Bronchopulmonary Dysplasia and Chronic Lung Disease of Infancy: Strategies for Prevention and Management

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Abstract

Remarkable advances in the treatment of neonatal respiratory disorders, such as antenatal glucocorticoid therapy, surfactant replacement therapy and alternative modes of ventilation, have reduced neonatal mortality and acute respiratory morbidity. However, bronchopulmonary dysplasia and chronic lung disease of infancy remain a substantial complication, especially among the most immature infants. The pathogenesis of chronic lung disease is complex and multifactorial. Prevention and treatment will require a comprehensive multiprong approach with specific interventions and practices focused on different levels of the pathways leading to chronic lung changes. Future improvements in care will require a better understanding of lung development and lung repair mechanisms. However, the ultimate and most effective approach should be a relentless pursuit for measures to prevent premature births.

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Changing Epidemiology

Bronchopulmonary dysplasia (BPD) and chronic lung disease of infancy (CLD) are two chronic pulmonary conditions which are the result of incomplete resolution or abnormal repair of lung injury in the neonatal period.[1] Although BPD and CLD are closely related, they have differing diagnostic criteria and the spectrum of severity of these conditions is wide. There are some indications that BPD and CLD are second only to asthma among chronic lung diseases in paediatrics.[2]

Northway and associates[3] were the first to describe the classic form of BPD in 1967 in premature infants who had severe respiratory distress syndrome (RDS) and received prolonged aggressive mechanical ventilation with high positive airway pressures and inspired oxygen concentrations. Their clinical and radiographic course ended with severe chronic lung changes characterised by persistent respiratory failure with hypoxaemia and hypercapnia, frequent cor pulmonale, and a chest radiograph that revealed areas of increased density due to fibrosis and collapse surrounded by areas of marked hyperinflation. The term "bronchopulmonary dysplasia" was used to emphasise the involvement of all the tissues of the lung in the pathologic process. BPD may occasionally affect full term neonates with various underlying lung disorders (such as meconium aspiration syndrome, pulmonary hypertension, pulmonary hypoplasia and pneumonia), if they sustain sufficient lung injury with disrupted development and abnormal healing.[4]

Currently, this severe form of classic BPD is becoming less common and has been replaced by a milder form of chronic lung damage that occurs in many very small preterm infants, most of them receive antenatal steroids and postnatal surfactant replacement therapy. Because of these therapies, they experience a mild initial respiratory course and, therefore, are not exposed to aggressive ventilation or high inspired oxygen concentrations. The "late BPD" category is observed in the very-low-birth-weight (VLBW; less than 1500 g) and extremely-low-birth-weight (ELBW; less than 1000 g) infants, with little or no lung disease at birth, but they slowly acquire the need for supplemental oxygen or even ventilatory support in the second or third week of life, primarily for management of apnoea and poor respiratory effort. In between the "classic" and "late" categories of BPD is an intermediate group of similarly small infants who have mild to moderate respiratory failure at birth, appear to recover, then slowly experience a progressive deterioration in lung function over time.

BPD can be diagnosed on the 28th day of life in infants who continue to require supplemental oxygen, have an abnormal physical examination with tachypnoea, wheezes

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and retractions and have an abnormal chest radiograph.[4] This definition of BPD is useful in making inter-neonatal intensive care unit comparisons of clinical outcomes, and for internal quality control. An infant is said to have CLD if, at 36 weeks postmenstrual age, there is a continued requirement for supplemental oxygen, an abnormal physical examination as described above and an abnormal chest radiograph.[5] Many infants who meet the criteria for BPD on the 28th day of life will be sufficiently recovered by 36 weeks postmenstrual age that they do not meet criteria for the diagnosis of CLD. The diagnosis of CLD is a better predictor of clinical respiratory difficulty during the first year of life.[5]

Pathogenesis

The primary aetiological factors in the development of BPD and CLD are an immature lung; direct injury by oxygen and mechanical ventilation (barotrauma or volutrauma); and further injury to the lung, which occurs when lung inflammation is initiated by supplemental oxygen and mechanical ventilation.[1,4]

When preterm birth is accompanied by RDS and respiratory failure, there are quantitative deficiencies of surfactant, antioxidant defences and inhibitors of proteolytic enzymes.[4,6] Mechanical ventilation disrupts epithelial surfaces, allowing plasma proteins to enter the airways, stretches and damages the walls of developing small conducting airways and alveolar septa, resulting in rupture of these fragile elastin-based structures. Supplemental oxygen in the small airways is accompanied by formation of oxygen radicals, which damage cell membranes and interior cellular structures. The antioxidant deficient preterm lung is poorly equipped to handle these oxygen radicals. Both mechanical ventilation and supplemental oxygen damage the lung directly and initiate an influx of neutrophils into the lung with consequent lung inflammation. This inflammatory response can also be triggered by pulmonary oedema, and systemic or pulmonary infections acquired before or after birth. While neonates with RDS usually have an influx of neutrophils into the lung, those who develop BPD have larger numbers of neutrophils and longer duration of influx in comparison to those who recover from RDS without complication.[4,6,7] These neutrophils release several pro-inflammatory mediators and proteolytic enzymes, most prominently elastase, which digest alveolar septa and other structures within the developing lung. The preterm lung is deficient in proteinase inhibitors and consequently is unable to adequately control neutrophil lung damage. Infants who develop BPD have more pronounced proteinase-induced lung damage than infants who recover from RDS without complication.[4,6,7] This imbalance between exaggerated pro-inflammatory mediators and an immature host ability to counter the pro-inflammatory response plays an important role in the lung injury and abnormal repair that leads to BPD and CLD.

Once established, the inflammatory cascade is self-perpetuating as more neutrophils are recruited into the lung. Even as mechanical ventilation and supplemental oxygen are withdrawn with the resolution of RDS, continuing inflammation perpetuates the lung damage. Several protein and lipid mediators of inflammation are present in greater amounts in lung fluid of infants who develop BPD than that found in those who recover from RDS without complication.[4,6,7] Among the markers of inflammation that have been found in high concentrations in tracheobronchial secretions are neutrophils, macrophages, leukotrienes, platelet activating factor, interleukins, and fibronectin and selectin, which are associated with the development of pulmonary fibrosis.

The duration and intensity of mechanical ventilation, oxygen exposure and inflammation, coupled with the extent of immaturity and destruction of the developing lung, lead to the development of BPD and CLD. A genetic predisposition to the development of BPD has been raised because of a greater risk of BPD in families with a strong family of asthma.[8] This may be one of the possible reasons why some neonates resolve RDS in an uncomplicated manner while others develop BPD.

The pathogenesis of CLD is complex and multifactorial. It is likely that reduction in CLD will require a comprehensive multifaceted approach with specific interventions and care practices focused on different aspects of the pathway that leads to CLD. The extent that strategies reduce vulnerability to lung injury, reduce initial and ongoing lung damage, and promote normal lung growth and development will determine the net effect on the incidence and severity of CLD.

Prevention of Premature Birth and its Adverse Effects

The inverse association of CLD with gestational age and birth weight is well recognised. The Vermont-Oxford Network reported a 60% incidence of CLD in survivors who weighed 501 to 750 g at birth, a 39% incidence among survivors who weighed 750 to 1000 g and a 21% incidence for those with birth weight of 1001 to 1250 g.[9] CLD primarily affects infants with the most functionally and structurally immature lungs. Prevention of premature birth, especially extreme prematurity, would reduce the occurrence of CLD. Unfortunately, numerous "prevention of prematurity" strategies have been tried without consistent success and the incidence of preterm birth has not decreased in the past decade.[10]

Prevention of CLD should start prenatally by attempting to prolong pregnancy as much as possible in cases of preterm labour. By postponing birth a few days or weeks,

it is possible to substantially reduce the risk of CLD in the offspring. The most significant contribution of tocolysis has been the delay afforded for the use of antenatal glucocorticoid therapy. Antenatal steroids accelerate lung maturity via induction of surfactant production, induction of antioxidant enzymes and structural changes.[11] This has been shown to reduce the incidence and severity of RDS and the subsequent development of CLD.[12] There is no evidence that multiple courses (more than 3 courses) of antenatal steroids are more beneficial than one or two complete courses. Recent evidence suggests that multiple courses may result in worse pulmonary outcome.[13,14] Antenatal prophylaxis with a combination thyrotropin-releasing hormone (TRH) and glucocorticoid therapy had shown some initial benefit. However, a large multicentre trial (ACTOBAT Study) failed to show improvement in neonatal respiratory outcome.[15] The TRH-treated infants had an increased risk of RDS and adverse neurological outcomes. Therefore, TRH could not be recommended for prevention of neonatal respiratory distress.

The relation between maternal infections and premature labour has been established.[16] Early detection of women with asymptomatic bacteriuria and bacterial vaginosis, followed by appropriate antibiotic therapy has decreased the occurrence of preterm delivery.

Preterm infants exposed to antenatal inflammation and chorioamnionitis are at increased risk of developing CLD.[17] Several inflammatory cytokines are found in higher concentrations in the amniotic fluid of mothers who deliver infants who develop CLD compared to those who give birth to infants who recover without CLD. The presence of maternal chorioamnionitis was also significantly associated with early elevation of tracheal inflammatory markers in the infants. In addition, several publications have suggested a higher risk of CLD in infants whose airways are colonised with *Ureaplasma urealyticum* and *Mycoplasma hominis* at birth, although this association has not been consistent.[18] These data raise the possibility that anti-inflammatory therapy may reduce the risk of CLD.

Surfactant Replacement Therapy

Both prophylactic and rescue surfactant replacement therapy have been shown to be effective in reducing the severity of RDS and the occurrence of pulmonary air leaks, and in increasing the survival in very premature infants. The effect of surfactant therapy on reducing the incidence of CLD is variable, although it does appear to have reduced the severity of CLD.[19,20] Early administration appeared to have marginal benefit over rescue treatment.[19,20] However, broad policies of providing immediate surfactant prophylaxis in the delivery room to all infants below a specified gestational age or birth weight will result in a number of newborns intubated, mechanically ventilated and treated with surfactant unnecessarily. Although it can be expected that exogenous surfactant administration may reduce the incidence and severity of CLD in infants who previously developed severe RDS, it is unlikely that it will have a significant effect on the CLD that occurs with increasing frequency in ELBW infants who required prolonged mechanical ventilation because of poor respiratory effort rather than severe RDS.

It has been known for some time that there exists significant variation in the incidence of CLD between neonatal intensive care units (NICUs), which persists even after controlling for patient characteristics.[21,22] Remarkably low incidence of CLD has been achieved in centres with less use of surfactant therapy, and less exposure to antenatal glucocorticoid therapy in contrast to the comparison NICUs with higher occurrence of CLD.[21,22] This variation may be attributed to neonatal care practices, such as initiation and application of mechanical ventilation, nutrition and fluid management, and practices that influence the risk of nosocomial infections. The fact that some NICUs can achieve lower rates of CLD strongly suggests that prevention, or at least reduction, of CLD is possible.

Prevention of Barotrauma and Volutrauma

BPD made its appearance after the introduction of positive-pressure mechanical ventilation for premature infants with RDS. Prior to that, chronic lung disease was reported only occasionally in infants treated with high oxygen concentrations, without positive-pressure ventilation. However, this condition, better known as pulmonary fibroplasia, was not the same as BPD, as there was mainly parenchymal fibrosis without the typical airway involvement in BPD, and the clinical course was much milder.[23] Pathological studies of premature infants have demonstrated marked distortion of the lung, especially the terminal bronchioles, during mechanical ventilation. BPD was mainly the result of overdistension of terminal airways by high inflating pressures at a time when the terminal spaces or alveoli could not be inflated easily because of surfactant deficiency. As a result of this cyclical bronchiolar stretching, terminal airway ischaemia and necrosis develop, which eventually lead to interstitial air dissection, interstitial emphysema, pneumothorax, and triggering a broad inflammatory response that further reinforces the initial lung injury.[24]

Although this injury mechanism has been termed barotrauma, studies indicate that high levels of positive pressure alone are well tolerated by the newborn lung if lung stretch is prevented. When chest expansion is physically restricted during mechanical ventilation in experimental animals, the inflation pressures remain high, but lung injury is remarkably reduced or absent. The real culprit is high tidal volumes associated with overdistension.[25] High

tidal volume ventilation can also increase lung microvascular permeability, which may augment oedema and result in the need for more aggressive mechanical ventilation.[26] Therefore, it would be more appropriate to speak of volutrauma.

The use of positive end-expiratory pressure (PEEP) during mechanical ventilation has been found to be protective against BPD.[27] Lung injury occurs when the alveoli are allowed to collapse during expiration and must be reopened or recruited again with each breath by high inflating pressures. The use of generous levels of PEEP prevents this phenomenon.[28]

It is interesting to note that infants treated with negative-pressure respirators between 1965 and 1975 never developed BPD, despite exposure to 100% oxygen for remarkably long periods.[29] The negative-pressure respirator was a highly inefficient ventilator. Even with ventilatory rates of 60 breaths per minute, it seldom corrected the arterial PCO_2 to below 45 mmHg, and therefore seldom overdistended the lung. Moreover, it oxygenated infants only if high levels of expiratory distending pressure were used, which may be protecting against lung injury.

There are reports on the association between low arterial PCO_2 values (less than 29 mmHg) and CLD, suggesting that the peak inflation pressure was too high in relation to the lung compliance. The excessive ventilation may contribute to CLD.[30,31] To reduce lung injury associated with excessive ventilation and hypocapnia, ventilatory strategies of permissive hypercapnia have been suggested, which allow higher $PaCO_2$ (45 to 55 mmHg) and avoid hypocapnia. Permissive hypercapnia was associated with a trend toward fewer days on ventilation, significantly fewer patients on assisted ventilation at 28 days of age and no increased complications.[32] Permissive hypercapnia to $PaCO_2$ levels above 55 mmHg is reasonable, but the optimal range of $PaCO_2$ levels is not known in premature infants.[33]

Therefore, although the association of mechanical ventilation and lung injury is indisputable, some ventilatory practices are more harmful than others. Mechanical ventilation must be used only when clearly indicated and a more "gentle" ventilatory strategy is desirable. This involves careful control of tidal volumes to ensure that the smallest possible tidal volume is used to avoid lung overdistension, the use of adequate PEEP to avoid atelectasis, and permissive hypercapnia to avoid excessive ventilation. An aggressive weaning policy should also be in place to limit the duration of mechanical ventilation as much as possible. The role of the endotracheal tube itself is difficult to separate from that of the mechanical ventilation, but the tube may hinder the drainage of bronchial secretions and increase the risk of pulmonary infections.

Early Use of Nasal Continuous Positive Airway Pressure

The collective evidence of injury induced by mechanical ventilation and excessive ventilation has led to a critical evaluation of the approach to mechanical ventilation and delivery room management of the newborn infants. The early use of nasal continuous positive airway pressure (NCPAP) has been championed as a strategy to reduce the need for endotracheal intubation and to reduce the injury due to initiation of mechanical ventilation.

This strategic goal to prevent or to reduce CLD is achievable even in ELBW infants, without changing short-term outcomes.[34] In two separate studies on the occurrence of CLD in several NICUs, the NICU with the lowest overall incidence of CLD used NCPAP early and often, used less mechanical ventilation, permitted higher $PaCO_2$ and lower pH values.[21,22] NCPAP was applied in the delivery room for premature infants with respiratory distress. Early NCPAP may improve oxygenation by early recruitment and stabilisation of the alveoli, decreasing the need for and duration of assisted ventilation, thus avoiding lung injury.[35]

For extremely premature infants at high risk for RDS, a combined approach of early administration of exogenous surfactant followed by rapid extubation to NCPAP has been recommended. Study showed that the need for mechanical ventilation was reduced by 50% in ELBW infants treated with surfactant and continuous positive airway pressure (CPAP) compared to similar infants who received CPAP alone.[36]

Alternative Ventilation Techniques

The findings that volutrauma, rather than barotrauma, is the principal mechanism of ventilator-induced lung injury have spurred the search for less damaging ways to apply conventional ventilation, and to the development of unconventional ventilation techniques.

High Frequency Ventilation

Over the past 15 years, there has been extensive interest in the use of different types of high-frequency ventilators utilising jet, flow interruption, or oscillation devices. The goal of high frequency ventilation (HFV) in neonatal respiratory failure is to achieve adequate gas exchange using smaller tidal volumes to maintain more uniform lung inflation and near constant mean airway pressure, and to avoid pressure swings. No human trials have directly compared the various types of HFV.

Jet ventilators usually cycle at frequencies between 3 and 10 Hz (180 to 600 cycles/min) and require a specialised triple-lumen endotracheal tube or a specially designed endotracheal tube circuit adaptor. This form of ventilation delivers a low-volume, high-velocity jet of gas, and there

is a background of gas flow from a respirator that permits conventional tidal breathing. The rationale is to avoid high peak and mean airway pressure. However, controlled trials have not demonstrated a significant decreased in the incidence of CLD.[37,38]

Flow interruption devices produce a rapid interruption of gas flow that results in an inspiratory jet at frequencies of 10 to 15 Hz. Again, no clear-cut advantage has been demonstrated for this mode of ventilation in preventing CLD. Adverse outcomes and poor neurological effects such as intracranial haemorrhage and periventricular leukomalacia in infants studied under this treatment regimen are reported.[38]

High-frequency oscillatory ventilation (HFOV) appears to be the most promising and logical strategy for effective ventilation among different modes of HFV. A small tidal volume of 1 to 2 mL delivered at frequencies of 8 to 16 Hz permits a low mean airway pressure and reduces the development of air leak.[39] Several controlled trials have been reported and subjected to meta-analysis. The HIFI study did not demonstrate a reduced incidence of CLD.[40] The trend from other studies was toward a reduced incidence of BPD at 28 to 30 days of age, but the difference was not statistically significant.[41] Initial studies of this ventilation strategy did not include use of exogenous surfactant.[40] A criticism of the HIFI study was that it may not have included sufficient peak inflation pressure to bring about recruitment of terminal respiratory units, thereby resulting in inadequate lung gas volume.[42] Subsequently, other studies have employed a "high-volume strategy".[43] Lung volume assessment is provided by serial chest radiographs, and mean airway pressure is increased if lung inflation appears inadequate. At this stage, the role of HFOV in preventing CLD is still controversial and the evidence of its benefits is not compelling. Results of additional ongoing trials may provide further evidence of its impact on pulmonary and neonatal outcome.[43]

Patient-Triggered Ventilation

Newer methods of conventional ventilation have evolved in which the mechanical ventilated breaths are synchronised with the patient's spontaneous inspiratory phase. The goal of patient-triggered ventilation (PTV) is to reduce asynchrony between the patients and the mechanical ventilator and improve the efficiency of gas exchange, thus reducing the need for ventilatory support.

Large multicentre trials comparing PTV with conventional ventilation have found no benefits of PTV and a trend toward higher pneumothorax rates with PTV in infants below 28 weeks gestation. There were no differences in mortality, oxygen dependency at 36 weeks postmenstrual age, or cranial ultrasound abnormalities. PTV infants were more likely to switch their assigned mode of ventilation compared to conventional mode and the failure rate was high. The trials also failed to show any difference in the incidence of CLD.[44,45]

Despite extensive studies, none of the new ventilatory techniques explored so far has been found to have significant impact on preventing and reducing the severity of CLD. There are even limited clinical experiences with other techniques, such as intratracheal pulmonary ventilation and liquid ventilation. A major weakness of many studies to date is the inability to control for the expertise of the operators of the ventilator. There is always the scientific challenge of studying and understanding the various ventilatory approaches. Furthermore, other neonatal intensive care practices, such as fluid and nutritional management, ventilation initiation and weaning criteria, and postnatal glucocorticoid therapy, are additional sources of variability that impact the pulmonary outcome.

Minimising Pulmonary Oxygen Toxicity and Boosting Antioxidant Defences

The detrimental effects of acute and long-term oxygen exposure on lung function and lung development have been known for decades, although oxygen alone will not produce the full pathology of classic BPD.[23] The pulmonary changes of oxygen toxicity are non-specific and consist of atelectasis, oedema and alveolar haemorrhage, inflammation, fibrin deposition, and thickening and hyalinisation of alveolar membranes. The capillary endothelium is particularly vulnerable, and the increased microvascular permeability causes plasma leakage into interstitial and alveolar spaces. Pulmonary surfactant may be inactivated and there is loss of mucociliary function of the tracheobronchiolar airways. Continued exposure to high oxygen is accompanied by influx of neutrophils containing proteolytic enzymes. In addition, the anti-proteinase defence system may be similarly impaired by prolonged high oxygen exposure, favouring proteolytic damage to the alveolar structure.[6,7] The mechanism of pulmonary oxygen toxicity is related to the accelerated production of toxic oxygen free radicals during hyperoxic exposure and inflammation, which overwhelms the infant's endogenous antioxidant defences.[46]

It is impossible to define a safe level or duration of oxygen exposure for infants with immature lungs. Oxygen-induced lung injury depends not only on the inspired oxygen concentrations, but also on an imbalance between oxidant production and oxidant destruction within specific lung cells. Lung levels of antioxidant enzymes have been found to increase with gestation, but so do enzyme systems that increase oxidant production, so that the oxidant/antioxidant balance remains relatively constant throughout

gestation. The immature infant's susceptibility to oxygen injury may be attributed to an inability to respond rapidly to oxygen exposure by inducing antioxidant production and by inhibiting oxidant production.

Past research has focused mainly on the role of lung antioxidant enzymes in the defence against oxygen injury, such as superoxide dismutase, catalase and glutathione peroxidase. Augmentation of lung antioxidants by inducing the enzyme systems, or by direct supplementation, may offer some protection from oxygen toxicity. Antenatal glucocorticoids is known to induce the production of antioxidant enzymes.[11] Future strategies to reduce oxidant-mediated lung injury will likely be based on a better understanding of the regulation of the oxidant-and antioxidant-producing pathways, especially on enzymatic sources of oxidant production, and on the key role of non-enzymatic antioxidants, such as vitamin E and glutathione, and proteinase inhibitor.

Vitamin E exerts its antioxidant activity at the level of cell membrane by scavenging free radicals. Because of low vitamin E stores at birth and increased oxidant stresses faced by preterm infants, supplementation of the diet of premature infants with vitamin E has been studied. However, enthusiasm for vitamin E as an antioxidant for prevention of CLD declined after clinical trials failed to show a benefit.[47,48] Vitamin E does not prevent lung injury and vitamin E deficiency is not associated with an increased incidence of CLD.[49]

Superoxide dismutase (SOD) enzymes have been studied. A multicentre, randomised, blinded, placebo-controlled trial of recombinant human SOD therapy showed no difference between treatment groups with respect to the primary outcome, death, CLD at 28 days of age and other respiratory outcome. However, there was less grade III/IV intracranial haemorrhage and less periventricular leukomalacia in the rhSOD group.[50]

Because infants with RDS and subsequent CLD have low functional levels of proteinase inhibitor activity, a randomised trial of prophylactic intravenous alpha$_1$-proteinase inhibitor therapy in infants less than 24 hours of age was conducted.[51] Although the incidence of CLD was lower in the treated group, it was not quite statistically significant, although there was a significantly lower incidence of pulmonary haemorrhage in the treated group. No other adverse effects of this therapy were noted.

Oxygen therapy is a double-edged sword for the premature infants with respiratory failure. Although it is necessary to reduce the inspired oxygen concentrations as quickly as possible to avoid oxygen toxicity, it is equally important to maintain the PaO_2 at a level sufficient to ensure adequate tissue oxygenation to promote normal somatic growth and neurological development, and to avoid pulmonary hypertension and cor pulmonale that can result from chronic hypoxaemia. Infants with CLD also respond with increased airway resistance to episodes of acute hypoxaemia. The PaO_2 should be maintained above 50 to 55 mmHg to prevent the effects of hypoxaemia. Oxygen can be administered through a hood, face mask, or preferably a nasal catheter, which interferes minimally with other aspects of infant care and it allows low flow rates to be used. In the presence of tracheomalacia and increased airway resistance, nasal CPAP may be necessary to improve or stabilise gas exchange. Because oxygen consumption increases and the PaO_2 may decrease during feedings, a higher inspired oxygen concentration may be necessary. In many cases, oxygen therapy is required for several months. Many of these patients are discharged with oxygen therapy at home. Adequacy of gas exchange should be monitored by determining arterial blood gas levels at intervals dictated by the child's clinical condition. Blood gas determinations by arterial puncture are usually not reliable because the infant responds to pain with crying and apnoea. Transcutaneous PO_2 electrodes are also inaccurate in these infants because they underestimate the true PaO_2. Pulse oximeters offer the most reliable estimate of arterial oxygenation and have the advantage of simplicity of usage and the possibility of assessing oxygenation during feeding, crying or sleep. Oxygen saturation should be maintained at least in the range of 90% to 95%, although this may vary somewhat with the clinical status of any given infant.

The Role of Pulmonary Oedema

Interstitial pulmonary oedema is one characteristic component of the pathogenesis of CLD. Clinical events that exacerbate pulmonary oedema, such as excessive fluid administration and haemodynamically significant patent ductus arteriosus (PDA), further compromise the lung function, perpetuating a cycle in which more aggressive respiratory support is required, which produces more lung damage.

A controlled trial of fluid restriction in the management of RDS has established that reduced fluid administration is associated with a decreased incidence of CLD.[52] Analysis of NICU practices further concluded that the major cause of CLD was excessive fluid and colloid administration.[27]

High fluid intake increases the incidence of a clinically significant PDA. Increased pulmonary blood flow as a consequence of the left-to-right shunting through the PDA and the resulting increase in interstitial fluid cause a decrease in pulmonary compliance. The presence of a PDA also has been associated with elevated concentrations of myeloperoxidase in the tracheobronchial fluid, suggesting that the increased pulmonary blood flow may result in

damage to the pulmonary endothelium and adhesion and migration of neutrophils into the lung tissue, thus contributing to the progression of the inflammatory cascade.[53] All this explains the strong association between the duration of the PDA and the increased risk of CLD.

Infants with CLD also have a predisposition to fluid accumulation in their lungs. There are functional alterations in the pulmonary vascular resistance, plasma oncotic pressure, and capillary permeability that favour extravascular accumulation of fluid. Pulmonary vascular pressure can be increased because of hypoxaemia, hypercapnia, reduced pulmonary vascular bed, and to left ventricular dysfunction that has been described in patients with chronic respiratory failure. Plasma oncotic pressure may be decreased because of decreased plasma protein concentration resulting from inadequate nutrition. Capillary permeability may be increased secondary to the effects of high oxygen exposure, barotraumas, and infection on the capillary endothelium. Finally, lymphatic drainage may be impaired because of compression of the pulmonary lymphatics by interstitial fluid or gas or fibrous tissue and also from increased central venous pressure in cor pulmonale.

Infants with CLD, therefore, tolerate excessive fluid or even normal amounts of fluid intake poorly and have a marked tendency to accumulate excessive fluid in the lung. Early closure of symptomatic PDA and judicious fluid administration are strategies that reduce pulmonary oedema and its contribution to CLD.

Water and salt intake should be limited to the minimum required to provide the necessary calories for their metabolic needs and growth. When increased water persists despite fluid restriction, diuretic therapy has been used to reduce pulmonary oedema and to improve pulmonary mechanics, as well as to reduce supplemental oxygen requirements in infants with evolving or established CLD. Diuretics are used for their diuretic properties, and clinicians have always hoped, without much evidence, that diuresis will permit a higher caloric intake and that improved lung mechanics will spare ingested calories for somatic growth and lung repair. Diuretics also have non-diuretic properties that may have beneficial effects on lung function, such as vasodilatation and airway dilatation.[54,55]

Frusemide is the most commonly used diuretics. Other diuretics, such as chlorothiazides and spironolactone, have been used, but may be less effective and side effects may not be significantly reduced.[54,55] During the acute phase of CLD in hospitalised infants, frusemide therapy is used intermittently when symptoms of acute fluid intolerance occur, such as rapid weight gain, systemic oedema and increased respiratory symptoms or oxygen requirements that cannot be explained by infection. Two types of infants with CLD should be considered for long-term frusemide therapy: the continuously hospitalised, ventilator-dependent infant with severe BPD, and the unventilated infant whose oxygen requirement exceeds 35% to 40%, who thus cannot go home safely. The role for continuous diuretic therapy in infants with mild to moderate CLD is unclear, especially in view of the risks of the therapy and the lack of long-term studies.

Complications of chronic diuretic therapy include hypokalaemia, hyponatraemia, hypochloraemia, metabolic alkalosis, hypercalciuria with nephrocalcinosis (which may compromise bone mineralisation and exacerbate osteopenia of prematurity) and possible hearing deficits. Supplementation with potassium chloride and occasionally sodium chloride is required to prevent metabolic alkalosis and hypoventilation. Some of these side effects may be reduced by using an alternate-day frusemide therapy regiment.[56] This approach may be useful either as initial therapy for infants with moderate disease or as a way to wean infants from daily diuretic therapy. There have been several trials of inhaled frusemide therapy for CLD. Results of these studies are equivocal, and it cannot be recommended at this time.

Control of Infection

Increasing evidence supporting the role of infection in the development of CLD is becoming available. This appears to be especially important in very small infants who develop CLD after receiving prolonged mechanical ventilation because of poor respiratory effort rather than because of severe underlying lung disease. In these infants, the occurrence of nosocomial infections is associated with a marked increase in the risk of developing CLD.[57] The variation in nosocomial infection rates between NICUs may in part explain the variation in CLD rates among NICUs.[27]

A prospective epidemiological study to identify the primary risk factors that predispose these infants to CLD revealed that after prematurity, the presence of systemic infections and episodes of symptomatic PDA were the stronger predictors for the development of CLD. When both complications (infection and PDA) occurred concurrently, they produced a synergistic interaction, further increasing the risk for developing CLD.[53] The presence of systemic infections in the preterm infant adversely affects closure of the ductus, often inducing ductal opening after the first week of life and failure to respond to medical treatment with indomethacin. This is most likely due to the elevated serum levels of prostaglandins and tumour necrosis factor observed in infants with infections. In addition, infants who have serious infections frequently have complications that prevent or delay the medical or surgical treatment of the PDA. As a result, the ductus remains open

for prolonged periods of time, maintaining an increased pulmonary blood flow and increased lung fluid.

Independent of the interaction between infections and PDA, the presence of pulmonary or systemic infections can produce activation of pulmonary alveolar macrophages and margination and activation of neutrophils in the pulmonary circulation, which triggers the release of inflammatory mediators that activate the inflammatory cascade in the lung.

Any infection can have serious consequences for the child with CLD, and bacterial, viral or fungal infection generally results in profound setback. Cytomegalovirus infection after birth has been associated with a marked increase in CLD, and respiratory syncytial virus infection is a major cause of deterioration and rehospitalisation in these infants. Measures to prevent pulmonary nosocomial infections are important. These include careful hand washing before handling the airway, maintenance of sterility of the respiratory equipment and isolation from individuals with respiratory infections.

As mentioned before, some studies have noted an association between early colonisation of the airway and later development of CLD with unusual organisms: *Ureaplasma urealyticum, Mycoplasma hominis, Chlamydia trachomatis;*[18] but results have not been consistent. There is also increasing evidence that maternal infections and specifically chorioamnionitis are associated with an increased risk of CLD in the infant.[17] The potential for reduction of this type of inflammation to reduce the occurrence of CLD should be further researched.

Anti-inflammatory Therapy

The rationale for exogenous administration of corticosteroids to treat and prevent CLD is based on the prominent role that inflammation is believed to play in the pathogenesis of CLD and the anti-inflammatory effects of corticosteroid therapy. Initially, systemic corticosteroid therapy was used in infants who were failing to wean from assisted ventilation, often at about 4 to 6 weeks of age. The expectation was to facilitate weaning from the ventilator. As evidence accumulated that pulmonary inflammation occurred early in the course of many preterm infants, subsequent studies focused on initiating therapy as early as before 2 weeks of age in the hope that earlier intervention would prevent the development of CLD.

The proposed mechanisms for the beneficial effect of corticosteroids in CLD include enhanced production of surfactant and antioxidant enzymes, decreased bronchospasm, decreased pulmonary and bronchial oedema and fibrosis, and reduction in pulmonary inflammatory mediators, such as neutrophils and macrophages, proteinases, tumour necrosis factor and interleukins, as well as inhibition of leukotriene and fibronectin synthesis.[58,59]

Potential complications of prolonged corticosteroid therapy include infection, hypertension, hyperglycaemia, adrenocortical suppression, somatic and lung growth suppression, hypertrophic cardiomyopathy and gastrointestional catastrophies (such as bleeding, perforation and necrotising enterocolitis). Of particular concern is the evidence that prolonged treatment with systemic dexamethasone is associated with increased risk of periventricular leukomalacia and long-term neurological deficits such as cerebral palsy.[60,61] The coexistence of important benefits and potential major adverse effects has created a dilemma regarding the use of systemic corticosteroid therapy. Until more information on efficacy and safety is available, it appears prudent to use systemic steroids only after the first 2 weeks of life and in infants who show clear evidence of progressive pulmonary damage and remain oxygen and ventilator dependent. The duration of therapy should be limited to the minimum necessary in as low a dose as possible to achieve the desired effects.

Early adrenal insufficiency has been suggested as a contributing factor in CLD in the smallest infants. Infants with lower cortisol levels in the first week of life have an increased incidence of PDA, more lung inflammation and increased incidence of CLD.[62] Early, prophylactic "physiologic replacement" hydrocortisone therapy resulted in increased survival without CLD, an effect that was more apparent in infants born from mothers with chorioamnionitis.[63] The dose of hydrocortisone used is equivalent to less than 10% of the commonly used starting dose of 0.5 mg/kg/day of dexamethasone. Further study will be necessary to determine whether physiological replacement hydrocortisone therapy is effective in reducing CLD and whether it is free of the adverse effects associated with systemic dexamethasone therapy.

In an attempt to induce the beneficial effects on the lung but minimise the systemic side effects, steroids have been administered by nebulisation to a group of ventilator-dependent infants. This therapy resulted in a significant improvement in lung compliance and resistance only after 3 weeks of treatment. More recent studies showed that inhaled steroids may reduce the need for systemic steroids, reducing the side effects associated with prolonged systemic therapy.[64] The ultimate role of inhaled steroids in treatment of CLD is yet to be defined. More must be learned regarding how to optimise its administration to premature infants, ventilated and non-ventilated. Currently, inhaled steroids must be delivered by metered-dose inhaler to achieve respirable particle size. Given the present state of available equipment and knowledge, the prescribed dose of aerosol therapy has little to do with the dose delivered. New

formulation of corticosteroids and newer delivery devices may facilitate the efficiency of aerosol delivery.

Increased Airway Resistance and Bronchodilator Therapy

Increased airway resistance plays an important role in the pathophysiology of CLD. Airway obstruction may be secondary to the bronchiolar epithelial hyperplasia and metaplasia, and to mucosal oedema resulting from trauma, oxygen toxicity and infection. Pulmonary oedema secondary to PDA or fluid overload may increase airway resistance. Infants with severe CLD may also have airway smooth muscle hypertrophy and airway hyper-reactivity.[8] Inflammatory mediators, such as leukotrienes, are present in high concentration in the airways of infants with CLD and also may contribute to the increased airway resistance. Some infants with severe CLD develop tracheo-bronchomalacia, which may contribute to airway obstruction especially during periods of agitation and increased intrathoracic pressure.[65]

Increased airway resistance increases the work of breathing and contributes to maldistribution of the inspired gas, favouring uneven lung expansion and ventilation/perfusion mismatch. The resulting hypoxaemia not only further increases the airway resistance, but also increases the pulmonary vascular resistance. Maintenance of adequate oxygenation is important to avoid bronchoconstriction.

Short-term clinical trials of bronchodilator therapy have demonstrated improvement in both lung mechanics and gas exchange.[66] Most of these studies have examined only the acute response to single doses of a drug. However, many clinicians rely on these agents for long-term therapy, believing that the reduction in airway resistance can reduce the incidence and severity of subsequent lung damage.

Inhaled bronchodilator therapy, including beta-agonists and anticholinergics, is frequently used in infants with CLD, especially in the management of acute exacerbations of airway obstruction with wheezing or hypercarbia.[66] Disadvantages with this mode of therapy include difficulty with administration of the drug and irregular drug delivery as it is uncertain what percentage of medication is actually delivered to the airways with nebulised or metered dose administration. In addition, infants with tracheo-bronchomalacia may paradoxically worsen with bronchodilator therapy probably by increasing large airway instability.[65] Side effects of beta-agonists include tachycardia and possible arrhythmias, hypertension, tremor and hyperglycaemia. The clinicians should also be mindful of the short duration of action and the side effects, including the possibility of rebound bronchospasm.

Methylxanthines, such as aminophylline, theophylline, and caffeine, are well-known respiratory stimulants frequently used in hastening the weaning from ventilator and in recurrent apnoea of prematurity. They also have diuretic properties and improve respiratory muscle contractility. These drugs may have a bronchodilator effect, but the effect has been difficult to measure directly. Aminophylline and theophylline have a narrow therapeutic window and steady-state serum levels should be closely monitored. Caffeine has a wider therapeutic window and fewer side effects.

Because of the increased concentrations of leukotrienes in bronchial secretions of infants with CLD, cromolyn sodium has been suggested as a drug to prevent airway hyperreactivity and reduce airway resistance. It does not provide direct bronchodilation and, therefore, should not be used acutely. The effect of cromolyn therapy may take a few weeks to become apparent and experience is too limited to recommend its widespread use.

Growth Failure and Nutritional Management

Growth failure is a significant issue for children with CLD. The importance of optimising nutritional management in these children cannot be overemphasised, but there is no agreement about how this goal should be met. Adequate nutrition is not only important in maintaining the rapid rate of growth of these infants, but also needed for lung repair. As a group, VLBW infants remain small during at least the first several years of life. They tend to be between the tenth and twenty-fifth percentile for height and weight, but they consistently follow a growth curve. Children with CLD may fail to thrive and demonstrate a flattened growth curve. Growth failure in CLD can be due to inadequate caloric intake and inadequate oxygenation.[4,6]

Overaggressive weaning from oxygen without appropriate monitoring will result in poor growth. Growth failure is known to occur from parental non-compliance with a home oxygenation programme, and growth resumes when supplemental oxygen is restarted. Growth failure may also result from unsuspected hypoxaemia during sleep and can be reversed by appropriate oxygen supplementation.[67] Therefore, the infant should be monitored with a pulse oximeter in all behavioural states for episodes of desaturations.

Inadequate caloric intake is relative. Children with CLD have an elevated resting metabolic rate and increased work of breathing. As such, they may fail to grow with a caloric intake that would easily support growth in a child without CLD. In addition, frequent respiratory exacerbations, fluid restriction protocols and poor feeding because of chronic illness, such as neurological problems and severe oral aversive behaviour, all contribute to growth failure.[4,6]

A realistic goal in nutrition therapy for infants with moderate CLD would be to provide a caloric intake of 110

to 150 kcal/kg/day to produce a weight gain of 15 to 30 g/day. The use of increased caloric density of feeding may be used to maximise the intake of calories while restricting fluid intake to prevent pulmonary oedema. Formulas designed for premature infants with a caloric density of 24 to 27 kcal/oz can be used. Increasing the caloric density of infant formulas to greater than 30 kcal/oz with glucose polymers or medium chain triglycerides should be done with great care, as excessive glucose intake may result in increased CO_2 production and worsen the respiratory distress. Breast milk can also be supplemented to provide increased caloric density.

The use of vitamin A in CLD has been studied. Infants with severe CLD have been shown to have lower plasma levels of vitamin A, and a deficiency of this vitamin in experimental animals results in loss of ciliated epithelium and squamous metaplasia in the airways, changes similar to those observed in CLD. Studies in preterm infants with severe RDS suggest that vitamin A supplementation has a statistically significant, but clinical modest effect in reducing CLD.[68] The use of vitamin A, therefore, deserves further consideration as a possible component in the prevention of CLD. The serum levels of vitamin A may increase during systemic steroid therapy. Vitamin A should be withheld during steroid therapy to avoid potential toxicity.

While most of the infants with CLD need a high caloric intake, some of them with oral aversive behaviour will need speech and swallow evaluation and therapy. For these infants, gentle care, pleasant oral stimulation and a quiet environment are crucial elements for a successful nutritional programme and may be more important than type of formula or total caloric intake. However, even with an optimal environment, some infants with CLD will not begin to grow well until lung repair is well under way, as evidenced by a fall in oxygen requirement and a reduction of symptoms.

Conclusion

BPD and CLD remain one of the most significant costs of survival for VLBW infants. Is BPD the inevitable consequence of extreme prematurity and respiratory failure or can the causal pathway to BPD be interrupted by postnatal therapy? Many of the risk factors for the evolution of this complex and multifactorial disorder are well known. Although some of these risk factors can be modified after birth, others, such as lung immaturity and impaired lung repair, are less well understood and, therefore, have been less susceptible to therapy. Clinical experience indicates that prevention or reduction in CLD can be achieved through a comprehensive strategy of minimising inciting events, optimising management and specific therapies aimed at intrinsic vulnerabilities. In the future, powerful molecular biology techniques, genetically-engineered drugs and human gene therapy may provide exciting possibilities and promises. However, the ultimate and most effective approach is a relentless pursuit of measures to prevent premature births.

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QUESTIONS

1. The following factors contribute to the development of neonatal chronic lung disease:
   a. It occurs in premature infant exclusively
   b. Positive pressure ventilation
   c. Pulmonary oedema
   d. Prolonged oxygen exposure
   e. Protracted use of endotracheal tube

2. Comment on the following regarding the use of antenatal steroids in bronchopulmonary dysplasia (BPD):
   a. It works solely by induction of surfactant production
   b. It works better when combined with thyrotropin releasing hormone (TRH)
   c. Multiple courses are better than one or two courses
   d. It complements the effect of postnatal surfactant replacement therapy
   e. It predisposes the mother to chorioamnionitis

3. Comment on oxygen and ventilation therapy in the development of BPD:
   a. BPD has not been associated with negative pressure ventilation
   b. Oxygen exposure alone is sufficient to lead to the development of BPD
   c. Volutrauma is more important than barotraumas
   d. BPD can be prevented by keeping the PaO_2 between 50 and 70 mm Hg
   e. High-frequency ventilation is better than conventional mode of ventilation

4. A child with BPD who fails to thrive can be due to the following:
   a. Over-exposure to oxygen
   b. Inadequate nutritional intake
   c. Late use of postnatal steroids
   d. Insufficient use of diuretics
   e. Frequent nosocomial infections

5. Comment on the following methods of treatment of BPD:
   a. Early postnatal steroids is preferable to late administration
   b. The use of vitamin A has only a modest effect on the development of BPD
   c. Patent ductus arteriosus should be vigorously treated with diuretics.
   d. Early use of nasal CPAP is associated with significant reduction of BPD
   e. Infections and PDA are synergistic in increasing the risk of BPD

ANSWER SHEET

Continuing Professional Development:
Bronchopulmonary Dysplasia and Chronic Lung Disease of Infancy:
Strategies for Prevention and Management

Question 1		Question 2		Question 3	
a) True ○	False ○	a) True ○	False ○	a) True ○	False ○
b) True ○	False ○	b) True ○	False ○	b) True ○	False ○
c) True ○	False ○	c) True ○	False ○	c) True ○	False ○
d) True ○	False ○	d) True ○	False ○	d) True ○	False ○

Question 4		Question 5	
a) True ○	False ○	a) True ○	False ○
b) True ○	False ○	b) True ○	False ○
c) True ○	False ○	c) True ○	False ○
d) True ○	False ○	d) True ○	False ○

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