Chronic lung disease in preterm neonates

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Background: **With advances in neonatal intensive care, increasing numbers of preterm neonates are now surviving. In the past they would have died before there was time to develop chronic lung disease (CLD). Based on the definition of a neonate requiring any form of respiratory therapy (oxygen or assisted ventilation) at 36 weeks' post-menstrual age, the CLD rate in Australia is 52% in those <28 weeks and 12% in those 28-32 weeks gestation. The high CLD rate in the former group is due to their improved survival rates (one-year survival rate of infants born in the State of Victoria is 41% at 23 and 24 weeks, 73% at 25 weeks, and 88% at 26 weeks).**

Data sources: **Randomized controlled trials (RCTs), including meta-analyses and Cochrane reviews on the prevention and treatment of CLD were identified in the published literature.**

Results: **The following perinatal strategies were found to be effective in preventing or minimizing CLD: antenatal corticosteroids, postnatal surfactant, reduced oxygen saturation targeting at 89%-94%, early use of continuous positive airway pressure, synchronized ventilation, permissive hypercapnia ventilation strategy, high frequency oscillatory ventilation, closure of symptomatic patent ductus arteriosus with indomethacin, reduced fluid intake, and inhaled nitric oxide. Several anti-inflammatory and anti-oxidant agents have been found in RCTs to be effective, including vitamin A and recombinant human superoxide dismutase. Clinical management after the development of CLD includes appropriate oxygen and ventilation strategies, fluid restriction, and diuretic and bronchodilator therapy. Postnatal corticosteroid therapy is efficacious but its side-effect is increasing. The risk of cerebral palsy outweighs the benefit of therapy. Only in severe CLD, low-dose and short-course dexamethasone should be used.**

Conclusion: **Ongoing basic and clinical research is required to identify perinatal and neonatal interventions that are effective in either preventing or treating CLD in preterm neonates.**

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Key words: **chronic lung disease; bronchopulmonary dysplasia; respiratory failure; prematurity; neonatal intensive care**

Introduction

The increasing significance of chronic lung disease (CLD) in the neonatal intensive care unit (NICU) is a result of the increased survival of extremely small and preterm infants and a more aggressive management policy for respiratory failure. One NICU reported a three-fold increase in the incidence of CLD in very low birthweight (<1500 g) infants over the period of 1976-1990, with an estimated 72% of the increase being explained as averted neonatal death.[1] Many survive with persistent pulmonary dysfunction, the etiology of which remains poorly understood. CLD consists of several descriptive categories which have a number of clinical features in common.

Nomenclature

In 1967, Northway et al[2] described oxygen dependent infants with a coarse reticular pattern on chest X-ray following respiratory distress syndrome (RDS) and ventilator therapy, and called the condition bronchopulmonary dysplasia from its pathological appearance. Even earlier in 1960, Wilson and Mikity[3] reported infants with mild or no respiratory disease in the first week, who nevertheless later developed a similar clinical and X-ray picture. The term chronic pulmonary insufficiency of prematurity (CPIP) was used by Krauss et al[4] in 1975 to describe infants with a similar clinical course whose chest X-rays had a hazy appearance. In 1980, Edwards et al[5] described these infants as having "immature lungs" though

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they initially had normal chest X-rays and surfactant levels. In 1989, Hyde et al[6] proposed a nomenclature for CLD which distinguishes two types of CLD based on the chest X-ray: Type 1 defined as homogeneous or patchy ill-defined opacification without coarse reticulation, and Type 2 with the classical appearance of bronchopulmonary dysplasia consisting of streaky densities interspersed with small cystic translucencies. Currently CLD is defined as oxygen dependency at 36-week postmenstrual age or 28-day postnatal age in conjunction with persistent clinical respiratory symptoms and compatible abnormalities on chest radiographs.[7-10] This definition for CLD was recently reviewed by the National Institute of Health sponsored workshop on CLD,[10] which specified diagnostic criteria to include the need for oxygen, positive pressure ventilation and continuous positive airway pressure (CPAP) along with postnatal age to better characterize the severity of CLD (Table 1).

Incidence

The incidence of CLD in infants with RDS who received intermittent positive pressure ventilation (IPPV) is closely related to gestational age and birthweight. With the advent of surfactant therapy, use of antenatal steroids and gentle ventilation, CLD is now less frequent in infants >1200 g and >30 weeks gestation. Infants of less than 26 weeks are those who are more commonly affected. It is found in 30% infants with birthweight <1000 g,[10] 23% infants <1500 g in a US study,[11] and 26% infants in a Canadian study.[12] According to the National Institute of Child Health and Development (NICHD) Neonatal Network,[11] the incidence of CLD in patients weighing 501-1500 g at 36 weeks increased from 19% in 1990 to 23% in 1996 and remained at 22% in 2000. Sixty percent of infants <1500 g who required prolonged mechanical ventilation were noted to be oxygen dependent at 28 days and 30% remained oxygen dependent at 36 weeks. The risks of developing CLD increase by 2-3 times for each lower week of gestation.[13]

Pathogenesis

The most important factor in the pathogenesis of bronchopulmonary dysplasia is prematurity with its antecedent arrest in the alveolar development and lung vasculature. This is explained by the fact that the alveolar stage of lung development is from 36 weeks gestation to 18 months postnatally, most of which occurs 5-6 months after birth at term. Together with respiratory failure, the need for mechanical ventilation and a genetic predisposition, a scenario for acute lung injury and inflammatory response is created leading to the development of CLD. Genetic polymorphism may play a role in the development of CLD in infants by influencing (a) the degree of lung maturity, (b) the intensity of inflammatory response and tendency for fibrosis, (c) the ability of antioxidant enzymes to protect the lung from free radical damage, and (d) the ability of the neonatal lung and vascular tissue to mature and form alveoli. Infants with a family history of asthma are at increased risk of CLD.[14-16]

Volutrauma

The presence of excessive tidal volume and decrease of lung compliance results in overdistension with resultant leakage of fluid in the alveolar space due to stress fractures in the capillary endothelial membrane. The contribution of overdistension versus high peak inspiratory pressure (PIP) is a source of controversy, but it has been demonstrated in animal models that the prevention of overdistention avoids a significant increase in microvascular permeability.[17] The risk of CLD is thought to be reduced with early use of nasal CPAP, this theory being based on a comparison of practices in the two neonatal units in Boston and

Table 1. Definition and diagnostic criteria

	<32 weeks	≥32 weeks
Assessment time point	36 weeks PMA or discharge to home or whichever comes first	>28 days but <56 days postnatal age or discharge to home, whichever comes first
Treatment with oxygen	>21% for at least 28 days	>21% for at least 28 days
Mild	Breathing room air at 36 weeks PMA or discharge, whichever comes first	Breathing room air by 56 days postnatal age or discharge, whichever comes first.
Moderate	Need for <30% oxygen at 36 weeks PMA or discharge whichever comes first	Need for <30% oxygen at 56 weeks PMA or discharge whichever comes first
Severe	Need for ≥30% oxygen and/or positive pressure (IPPV or nCPAP) at 36 weeks PMA or discharge, whichever comes first	Need for ≥30% oxygen and/or positive pressure (IPPV or nCPAP) at 36 weeks PMA or discharge, whichever comes first

PMA: post-menstrual age; IPPV: intermittent positive pressure ventilation; nCPAP: nasal continuous positive airway pressure.

New York.[18] Permissive hypercapnia is also thought to reduce the risk of CLD, based on a study reporting that infants with pCO_2 <30 mmHg have 5.6 the risk of CLD compared with those whose lowest pCO_2 was ≥40 mmHg.[19] The beneficial effect of hypercapnia in lowering the risk of CLD was confirmed in a Cochrane Review on infants born at 501-750 g.[20] Although concerns had been expressed regarding effects of hypercapnia and respiratory acidosis on neurodevelopment and intraventricular hemorrhage, clinical reports had reported the opposite result, that is, mechanically ventilated infants with pCO_2<17 mmHg during the first three days had an increased risk of moderate to severe periventricular echodensity, large periventricular cysts, grade III and IV intracranial hemorrhage and cerebral palsy.[21]

Oxygen toxicity

Experimental evidence suggests that pulmonary oxygen toxicity is a major factor.[22] Oxygen alone can arrest septation of lungs that are in the saccular stage of development.[23,24] The combination of increased oxygen requirement coupled with deficient antioxidant activity and nutritional deficiencies due to delayed feeding in these preterm infants make them susceptible to oxygen toxicity. Reactive oxygen radicals produced by univalent reduction of oxygen lead to cytotoxic changes due to protein enzyme inactivation, lipid peroxidation, membrane alteration, and DNA cross linkage and schism. Evidence of free oxygen radical injury was reported in infants <1500 g with CLD.[25]

Inflammation

Maternal chorioamnionitis is associated with an increased risk of CLD.[26] Preterm labour and delivery frequently occurs after intrauterine infection,[27] and elevated levels of proinflammatory cytokines in amniotic fluid are associated with an increased risk of CLD.[28] Early respiratory infection has also been linked to CLD.[29]

Other factors

The development of CLD has been reported to be associated with pulmonary interstitial emphysema,[30,31] patent ductus arteriosus (PDA),[32,33] delayed diuresis,[34] fluid overload,[35,36] vitamin A deficiency,[37] vitamin E deficiency,[38] selenium deficiency,[39] magnesium deficiency,[40] and intravenous fat infusion.[41,42]

Pathology and pathophysiology

The pathology of CLD is one of disturbances of postnatal lung growth following preterm birth, secondary to continuous scarring and repair.[43] Histological abnormalities are frequently found in infants who died before clinical and radiological signs become evident.[44] When RDS resolves, intra-alveolar exudate may be absorbed into the alveolar wall resulting in interstitial fibrosis or it may be organized *in situ* to obliterate the alveolar space. During the first week, there is destruction of alveolar epithelial and capillary endothelial cells together with the development of interstitial and perivascular edema. Bronchiolar necrosis, squamous metaplasia, smooth muscle hypertrophy and loss of ciliated cells also occur. From the second to third week, there is an increase in macrophages, plasma cells and fibroblasts. There is bronchial as well as more extensive bronchiolar injury which, in severe cases, may progress to an obliterative bronchiolitis. In the subsequent weeks, regions of atelectasis with peribronchial and interstitial fibrosis can be found alternating with focal compensatory and destructive forms of emphysema. The lymphatics become tortuous and the reticulum, collagen and elastin fibres in the alveolar walls increase. Evidence of active epithelial regeneration can be found but there is also evidence of failure of multiplication of alveoli within at least some units. In severe fatal CLD, there is marked impairment of lung growth with decreased alveolar number and reduced lung internal surface area. In addition, bronchial and bronchiolar muscle hypertrophy and bronchial gland hyperplasia are important contributing factors to airflow limitation.[45] In infants who died of CLD in the current surfactant era, there is less evidence of fibrosis and more uniform inflation, the large and small airways are free of epithelial metaplasia, smooth muscle hypertrophy and fibrosis, and there are larger and fewer alveoli suggestive of interference with septation.

Pulmonary resistance was found to be increased from the first week after birth in infants who subsequently developed CLD.[46] Additional pulmonary function abnormalities documented in the first year include relative hypoxia, CO_2 retention, increased respiratory rate, decreased tidal volume, elevated minute ventilation, reduced compliance, thoraco-abdominal asynchrony, maldistribution of ventilation, reduced functional residual capacity, airway collapse from tracheobronchomalacia, lobar emphysema and atelectasis resulting from air trapping, lower airway obstruction demonstrated by expiratory flow limitation, bronchial hyperactivity, increased work of breathing and oxygen consumption, and respiratory muscle fatigue.[47-54] Leukotrienes, which are potent constrictors of the airway, were found to be increased in tracheal lavage fluid of infants with CLD and may contribute

to the increased airway resistance.[55] In CLD, the pulmonary circulation becomes progressively abnormal with intimal thickening of small and medium-sized pulmonary arteries which narrow significantly. These changes in the pulmonary vasculature could be secondary to persistent hypoxia in CLD. Pulmonary artery pressure is raised and the level correlates with the severity of CLD.[56-61]

No pathognomonic histological features are seen in the lungs of infants dying from Wilson-Mikity syndrome. There are areas of collapse and foci of hyperinflation with thickened intra-alveolar septa. Pulmonary function studies show carbon dioxide retention, intrapulmonary right-to-left shunting, reduced compliance, raised resistance, reduced functional residual capacity with air trapping and increased work of breathing.[62-64] High pulmonary vascular resistance occurs in those who develop cor pulmonale.[65] The main pathophysiological abnormality in CPIP is a reduction in functional residual capacity. Possible mechanisms include postnatal surfactant deficiency, respiratory muscle fatigue and persistent secretion of lung fluid. CPIP occurs primarily in extremely preterm infants <1000 g birthweight, all of whom have abnormal pulmonary mechanics through to 8 weeks of age with the lowest compliance and highest resistance at 2 weeks.[66] The diagnosis of the various forms of CLD is imprecise and it is probable that there is overlap in the pathology and pathophysiology of what are being described as bronchopulmonary dysplasia, Wilson-Mikity syndrome, immature lung, and CPIP.

Clinical features

The mildest cases of CLD may only demonstrate a plateau in both inspired oxygen requirement and ventilator setting for several weeks before spontaneous resolution of their prolonged pulmonary insufficiency. Severe cases may continue for many months with either death from progressive respiratory failure or recovery occurring in late infancy. Recurrent pneumonia, subsegmental or segmental atelectasis, gastro-esophageal reflux and aspiration of feeds are common complications.[67] Infants with CLD experience more central apnoea[68] and obstructive apnoea[69] compared with control preterm infants. Even in the neonatal period, infants who develop CLD may have a modest elevation of systemic blood pressure by a mean of 5 mmHg[70] and this resolves prior to weaning from oxygen therapy.[71] Wheezing attacks associated with bronchospasm may develop. The syndrome of inappropriate antidiuretic hormone secretion may occur during episodes of acute respiratory distress.[72] Cor pulmonale may also develop secondary to pulmonary hypertension. Poor postnatal growth in severe cases of CLD is associated with low energy intake and high energy expenditure.[73,74] Tracheobronchomalacia is a cause of persistent respiratory failure and warrants a high index of suspicion.[75] Late sudden death while still in hospital can occur despite stable or improving clinical status and without apparent acute respiratory exacerbation.[76] Frequent unsuspected oxygen desaturation,[77] abnormal hypoxic arousal responses[78] and chloride depletion,[79] have been suggested as responsible for these unexpected deaths. Fetal hemoglobin synthesis in infants with CLD has been shown to be elevated, probably indicative of unsuspected intermittent hypoxemia during infancy.[80]

Measurement of markers of pulmonary inflammation in bronchoalveolar lavage may help to identify infants who subsequently develop CLD.[81-85] Early prediction of development of CLD is possible by logistic regression using clinical and radiological data in the first 10 days of age.[86-91] X-ray scoring systems, based on lung volume, presence of opacification, haziness, interstitial changes and cystic elements at 7 days of age, have been found to be useful in CLD prediction.[92] Evidence of increased pulmonary artery pressure as early as 7 days of age was found to predict the development of CLD in very low birthweight infants.[59,61]

Treatment

Oxygen and ventilator therapy

Management of established CLD should be directed at minimizing ventilatory support and overdistention by maintaining a low normal tidal volume, while maintaining adequate functional residual capacity with end-expiratory pressure. Minimizing ventilatory support may entail some degree of permissive hypercapnia. There is a general agreement though that the least injurious approach to ventilating these preterm infants is to avoid intubation and to stabilize functional residual capacity with CPAP. Intermittent mandatory ventilation (delivered in some form of patient triggered ventilation) is generally set at the lowest rate and peak inspiratory pressure to maintain a $PaCO_2$ at 60-70 mmHg. A positive end-expiratory pressure of between 2-4 cmH_2O is used to stabilize lung volume. PaO_2 should be kept above 50-55 mmHg to avoid an increase in pulmonary vascular pressure and right heart failure.[91-93] Infants with CLD also have hypoxic airway constriction which can be alleviated by increasing the inspired oxygen concentration.[94] Transcutaneous PO_2 always underestimates PaO_2

while transcutaneous PCO_2 usually overestimates $PaCO_2$ beyond 10 weeks of age.[95] Caution should be exercised when using transcutaneous measurements in CLD infants without *in vivo* calibration. Non-invasive oxygen saturation monitoring is a useful alternative.[96,97] Since the oxygen saturation in normal infants has been shown to be 97%-100%, oxygen saturation is recommended to be maintained at 95%-98% in infants with CLD.[98] However, recent randomized controlled trials (RCTs) have suggested benefits in targeting infants with a lower oxygen saturation of 89%-94%.[99,100] Nevertheless, these lower targets might have to be modified in CLD infants who have problem with recurrent apnoea, as it has been shown that an improvement in oxygen saturation with supplemental oxygen during pulse oximetry is effective in reducing both central apnoea and periodic breathing densities in infants with CLD.[101]

Fluid and diuretic therapy

Early stages of bronchopulmonary dysplasia are associated with alveolar and interstitial edema which are brought about by increased capillary permeability from lung injury, congestive heart failure from an existing PDA, and fluid overload. Because pulmonary edema is an important component of CLD, therapy used to assist weaning has included closure of PDA, fluid restriction to 100-120 ml/kg per day, and diuretic therapy. Diuretic results in diuresis, lung fluid reabsorption, and decreased pulmonary shunting. Animal studies have shown that frusemide reduces right ventricular preload by causing systemic vasodilatation and a fall in pulmonary vascular resistance. In infants with CLD, frusemide decreases total body water, extracellular water and interstitial water which may account for an improvement in pulmonary function.[101,102] The benefits of diuretic therapy reported from individual RCTs include improvement in compliance, resistance, minute and alveolar ventilation, venous admixture, maximal expiratory flow at functional residual capacity, oxygen and ventilator requirements, duration of oxygen and ventilator therapy and hospital mortality.[103-110] Frusemide 1 mg/kg intravenous or 2 mg/kg orally, chlorthiazide 20 mg/kg orally, hydrochlorthiazide 2 mg/kg orally and spironolactone 1.5 mg/kg orally, all given twice daily, have been used singly or in combination. Frusemide therapy in CLD infants is however associated with hypercalciuria, electrolyte imbalance, nephrocalcinosis, nephrolithiasis and secondary hyperparathyroidism, nephrolithiasis and cholelithiasis.[106,111-113] Renal calcification usually resolves after cessation of frusemide therapy, and chlorthiazide is believed to be beneficial as it reduces urinary calcium excretion.[114] In the long-term, bone mineral content is unaffected by diuretic therapy.[115,116] Frusemide-induced diuresis and natriuresis have been shown to decrease with chronic use[117] and, given as alternate-day therapy, it does not result in increased urine output, electrolyte abnormalities or increased urinary calcium excretion, even though the pulmonary function improvement remains.[110] Alternatively, nebulised frusemide given at a dose of 1-2 mg/kg has been shown to improve compliance, resistance and tidal volume without diuresis or renal side effects.[118-120] Given the concerns regarding chronic parenteral frusemide therapy, it should be restricted to the acute management of fluid overload. The combination of chlorthiazide and spironolactone is preferred for a long-term diuretic therapy. An RCT in extubated CLD infants has shown that such long-term therapy results in continued improvement of lung function and decreased oxygen requirements, though the duration of oxygen therapy was not reduced.[121]

Bronchodilator therapy

The rationale for their use is that infants with CLD have bronchiolar smooth muscle hypertrophy and reactive airway disease. Theophylline results in the same pulmonary function improvements as diuretics and has a synergistic effect when used with diuretic therapy.[108,122] Oral albuterol (0.15 mg/kg per dose q8h)[123] and intravenous salbutamol (30 μg/kg over 30 minutes)[124] have been shown to improve pulmonary compliance and resistance without major cardiovascular side effects in infants with CLD. Bronchospasm contributes to the high pulmonary resistance in CLD infants and can be relieved by nebulised bronchodilators as early as 25 weeks gestation and 2 weeks postnatal age. Benefits documented include significant improvements in compliance, resistance, tidal volume, functional residual capacity, PaO_2 and $PaCO_2$.[125-132] Isoproterenol, isoetharine and metaproterenol have been used, but the most common ones are salbutamol (200-600 μg) and ipratropium bromide (40-175 μg). When the latter two are used together, the response is increased in magnitude and duration. The use of a metered dose inhaler combined with a spacer device has been shown to be more effective compared to a jet nebuliser.[132]

Dexamethasone therapy

Proposed mechanisms of postnatal steroids in CLD include increase in surfactant synthesis, enhancement of beta-adrenergic activity, stimulation of antioxidant production, stabilization of cell and lysosomal membrane, breakdown of granulocyte aggregates with improvement in the pulmonary microcirculation,

inhibition of prostaglandin and leukotriene synthesis, removal of excess lung water, and suppression of the cytokine mediated inflammatory reaction in the lung. The urine output has been shown to increase after 12 hours of dexamethasone treatment, followed by improvement of lung compliance and oxygen requirement after 36 hours.[133] A number of studies have shown that dexamethasone improves lung function and facilitates weaning from assisted ventilation.[134-145] Although the duration of ventilation was significantly reduced, these studies did not show a significant impact on duration of supplemental oxygen therapy and length of hospital stay. One small RCT comparing a 42-day course (0.5 mg/kg per day for 3 days, 0.3 mg/kg per day for 3 days, 10% reduction of dose every 3 days, alternate days for 1 week when 0.1 mg/kg reached) with an 18-day course found that prolonged therapy significantly reduced the duration of oxygen therapy (mean 65 days vs 190 days), ventilator therapy (mean 29 days vs 73 days) and late neurodevelopmental disability.[146] Prolonged dexamethasone therapy has also been suggested to reduce the incidence of cryotherapy for retinopathy of prematurity.[147] Pulse dexamethasone therapy (0.5 mg/kg per day for 3 days at 10-day intervals) commenced at 7 days of age has been shown in a RCT to decrease the incidence of CLD without growth impairment, although the pulses did cause transient slowing of growth and hyperglycemia.[148,149]

Dexamethasone results in suppression of the hypothalamic pituitary adrenal axis function with recovery one month after stopping therapy.[150-154] A low basal cortisol level in some infants may indicate the need for temporary corticosteroid replacement during severe illness. Dexamethasone increases the number of total and immature neutrophils in the peripheral blood but does not affect the immature to total neutrophil ratio which remains reliable for the diagnosis of sepsis.[155,156] In a case-controlled study[157] and a large RCT,[142] dexamethasone was not found to increase the incidence of bacterial sepsis. Systemic hypertension[158,159] and glucose intolerance[158] are commonly reported problems. An increase in protein catabolism, a rise in blood urea nitrogen and amino acid concentration, and a transient suppression of weight gain during the first week of treatment, has been documented during dexamethasone therapy.[160-164] Catch-up growth is poor in infancy.[165] Gastroduodenal ulceration and perforation have been reported although the estimated risk is low (2%-3%).[166] Intravenous ranitidine at 0.06 mg/kg per hour was found to increase and maintain gastric pH above 4 during dexamethasone therapy,[167] but does not always prevent gastrointestinal complications. Hypertrophic obstructive cardiomyopathy is one side-effect which must be closely monitored with echocardiography.[168-171] Nephrocalcinosis[172] and periventricular leukomalacia[173] have also been suggested as possible complications of dexamethasone therapy. To avoid the side-effects of systemic dexamethasone, a method of delivering aerosolized beclomethasone dipropionate directly to the lungs of intubated infants has been developed.[174,175] Although it has a slower onset of action compared with systemic steroid,[176] its use is associated with a decrease in the systemic dose of dexamethasone and an improvement of weight gain.[177] Studies using 150-1000 μg/d of inhaled steroids in 3-4 divided doses have shown significant improvements in airway resistance, lung compliance and reduced oxygen requirement,[178,179] and a higher success rate for endotracheal extubation.[180] However, a Cochrane Review has shown no significant difference between inhaled and systemic steroids for treatment of CLD.[181]

Additional therapy

Nutritional factor has received increasing attention in infants with CLD.[182] Lung healing is influenced by nutrients, antioxidants, eicosanoids, growth factors, peptide hormones, inflammatory cells, and component of the extracellular matrix. Even in the absence of dexamethasone therapy, infants with CLD often manifest growth failure which correlates with their elevated oxygen consumption.[183] Dietary supplements should be used to provide an energy intake of >150 kcal/kg per day. A high-fat milk formula has the advantage of diminishing carbon dioxide production and thus respiratory quotient.[184] Blood transfusions increase systemic oxygen transport and decrease oxygen utilization and oxygen consumption[185] as well as reduce the frequency of apnoea and bradycardia.[186,187] Most NICUs would transfuse infants who are oxygen or ventilator dependent when their hemoglobin falls below 80 g/L. Frusemide (1 mg/kg) given intravenously after a booster transfusion improves pulmonary compliance, tidal volume and minute ventilation in infants with CLD.[188]

Fibreoptic bronchoscopy is useful in the diagnosis of subglottic stenosis and other airway abnormalities in CLD infants on long-term ventilation.[189] Balloon dilatation has been shown to be a promising treatment for acquired bronchial or tracheal stenosis in infants.[190] Prolonged nasal intubation for CLD can result in midfacial hypoplasia.[191] Positioning, feed thickening, antacids and cholinergics have not consistently reduced gastro-esophageal reflux in infants with CLD. A small RCT has shown that intravenous immunoglobulins significantly reduce the number of pneumonic episodes though not septicemic episodes in infants with CLD.[192]

Following extubation, those who require ≤30% oxygen can continue to receive their supplemental oxygen via a nasal catheter connected to a low flow meter, usually starting at 0.5 L/min reducing progressively to less than 0.1 L/min before oxygen therapy is ceased. Care is required to avoid errors in the low flow oxygen delivery system which can account for worsening of respiratory failure in some infants.[193] Nursing in the prone position has been shown to improve oxygen saturation, decrease pulmonary resistance and lower the heart rate.[194,195] A program of individualized and environmental care for infants with CLD has been shown to facilitate respiratory recovery and to improve their mental and psychomotor developmental scores in infancy.[196] Breathing a lower density gas mixture such as helium-oxygen results in a significant decrease in pulmonary resistance and work of breathing in CLD[197] but unexpected hypoxemia can result with this treatment.[198]

Treatment with a calcium antagonist, nifedipine (4-6 mg q6h orally)[199-201] has been shown to reduce pulmonary vascular resistance and pulmonary arterial pressure in infants with CLD complicated by pulmonary hypertension. Inhaled nitric oxide has also been used in infants with CLD with significant improvement in their oxygenation,[202] probably by improving ventilation-perfusion matching, reducing pulmonary vascular resistance, and reducing bronchial tone. Sildenafil (Viagra) has been used in neonates with persistent pulmonary hypertension in the first week after birth, but only limited experience is available for its use in CLD infants with pulmonary hypertension.

An oxygen saturation of 92% or more after 40 minutes of 'room air challenge' best predicts readiness for weaning from low-flow oxygen to room air in infants with improving CLD.[203] Home oxygen therapy is safe and effective in reducing hospital stay and treatment costs and in promoting weight gain.[204-207] Immunisation against pertussis should begin at three months of age, whether or not the infant is in hospital. Ribavirin used in the treatment of suspected viral infections (adenovirus and influenza A and B) in infants with CLD has been shown in a RCT to accelerate recovery from acute respiratory deterioration and improved lung function at follow-up.[208]

Vitamin A is an important nutrient responsible for lung recovery from injury and promotion of orderly growth and differentiation of regenerating epithelial tissues. Preterm infants with CLD are often vitamin A deficient, and administration of vitamin A can potentially improve their vitamin status as well as accelerate recovery from CLD. An increase in the levels of vitamin A and retinol binding protein with administration of postnatal steroids suggests that the beneficial pulmonary response to corticosteroid might be partly due to the increase in vitamin A levels.[209] Recombinant human erythropoietin was thought to be effective in reducing blood transfusions which may exacerbate free radical damage leading to CLD. However, a RCT did not show that it reduced duration of ventilatory support and only a marginal reduction in the duration of oxygen therapy was observed.[210] One study did not show evidence of oxidative injury from blood transfusion which increases the risk of CLD.[211]

Although an association has been reported between PDA or fluid overload with CLD, meta-analysis of RCTs did not support the hypothesis that PDA closure with indomethacin or surgery reduces the incidence of CLD.[212] Nevertheless, the meta-analysis of RCTs in which indomethacin therapy was given for asymptomatic PDA showed a significantly shorter duration of oxygen therapy in infants <1750 g and of ventilatory therapy in those >1000 g.[213] The meta-analysis of RCTs in which indomethacin therapy was given for symptomatic PDA showed a significant improvement in cardiorespiratory status as well as a reduction in mortality rate. Therefore, although the incidence of CLD was not affected, the data suggested that the severity of CLD was reduced.

Prevention

The best prevention is to avoid preterm birth and RDS. Antenatal tocolytic agents are effective in delaying preterm labor sufficient to permit antenatal corticosteroid therapy. A case-controlled study in infants <1750 g birthweight ventilated within 12 hours of birth has shown that those whose mothers had received a complete course of antenatal corticosteroids had a lower risk of developing CLD.[214] An RCT in women with preterm labor at 26-34 weeks gestation also showed a significant reduction in the incidence of CLD (9% vs 23%).[215] Although preliminary reports from RCTs of combined maternal treatment with corticosteroids and thyrotropin-releasing hormone (TRH) suggested an acceleration of lung maturation superior to that achieved with corticosteroids alone.[216] A large RCT showed that TRH is ineffective and is associated with worse late outcome.[217,218] Administration of bubble CPAP in the delivery room with permissive hypercapnia (pCO_2 65-70 mmHg) has been suggested as an effective measure to prevent CLD.[219-223] Since these studies used inter-hospital comparisons and historic controls, the hypothesis needs to be properly tested by RCTs. Three Cochrane reviews were published to compare the use of dexamethasone for prevention of CLD given <7 days, 7-14 days, and

>21 days (Table 2).[224-226] Dexamethasone 0.5 mg/kg per day was the initial dose used in these RCTs, and the course was tapered over a variable period ranging between 7 days to 42 days.

Dexamethasone started at <96 hours results in a reduction in the CLD rate, combined mortality/CLD rate, earlier extubation, and severe ROP rate, but also an increase in the cerebral palsy rate. Started at 7-14 days, it results in a reduction of both mortality and CLD rates, earlier extubation, but also an increase in the infection rate. Started >21 days, it results in a reduction of the combined mortality/CLD rate, earlier extubation, need for home O_2, but also an increase in ROP rate. The American Academy of Pediatrics and Canadian Pediatric Society have stated that dexamethasone should not be routinely used for the prevention as well as for the treatment of CLD in preterm infants.[227] They further recommended that (a) postnatal use of systemic dexamethasone should be limited to carefully designed RCTs, (b) long-term neurodevelopmental assessments should be carried out in infants who have been given postnatal dexamethasone, (c) clinical trials should be done to investigate the use of alternative anti-inflammatory corticosteroids, both systemic and inhaled, and (d) postnatal steroids should be limited to exceptional clinical circumstance wherein parents should be fully informed about the short- and long-term risks and agree to treatment.

A Cochrane review on the use of bronchodilators in CLD[228] only showed one study dealing with prevention of CLD.[229] No evidence was found that salbutamol reduces mortality or CLD. Superoxide dismutase (SOD), an antioxidant enzyme, is the primary cellular defence against oxygen free radicals. Administration of bovine SOD in infants <1500g with RDS during their period of oxygen and ventilatory therapy has been shown in an RCT to reduce the incidence of CLD.[230] Recombinant human SOD, administered by the intratracheal route, is now available for clinical trials.[231,232] Allopurinol, an inhibitor of xanthine oxidase which is an enzyme capable of generating superoxide radicals, has been shown in an RCT to be of no benefit.[233] Inositol (120-160 mg/kg/d) has been shown to reduce the CLD rate, possibly because it potentiates corticosteroid-induced acceleration of lung maturation.[234] Vitamin A, important for the maintenance of epithelial cell differentiation and integrity within the respiratory tract, has been shown to reduce the CLD rate,[235] especially if given early from 2-4 days after birth.[236] However, a meta-analysis of all published RCTs did not show a significant effect, and it has been suggested that a dose of 5000 IU/dose 3 times a week might be needed for it to be effective.[237] Preterm infants may also be susceptible to oxygen-induced lung injury because they are deficient in vitamin E, a major natural antioxidant in the body. However, a meta-analysis of 8 RCTs of prophylactic vitamin E did not show that it protects the infants from developing CLD.[212] Vitamin E therapy increases the risk of septicemia and necrotizing enterocolitis probably by decreasing the oxygen dependent intracellular killing ability of neutrophils.[238] An RCT has failed to show that aerosolised cromolyn sodium reduced the incidence of CLD.[239] Infants ventilated with a helium-oxygen mixture were found in an RCT to have lower inspired oxygen, shorter duration of ventilation, less CLD and lower mortality.[240]

Prognosis

A turning point is usually reached half-way through the course of assisted ventilation when an improvement

Table 2. Dexamethasone for prevention of CLD

	<96 hours 21 RCTs (3072 infants)	7-14 days 7 RCTs (669 infants)	>21 days 9 RCTs (562 infants)
Mortality	Unaffected	Reduced (rr=0.44, 95% CI, 0.24, 0.8)	Unaffected
CLD	Reduced (rr=0.69, 95% CI 0.6, 0.8)	Reduced (rr=0.62, 95% CI , 0.47, 0.82)	Borderline (rr=0.76, 95% CI 0.58, 1.0)
Combined mortality/CLD	Reduced (rr=0.86, 95% CI 0.79, 0.94)	Reduced (rr=0.63, 95% CI, 0.51, 0.78)	Reduced (rr=0.73, 95% CI 0.58, 0.93)
Earlier extubation	Yes	Yes	Yes
Reduced need for home O_2	No	No	Yes
Hyperglycemia	Increased	Increased	Glycosuria
Hypertension	Increased	Increased	Increased
Hypertrophic cardiomyopathy	Increased	Increased	Increased
Gastrointestinal bleeding	Increased	Increased	Unaffected
Necrotising enrterocolitis	Unaffected	Unaffected	Unaffected
Infection	Unaffected	Increased	Unaffected
Pulmonary air leaks	Unaffected	Unaffected	Unaffected
Severe retinopathy of prematurity	Reduced	Unaffected	Increased
IVH/PVL	Unaffected	Unaffected	Unaffected
Cerebral palsy	Increased	Unaffected	Unaffected

in carbon dioxide tension, tachypnoea and weight gain is observed. Transient systemic hypertension, which may develop in the first year, responds well to antihypertensive therapy.[241,242] Most postneonatal hospital deaths in very low birthweight infants occur in those with severe CLD.[243] The degree of gas exchange impairment assessed at one month correlates with duration of oxygen therapy,[244] and that assessed at a postconceptual age of 36-40 weeks correlates with the degree of pulmonary dysfunction at one year.[245] Logistic regression analysis has shown that a combination of ventilatory parameters such as the mean airway pressure, inspired oxygen concentration and peak inspiratory pressure at 1-2 months of age are good predictors of mortality.[246-248] Late death from progressive respiratory failure correlates strongly with the occurrence of cyanotic episodes during the first 6 months which require sedation or muscle paralysis to maintain gas exchange.[248] The same study showed that the mortality was about 50% in those who remained oxygen and ventilator dependent at 6 months of age. Echocardiography, cardiac catheterization and angiography may provide important diagnostic and prognostic information on survivors with pulmonary hypertension complicating CLD.[249-251]

Infants with CLD have a post-discharge mortality of 11%-20%.[252-254] Infection with respiratory syncytial virus (RSV) is a major cause of acute respiratory deterioration and rehospitalization in young children with CLD.[255,256] Prophylaxis with monthly RSV immune globulin (750 mg/kg IV) has been shown to be a safe and effective means of reducing the incidence and days of RSV hospitalization in these high-risk infants.[257,258] However, neither treatment with RSV immune globulin nor ribavirin improve the outcome of these infants with RSV-associated respiratory failure.[259,260] Continued medical morbidity remains high, with recurrent episodes of wheezy attacks, pneumonia and otitis media, many of which require hospital readmissions in the first two years.[261,262] The incidence of sudden infant death syndrome (SIDS) was reported to be seven times greater in CLD compared with infants with similar birthweights without CLD[263] although more recent experience, involving closer monitoring of oxygenation status and provision of home oxygen, has shown no increased risk from SIDS.[264] Infants with oxygen saturations below 90% in room air at hospital discharge have an increased risk of SIDS or acute life-threatening event.[265]

Pulmonary mechanics improve with age.[266-268] Formation of new alveoli leads to an increase in lung volume and improvement in compliance. An increase in the rate of airway growth leads to an improvement in airway resistance. Most children appear clinically normal by 3-4 years of age. However, one study showed that almost 80% continued to have an abnormal chest X-ray at 2 years.[269] Residual pulmonary dysfunction consisting of fixed airway obstruction, airway reactivity and hyperinflation can still be demonstrated in most adolescents and young adults who had CLD in infancy.[270-274] The clinical consequence of this dysfunction in the long term is not known.

Growth retardation is present in 30%-40% of survivors and major neurodevelopmental disabilities occur in 25%-42%.[275-281] It is generally not possible to predict late disabilities in CLD survivors from perinatal data[261] though one study found that the need for additional oxygen at 36 weeks corrected postnatal gestational age is useful for predicting an abnormal outcome.[282] Two studies found no correlation between the duration of oxygen or ventilator therapy and neurodevelopmental outcome,[283,284] although two other studies showed that the duration of ventilation is the most powerful predictor of neurodisability in CLD survivors.[277,285] The presence of dysmature patterns in the near-term or term electroencephalogram has been shown to be associated with a less favourable outcome.[286] Survivors of severe CLD have been reported to develop an extrapyramidal movement disorder involving the limbs, neck, trunk and oral-buccal-lingual structures.[287]

Conclusions

No precise or uniform diagnostic criteria exist for CLD. The relationship between anatomical immaturity, surfactant deficiency, oxygen exposure and mechanical ventilation in the pathogenesis of this condition remain enigmatic. Current therapies for established CLD do not dramatically alter the disease process or prognosis.[288-291] The greatest benefit would probably come from methods to prevent or treat preterm labor but much more research is required before effective strategies can be developed. The future promise of prevention of CLD appears to rest in the antenatal intervention of preparing the lungs with corticosteroids for surfactant treatment after birth, while research continues into better ways to minimize oxygen toxicity, volutrauma and inflammatory reaction in the lung.

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