, other ventilated infants with dys-synchronous breathing on ventilation – ‘fighting the ventilator’ – benefit from acute muscle relaxation through reduced oxygen requirement and probable reduced risk of air leak. Muscle relaxation should be considered for infants on very high pressure ventilation or when oxygenation is difficult in association with dys-synchronous breathing, but its duration of use should probably be minimized.

**Respiratory stimulants**

Caffeine has several pharmacological effects, including improved respiratory drive, and it may help earlier extubation following mechanical ventilation.

**Antibiotics**

Group B streptococcus (GBS) infection carries the risk of mortality and adverse neurological sequelae in preterm infants. Symptoms of early-onset GBS chest infection may be indistinguishable from RDS. It is therefore good practice to screen infants with respiratory distress for sepsis and to commence antibiotic treatment until infection is excluded.

The role of other infective organisms (e.g. *Ureaplasma urealyticum* and their antimicrobial treatment in the pathology of RDS and its evolution to BPD remains unclear.

**Patent ductus arteriosus**

The management of PDA in RDS remains controversial and detailed discussion of this is beyond the scope of this review. Despite theoretical respiratory benefits, unselected prophylactic pharmacological closure of the PDA does not improve long-term outcome. Similarly, there is insufficient evidence for benefit from routine pharmacological or surgical closure of established PDAs, and decisions on whether and when to attempt closure need case-by-case assessment of the clinical impact of the left-to-right shunt on respiratory performance and progress.

**Supportive treatment**

Other supportive management of infants with RDS (fluid and nutritional management, cardiovascular support, thermal control, etc) is likely to be important in determining both mortality and morbidity in these infants, but these issues constitute general care of preterm infants and are beyond the scope of this review.

**Conclusions**

The management of RDS in preterm infants has contributed to major improvements in survival, but the legacy in the most
preterm survivors is a high level of lung damage and chronic respiratory impairment. There is now a very wide and constantly increasing range of available supportive technologies, but because of the multiple factors influencing respiratory outcome, study design is difficult and the evidence base for relative effectiveness, safety and improved long-term outcomes for many is weak or non-existent. Because of the pathological cascade which characterizes RDS, the most effective therapeutic interventions are likely to be those instituted at the very beginning of life. ◆

References


Practice points

- At resuscitation, initially use air or low oxygen concentrations. Only increase oxygen concentration if the heart rate remains less than 100 bpm or oxygen saturation remains unacceptably low after 5 min. Pulse oximetry is useful to monitor heart rate and to avoid hyperoxia.
- If positive pressure ventilation is required at resuscitation, use pressure limiting devices to avoid large tidal volumes. For infants at risk of RDS but not requiring intubation, commence CPAP support of at least 5–6 cm H2O via prongs to establish alveolar recruitment and a functional residual capacity.
- In premature infants whose clinical condition requires emergency intubation or in whom elective intubation (less than 27 weeks) has been chosen, it is good practice to administer exogenous surfactant as early as possible.
- Although the development of BPD is multifactorial and poorly understood, techniques and strategies that reduce the duration of mechanical ventilation are likely to be helpful in preventing lung injury.
- Non-invasive ventilation (CPAP and BiPAP) following extubation reduces the need for re-intubation. Caffeine therapy may facilitate successful extubation.
- Supportive aspects of clinical management of the preterm baby – thermal, fluid and nutritional care, sepsis treatment and cardiovascular support – may be just as important in determining respiratory outcome as direct respiratory interventions.