Chronic Lung Disease (CLD) persists as one of the major complications in premature infants who require prolonged mechanical ventilation. Moreover, the increasing survival of very immature infants in recent years has produced an increase in the number of infants at risk for developing this complication. The classic form of bronchopulmonary dysplasia (BPD) was described in premature infants who were ventilated for more than 28 days. Because of the increasing survival of extremely premature infants and the development of new techniques to prevent lung injury, CLD has become a major complication in preterm infants who require mechanical ventilation for less than 28 days. CLD results from the interaction of multiple factors that can injure the immature lung. For this reason, the prevention must be based on the elimination of all the factors implicated in its pathogenesis. Clinical and epidemiological data strongly suggest that infections, either prenatal or nosocomial, and the presence of a patent ductus arteriosus (PDA) play a major role in the development of CLD in these infants. For this reason, efforts to prevent CLD in extremely low birth weight infants should include an aggressive approach to the prevention and treatment of prenatal and neonatal infections and an early closure of the PDA.

KEYWORDS: Prematurity, chronic lung disease, bronchopulmonary dysplasia, lung injury, mechanical ventilation, patent ductus arteriosus, inflammation
originally by Northway and colleagues in 1967 and was more common prior to the introduction of antenatal steroids and postnatal surfactant therapy. This form is usually seen after severe respiratory failure due to pneumonia or respiratory distress syndrome (RDS). These infants require mechanical ventilation with high airway pressure and inspired oxygen concentration during the first days of life, and frequently their course is complicated by pulmonary interstitial emphysema. This complication further compromises gas exchange requiring increases in ventilatory support and inspired oxygen concentration, which further aggravate the lung damage. Other complications, such as persistent patent ductus arteriosus (PDA) with associated left ventricular failure and pulmonary edema, as well as nosocomial infections frequently develop in these patients and contribute to the progression in severity of their lung damage.

Despite all therapeutic efforts, these infants frequently remain oxygen and ventilator-dependent beyond the first weeks and chronic radiographic changes characterized by densities, linear-reticular opacities, and in some cases cystic changes begin to appear at this stage. These changes evolve later into the classical radiographic picture of advanced BPD characterized by hyperinflation of the lower lobes and areas of increased densities reflecting patchy atelectasis and fibrosis.

Once severe lung damage has developed, these infants require mechanical ventilation and increased inspired oxygen concentration for several weeks, months, or sometimes years. Infants with more severe lung damage may die of progressive respiratory failure. Mortality rates of approximately 30 to 40% have been reported in infants with severe CLD, and most of them occur during the first year of life secondary to respiratory failure, intercurrent infections, or intractable cor pulmonale.

Follow-up studies in infants with severe CLD have shown that pulmonary function may remain abnormal for many years, even though the infants may be asymptomatic. A high incidence of obstructive airway disease has been observed at 8 years of age in a small group of survivors with BPD. Northway and associates have reevaluated pulmonary function in their original cohort of infants with severe BPD reported in 1967. At an age ranging between 14 and 23 years, these adolescents and young adults still exhibited evidence of pulmonary dysfunction characterized by airway obstruction, airway hyper reactivity, and hyperinflation.

Infants with severe CLD also have more neurodevelopmental sequelae when compared with control groups, and they exhibit impaired growth curves. Although data from long-term studies is scant, it is apparent that neurodevelopmental prognosis not only depends on the severity of the CLD, but on the presence of other risk factors for developmental delay that occur frequently in infants with CLD, such as intracranial hemorrhage, hearing impairment, and retinopathy of prematurity. Infants with severe CLD have also been reported to have an increased risk for sudden infant death, but the evidence for this is not conclusive.

With the introduction of surfactant replacement, increased use of antenatal steroids and improvements in ventilator management, the incidence of this severe form of CLD has decreased considerably and has been replaced by a milder form of lung damage.

**CLINICAL PRESENTATION OF THE NEW CLD**

The majority of small premature infants who develop CLD at present have a mild initial respiratory course and require prolonged ventilatory support for management of apnea and poor respiratory effort. These infants represent more than two third of all patients diagnosed with CLD in our institution. In contrast to infants with severe CLD, initially these infants require mechanical ventilation with low pressures and oxygen concentration, and therefore their exposure to the effects of baro-trauma and oxygen toxicity is minimal. These in-
fants require low or moderate initial concentration of oxygen for treatment of mild RDS that usually responds favorably to exogenous surfactant. This is often followed by a few days with minimal or no supplemental oxygen need (“honeymoon”). Many of them, however, have a progressive deterioration in their lung function over time, and their ventilatory and oxygen requirements increase, accompanied by signs of respiratory failure (tachypnea, retractions, etc.). This deterioration is frequently associated with bacterial or viral infections or heart failure secondary to a PDA. In these patients, the functional and roentgenographic lung changes are usually mild, sometimes showing only diffuse haziness that persists over time, without the coarse changes of nonuniform inflation and cystic nature that is observed in the classic severe form of CLD.

PATHOGENESIS OF THE NEW CLD

The major factors implicated in the pathogenesis of the classic severe form of BPD are thought to be barotrauma and oxygen toxicity. As mentioned before, most infants who develop this form of lung damage have severe initial respiratory failure and therefore are exposed to high positive airway pressures and inspired oxygen concentrations. Today, with the increased use of antenatal steroids and the administration of exogenous surfactant, the initial respiratory course is usually mild and, therefore, infants are exposed to much lower airway pressures and oxygen concentrations. Still, many of them gradually develop increasing oxygen requirements and show radiographic changes compatible with CLD that persist for weeks or months. Although it is possible that these low levels of airway pressure and oxygen exposure may be sufficient to damage the immature lung, it is likely that other factors play a more important role in the development of the lung damage observed in these infants.

Increasing evidence has accumulated recently suggesting that inflammation plays a major role in the pathogenesis of CLD. This inflammatory response can be triggered by a number of factors including ventilation with excessive tidal volumes, free oxygen radicals, increased pulmonary blood flow due to a PDA, and a variety of perinatal infections. The role of prenatal infections has been suggested by publications showing an increased risk for CLD in infants born to mothers with evidence of chorioamnionitis. Several inflammatory cytokines were found in higher concentrations in fetal cord blood and in the amniotic fluid of mothers who delivered infants who developed CLD in comparison with those who gave birth to infants who recovered without CLD. In addition, several publications have suggested a higher risk of CLD in infants whose airways are colonized with ureaplasma urealyticum at birth, but these data are confounded by higher colonization rates at lower gestational ages.

A significant increase in inflammatory cells, eicosanoids, and various cytokines has been reported in the airways of infants who subsequently develop CLD. This increase in cytokines concentration has been demonstrated from the first days after birth supporting the contention that at least in some infants the inflammatory process starts before birth and is secondary to an infection of the amniotic cavity and the fetal lung. Among the markers of inflammation that have been found in high concentrations in tracheobronchial secretions of infants who develop CLD are neutrophils, macrophages, leukotrienes, platelet-activating factor (PAF), IL6, IL8, and tumor necrosis factor (TNF).

Evidence of pulmonary alveolar macrophage (PAM) activation has been reported in infants who subsequently developed CLD. These activated PAM’S have been suggested as source of neutrophil chemoattractants, especially when exposed to hyperoxia. Neonates who develop CLD also have elevated concentration of fibronectin in lung lavage fluid. This large molecular weight protein is released from PAM, epithelial and endothelial cells, and fibroblasts and is associated with the development of pulmonary fibrosis.
An increase in elastase and an imbalance between elastase and α1-proteinase inhibitor (PI) in the lung has also been mentioned as an important mechanism for the development of neonatal lung injury.30–32 Urine excretion of elastic degradation products is greater in neonates who develop CLD than in controls.33 This is of particular relevance in light of recent evidence of a marked reduction in alveolar septation in lungs of infants who died with severe CLD.

Because of the increasing evidence linking infections and inflammation with the development of neonatal CLD we have also investigated the role of postnatal nosocomial infections in the pathogenesis of this complication. An epidemiological study to identify the main 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.34 Furthermore, when both complications (infection and PDA) occurred at the same time, they produced a synergistic interaction, further increasing the risk for developing CLD. As a consequence of the left-to-right shunting through the PDA, pulmonary blood flow and lung fluid increases, negatively affecting lung function and gas exchange, and thereby increasing the risk for CLD. The presence of a PDA has also been associated with elevated concentrations of myeloperoxidase in the tracheobronchial fluid, suggesting that the increased pulmonary blood flow may result in damage of the pulmonary endothelium and adhesion and migration of polymorphonuclear cells (PMNs) into the lung tissue.35

Searching for an explanation for the interaction between neonatal infection and PDA, we observed that the presence of a systemic infection in the premature infant adversely affects permanent closure of the ductus, often inducing ductal opening after the first week of life and failure to respond to medical treatment with indomethacin.34 A likely explanation for this interaction is the elevated serum levels of prostaglandins and tumor necrosis factor (TNF) observed in infants with infections. In addition, infants with 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, high capillary pressure, and increased lung fluid.

**PREVENTION OF THE NEW CLD**

The prevention of CLD is based on the elimination or reduction of those factors that are known to contribute to the process of lung injury in preterm infants.

**Acceleration of Lung Maturation**

The use of antenatal steroids effectively reduces the incidence and severity of HMD and because of this also reduces the risk of severe CLD.36 The increased use of antenatal steroids is one of the main reasons for the decrease in the incidence of the classical forms of BPD, but has not changed significantly the incidence of the new milder CLD.

**Perinatal Infections**

There is clear data suggesting an increased risk of CLD in infants exposed to prenatal and postnatal infections. For this reason, prevention and aggressive management of these infections plays an important role in the prevention of CLD. We have demonstrated that nosocomial infections are associated with reopening of the ductus arteriosus and this further increases the risk of CLD.34

**Exogenous Surfactant**

The introduction of surfactant replacement in infants with HMD has also improved substantially the respiratory course in these infants.37 Because of this, it is seldom necessary to use high airway pres-
sures and oxygen concentrations during mechanical ventilation. As a result of this, the incidence of lung damage due to barotrauma is infrequent today. Simultaneously, the use of surfactant has improved the survival of extremely low-birth-weight (ELBW) infants and this has increased the number of infants who are at risk for developing CLD masking the beneficial effect on the overall incidence of CLD.

**Gentle Ventilation**

It is clear that aggressive ventilation with high airway pressures and excessive tidal volumes can produce severe damage to the lung.\(^38\)–\(^40\) This is even more pronounced in the immature surfactant deficient lung.\(^41\),\(^42\) For this reason, it is essential to use mechanical ventilation judiciously utilizing the lowest pressures necessary to maintain alveolar volume and minute ventilation. To avoid volutrauma it is important to measure tidal volume and not to exceed volumes of 5–7 ml \(\times\) kg. The use of positive end-expiratory pressure (PEEP) is also critical to maintain functional residual capacity (FRC) and avoid alveolar collapse at end expiration. Insufficient PEEP is associated with marked increase in the ventilator associated lung damage. Whether high-frequency ventilation may decrease the risk of CLD is not clear.\(^43\),\(^44\) Although in theory high-frequency ventilation (HFV) should reduce the risk of volume induced lung damage, most recent prospective controlled trials have not shown clear beneficial effects when HFV is used in ELBW infants with uncomplicated hyaline membrane disease (HMD).\(^44\),\(^45\)

**PDA Closure**

There is ample evidence that the presence of a PDA is associated with increased risk of CLD. The increased pulmonary blood flow due to the left-to-right shunting through the ductus produces a decrease in lung compliance and pulmonary edema that interferes with gas exchange.\(^46\) This makes necessary the use of prolonged and more aggressive ventilation leading to CLD. It is therefore extremely important to close a PDA as soon as possible by using prostaglandin inhibitors or by surgical ligation.\(^47\)

**Fluid Intake**

Because lung injury is associated with capillary damage and increased water permeability, infants with evolving CLD have a great predisposition to develop pulmonary edema.\(^48\) For this reason these infants tolerate fluids poorly and should be restricted to the minimal intake necessary to keep a normal fluid and electrolyte balance and supply the necessary calories for growth.\(^49\)–\(^51\)

For the same reason, diuretics are frequently used in these infants to increase renal water losses.\(^52\)–\(^55\) It is important to point out that loop diuretics such as lasix may also have a direct effect on pulmonary fluid balance and reduce interstitial lung water independent from their renal effects.\(^56\)

Prolonged use of this type of diuretics is associated with hypochloremic alkalosis, and excessive calciuria with the consequent risk of nephrocalcinosis and osteopenia.

**Nutrition**

Adequate nutrition is difficult to achieve in infants with CLD because of poor tolerance to feedings and specially to high-volume intakes. On the other hand, it is important to supply them with enough calories to match their increased metabolic needs and assure adequate growth. Also, there are specific nutrients and vitamins that are frequently deficient in these infants and their lack may increase the severity of the lung damage.\(^57\)

Vitamin A plays an important role in the preservation of airway epithelium and alveolar septation. Small preterm infants are frequently vitamin A deficient and the supplementation of sufficient Vitamin A is difficult to achieve because of
the inactivation induced by light and the adhesion to the plastic of the infusion lines.58–60

The administration of Vitamin A, 5000 units every other day by i.m. injection, was shown to reduce the risk of CLD in a group of ventilated preterm infants.61,62 Although with vitamin E the data is less clear, because of its antioxidant properties it is also important to avoid Vitamin E deficiency specially in infants at high risk of CLD.

The same applies to the sulfur containing aminoacid glutathione that also plays an important role as antioxidant.

Corticosteroids

Because of the strong evidence that inflammation plays an important role in the pathogenesis of CLD, there is great interest in the use of exogenous corticosteroids during the early states of the disease to reduce its progression.53–65 Many reports have shown a rapid improvement in lung function after the administration of steroids, facilitating weaning from oxygen and the ventilator when compared with control infants who received placebo.66 The optimal age of treatment, dose schedule, and duration of therapy have not been established and long-term outcome has not always improved in treated infants.67 The possible mechanisms that explain the beneficial effect of steroids in CLD are numerous. Steroids can enhance production of surfactant and antioxidant enzymes, decrease bronchospasm, decrease pulmonary and bronchial edema and fibrosis, improve Vitamin A status, and decrease the response of inflammatory cells and mediators in the injured lung.68,69 Possible complication of prolonged steroidal therapy include masking the signs of infection, arterial hypertension, hyperglycemia, increased proteolysis, adrenocortical suppression, somatic and lung growth suppression, and hypertrophic cardiomyopathy.70–74 Of greater concern is the fact that long-term follow-up studies suggest that infants who received prolonged steroid therapy have worse neurological outcome than control infants.75–77 Because of the seriousness of some of these complications, until more information on efficacy and safety is available, the use of systemic steroids should be considered experimental and be limited to those infants who show clear evidence of progressive pulmonary damage and remain oxygen and ventilator dependent. The dose and duration of therapy should be limited to the minimum necessary to achieve the desired effects.78

In an attempt to minimize the systemic side effects, steroids have been administered by nebulization to infants at risk of developing CLD.79,80 This therapy produced some improvement in lung compliance and resistance only after several weeks of treatment. More recent studies have shown that inhaled steroids may reduce the use of systemic steroids avoiding the side effects associated with prolonged systemic therapy.81 The results with topical steroids are not conclusive enough to recommend routine use of this therapy either.

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