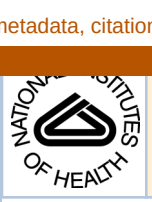

Published in final edited form as:

Semin Fetal Neonatal Med. 2009 December ; 14(6): 374–382. doi:10.1016/j.siny.2009.08.002.

Prevention of chronic lung disease

Matthew M. Laughon, MD, MPH[1], **P. Brian Smith, MD, MHS**[2], and **Carl Bose, MD**[1]

Matthew M. Laughon: matt_laughon@med.unc.edu; P. Brian Smith: brian.smith@duke.edu; Carl Bose: carl_bose@med.unc.edu

[1] University of North Carolina at Chapel Hill, Chapel Hill, NC, CB# 7596, 4th Floor, UNC Hospitals, Chapel Hill, NC 27599-7596, Phone: (919) 966-5063, Fax: (919) 966-3034

[2] Duke University, Durham, NC, PO Box 17969, Durham, NC 27715, Phone: (919) 668-8951, Fax: (919) 668-7058

Abstract

Considerable effort has been devoted to the development of strategies to reduce the incidence of chronic lung disease, including use of medications, nutritional therapies, and respiratory care practices. Unfortunately, most of these strategies have not been successful. To date, the only two treatments developed specifically to prevent CLD whose efficacy is supported by evidence from randomized, controlled trials are the parenteral administration of vitamin A and corticosteroids. Two other therapies, the use of caffeine for the treatment of apnea of prematurity and aggressive phototherapy for the treatment of hyperbilirubinemia were evaluated for the improvement of other outcomes and found to reduce CLD. Cohort studies suggest that the use of CPAP as a strategy for avoiding mechanical ventilation might also be beneficial. Other therapies reduce lung injury in animal models but do not appear to reduce CLD in humans. The benefits of the efficacious therapies have been modest, with an absolute risk reduction in the 7–11% range. Further preventive strategies are needed to reduce the burden of this disease. However, each will need to be tested in randomized, controlled trials, and the expectations of new therapies should be modest reductions of the incidence of the disease.

Keywords

chronic lung disease; bronchopulmonary dysplasia; prevention; prophylaxis; vitamin A; corticosteroids; caffeine

INTRODUCTION

After the development of chronic lung disease (CLD), medical care usually focuses on utilizing respiratory therapies that minimize further lung injury and optimizing nutrition and growth, with varying degrees of success. Therefore, because of the serious, long term health consequences of CLD, considerable effort has been devoted to the prevention of the disease. In this article, we examine the evidence of strategies that have been tested to prevent CLD. CLD most often begins with early lung injury from respiratory distress syndrome (RDS). Treatments that prevent or reduce the severity of RDS (e.g. surfactant replacement therapy) were developed with the hope that they would reduce the likelihood of developing CLD. Morbidities of prematurity, most notably persistent patency of the ductus arteriosus (PDA), may contribute to CLD. Prevention or treatment of PDAs has been advocated as strategies to prevent CLD. Various fluid and nutritional regimens have been utilized during the early neonatal period because of their potential to modify the likelihood of developing CLD. Finally, treatment of diseases or problems not related directly to the lungs (e.g. apnea of prematurity) may have an impact on vulnerability to CLD. We review evidence primarily

from randomized, controlled trials (RCTs), or the combined results of trials in meta-analyses, using the Cochrane Database of Systematic Reviews as the main source of information. Although meta-analyses, including the Cochrane reviews, suffer from a number of limitations, we believe that they provide the highest level of strength of evidence.[1 2]

TREATMENTS OF EARLY MORBIDITIES OF PREMATURITY

Surfactant Therapy

Following the development of exogenous surfactant preparations for the prevention and treatment of RDS, there were expectations that the use of these products would decrease the incidence of CLD. Surfactant therapy decreases mortality, particularly when used very soon after birth as a prophylactic strategy (compared to treatment after established RDS) and also reduces the incidence of lung injury as evidenced by a reduction in pneumothorax.[3] Unfortunately, surfactant therapy does not however, reduce the incidence of CLD among survivors.[4–6]

Since the original surfactant trials, two additional strategies of surfactant therapy have been reported. The first method is to administer surfactant during a brief period of intubation without obligatory mechanical ventilation (i.e. intubation, delivery of surfactant, and immediate extubation).[7] Benefits of this strategy have been reported in three trials.[8–10] However, a statistical reduction in CLD was not observed in any of these trials. In a Cochrane review, early surfactant treatment during a brief period of ventilation compared to later selective surfactant therapy in ventilated infants resulted in a reduced incidence of air leak and CLD (RR 0.51, 95% CI 0.26, 0.99), defined as oxygen therapy at 28 days.[11] However, the more common definition of CLD, oxygen therapy at 36 weeks post-menstrual age (PMA), could not be evaluated in this meta-analysis because it was not reported in all trials. In a more recent trial, not included in the Cochrane review, very early surfactant therapy administered in the delivery room without obligatory ventilation was demonstrated to reduce the risk of mechanical ventilation.[12] This study was not powered to examine CLD at 36 weeks PMA, and there was no statistically significant improvement in CLD.

Another strategy is to administer surfactant beyond the first postnatal week to infants in whom a secondary surfactant dysfunction may be present[13], and whose risk for CLD is high. In an RCT of surfactant therapy using this strategy, infants assigned to one of two doses of surfactant had a lower mean fraction of inspired oxygen (33%) at twenty-four hours after dosing, compared to infants assigned to the placebo group (39%).[14] However, there was no difference in the incidence of mortality or CLD between groups.

Conclusion—Surfactant replacement therapy is a standard of care for infants at risk for RDS or with established disease based on reductions in mortality and air leak. However, current evidence is insufficient to support alternate early surfactant treatment strategies (e.g. treatment without obligatory mechanical ventilation) or treatment beyond the immediate neonatal period for the prevention of CLD.

Closure of the Patent Ductus Arteriosus

Persistent patency of the ductus arteriosus (PDA) following preterm birth is common, particularly among the least mature infants, and is associated with neonatal morbidities, including CLD. [15 16] Shunting of blood from the systemic to pulmonary circulation may have an effect on the mechanical properties of the lung, such as a decrease in lung compliance [17 18], and these changes may provoke the need to increase ventilatory support. This cascade of events may increase the likelihood of CLD by increasing ventilator-induced lung injury.[19] This hypothesis is supported by a strong association between the presence of a

PDA and CLD. Although a causal relationship between a PDA and CLD has not been established, many clinicians attempt to close PDAs under the assumption that early closure decreases the likelihood of CLD and other morbidities.[20]

The Cochrane Reviews include two strategies to promote closure of PDAs: prophylactic treatment with cyclo-oxygenase (COX) inhibitors of infants at risk for PDAs and treatment with COX inhibitors of infants with asymptomatic PDAs identified by echocardiography.[21] [22] The review of prophylactic treatment with the COX inhibitor indomethacin suggests that there are several short term benefits of this therapy, including a reduction in the incidence of symptomatic PDA, serious intraventricular hemorrhage, and surgical ligation of PDAs. However, despite improvements in these outcomes, the incidence of CLD is not reduced.[23] Treatment with indomethacin of infants with asymptomatic PDAs appears to result in similar benefits.[22] There have been no reports of large, controlled trials of indomethacin for the treatment of symptomatic PDAs conducted in the post-surfactant era. However, a comprehensive report of older trials suggests a similar lack of reduction of CLD using this strategy.[24] Another COX inhibitor, ibuprofen, is as effective at promoting ductal closure, but like indomethacin, does not appear to reduce mortality or the likelihood of CLD.[25] Although there have been no recent controlled trials comparing outcomes following ligation compared to either placebo or medical therapy, a recent post-hoc analysis of an RCT of prophylactic PDA ligation[26] found that 48% of the infants allocated to prophylactic PDA ligation developed CLD compared to 21% in the control group.[27]

This lack of demonstrable impact of ductal closure on the incidence of CLD may have resulted, in part, from limitations imposed by study designs. Under the assumption that closure of the PDA is beneficial, virtually all clinical trials in the modern era have focused on the most expeditious way in which to close a PDA. None has addressed the more fundamental question of whether closing the PDA improves outcome. Those trials that have included control groups treated with a placebo have permitted treatment of a PDA that persisted after reaching a defined study endpoint, often within days after enrollment. This study design has resulted in high rates of treatment in the “placebo” group (usually in the range of 40%) and has diminished the likelihood of identifying the effect of PDA closure on other outcomes. Additionally, the ability to detect adverse effects of treatment is equally compromised.

Conclusion—Evidence does not support the prevention or treatment of PDAs, with the goal of closure, for the prevention of CLD.

Caffeine for Apnea of Prematurity

Caffeine is a methylxanthine used to treat apnea of prematurity. In a large RCT, the impact of treatment with caffeine on neurodevelopmental outcome was tested in infants with birth weights from 500 to 1250 g. Infants assigned to receive caffeine had a lower incidence of neurodevelopmental impairment, most notably cerebral palsy (4.4% in the caffeine group vs. 7.3% in the placebo group) and cognitive delay (33.8% vs. 38.3%).[28] One of the secondary outcomes of the trial was CLD. Infants in the caffeine group had an incidence of CLD of 36% compared to 47% of infants placebo group (adjusted odds ratio [OR], 0.63; CI 0.52 to 0.76; $p<0.001$). The mechanism by which caffeine reduced the incidence of CLD is uncertain. Positive airway pressure was discontinued one week earlier in the infants receiving caffeine.[29] Therefore, it is possible that caffeine reduced the exposure to mechanical ventilation thereby reducing ventilator induced lung injury.

Conclusion—Evidence supports the use of caffeine for the treatment of apnea of prematurity in extremely low gestational age newborns, with the probability that a secondary benefit will be a reduction of CLD.

Aggressive Phototherapy

Bilirubin is an efficient scavenger of oxygen and peroxyl radicals.[30] Because oxidative injury appears to be critical in the pathogenesis of CLD,[31] bilirubin may have a protective effect in the lung and decrease the likelihood of developing CLD. This possibility is supported by observations from a single center retrospective study in which infants with moderate and severe CLD had lower total bilirubin levels on the seventh postnatal day compared to infants that did not develop CLD.[32] However, in this study, infants with moderate and severe CLD had lower birth weights, and adjustments were not made for these differences or for exposure to phototherapy in the analyses. More definitive evidence about the potential influence of bilirubin and phototherapy on the development of CLD is available from a study in a large cohort of extremely low birth weight (ELBW; <1000 g birth weight) infants designed to examine the effect of phototherapy on death and neurodevelopment. In this study, infants were randomized either to aggressive phototherapy (starting at bilirubin levels of 5 mg/dL for all infants) or to conservative phototherapy (bilirubin levels were allowed to rise to 8 mg/dL for infants <750 g birth weight and 10 mg/dL for infants 751–1000 g birth weight).[33] There was no difference in mortality between the infants assigned to aggressive phototherapy (21%) compared to those assigned to conservative phototherapy (20%). Although CLD was not the primary outcome of the study, rates of CLD were reported as a secondary outcome. Contrary to expectations based on the hypothesized role of bilirubin in oxidative injury, the rate of CLD was significantly lower in the aggressive phototherapy group compared to the conservative phototherapy group (41% vs 48%; OR 0.86, 95% CI 0.78–0.96).

Conclusion—Evidence supports the use of aggressive phototherapy in infants with birth weights <1000 g, with the probability that a secondary benefit will be a reduction in CLD.

ANTI-INFLAMMATORY THERAPIES

Systemic corticosteroids: dexamethasone and hydrocortisone

Corticosteroids may affect pulmonary function and lung disease through several mechanisms. Fetal exposure causes increased surfactant synthesis and lung epithelial differentiation. In animals, early postnatal exposure causes increased surfactant synthesis. However, their role in modulating lung inflammation is the primary mechanism through which they may modify the likelihood of developing CLD.[34] Corticosteroids decrease recruitment of polymorphonuclear leukocytes to the lung, and reduce the production of prostaglandins, leukotrienes, elastase and other inflammatory mediators, and decrease vascular permeability and pulmonary edema formation. [34] Corticosteroids may also modulate repair after lung injury by reducing fibronectin production, and subsequent fibrosis, and increasing retinol concentrations (see Vitamin A below).

The use of corticosteroids for the prevention or treatment of CLD have been examined in numerous clinical trials over the past 25 years. Most have demonstrated short-term improvements in pulmonary function. Although these studies are not easily combined in meta-analyses because of variability in study design, two Cochrane reviews provide information about the effect of treatment with systemic steroids on the incidence of CLD. The reviews differ based on the timing of treatment. Early treatment was defined as beginning before eight postnatal days[35]; late treatment was defined as beginning after seven days of postnatal age.[36]

The review of early treatment examined 28 trials (20 used dexamethasone, 8 used hydrocortisone) that enrolled 3740 infants. Benefits of early treatment included decreased risks of CLD at both 28 days and at 36 weeks postmenstrual age (PMA) (RR 0.79, 95% CI 0.71, 0.88) and death or CLD at 28 days and at 36 weeks PMA (RR 0.89, 95% CI 0.84, 0.95). There were no differences in the incidence of mortality. Twelve trials examined the neurodevelopmental impact of corticosteroids and demonstrated an increase in the risk of cerebral palsy (RR 1.45, 95% CI 1.06, 1.98). The interpretation of neurodevelopmental outcomes in these studies is challenging because of varying quality of assessment across studies. However, impairment of motor function appears to be a risk associated with early treatment.

The review of late treatment examined 19 trials that enrolled 1345 infants. Benefits of late treatment included decreased risks of CLD at both 28 days and at 36 weeks PMA (RR 0.72, 95% CI 0.61, 0.85) and death or CLD at 28 days and at 36 weeks PMA (RR 0.72, 95% CI 0.63, 0.82). There was an increased risk of hyperglycemia, hypertension and hypertrophic cardiomyopathy among treated infants. There was not an increased risk of blindness, deafness, major neurosensory disability, or cerebral palsy. However, there was an increased risk of abnormal neurological examination. The implications of this finding are unclear in the absence of an increase in neurosensory impairment or cerebral palsy.

Given the concerns regarding the adverse effects of dexamethasone, hydrocortisone has been examined separately as an alternative therapy to prevent CLD. Eight of the trials reviewed in the Cochrane meta-analysis on early corticosteroids used hydrocortisone.[35] Hydrocortisone had little effect on the incidence of CLD at 28 days or 36 weeks PMA (RR 0.96, 95% CI 0.82, 1.12) and there was an increased risk of gastrointestinal perforations (RR 2.02, 95% CI 1.13, 3.59). Early hydrocortisone was not associated with neurodevelopmental impairment.

Although the risk of corticosteroid treatment for the prevention of CLD is not justified in all premature infants, there may be some populations in which the benefits outweigh the harm of this therapy. Doyle et al. suggest that the balance between benefit and risk may be modified by baseline risk for CLD. [37] In a meta-regression analysis of previous RCTs of corticosteroids, infants at high risk of developing CLD treated with corticosteroids were shown to be more likely to survive without neurodevelopmental impairment. This study suggested that a strategy of treatment would have net benefit if the risk for CLD of a population reached a certain threshold. Presumably, the decrease in the risk of cerebral palsy associated with CLD, by virtue of the beneficial effects of steroids in preventing CLD, outweighs the increase in CP caused by steroids.

Conclusions—Evidence does not support the use of corticosteroids for the prevention of CLD in populations of premature that include infants at relatively low risk of the disease. Caution in the use of corticosteroids has been advised by the American Academy of Pediatrics which recommends that systemic corticosteroids not be used outside the context of a clinical trial.[38] However, there may be populations with high baseline risk in which a reduction in CLD would be accompanied by improved survival without neurodevelopment impairment. Unfortunately, at this time, we do not have a mechanism for identifying these populations. Therefore, any strategies for the use of corticosteroids for the prevention of CLD would not be supported by evidence.

Inhaled corticosteroids

In addition to systemic therapy, corticosteroids may also be administered via an inhaler or, more commonly, nebulization. Eleven trials were analyzed in a Cochrane review examining the effect of early inhaled steroids beginning at less than two weeks postnatal age in

ventilator- dependent infants on the incidence of CLD.[39] There was no significant effect of inhaled steroids on either CLD (RR 0.97, 95% CI 0.62, 1.52) or mortality. The use of inhaled steroids for the prevention of CLD in infants not receiving mechanical ventilation has not been evaluated.

Conclusion—Evidence does not support the use of inhaled corticosteroids for the prevention of CLD.

Inhaled nitric oxide

Inhaled NO (iNO) improves oxygenation and reduces the need for extracorporeal membrane oxygenation in term and near-term infants with respiratory failure from a variety of causes including meconium aspiration syndrome, sepsis, and idiopathic persistent pulmonary hypertension.[40] Previous studies suggest that iNO can also improve gas exchange in premature newborns with hypoxemia caused by the respiratory distress syndrome or persistent pulmonary hypertension.[41] iNO may also have anti-inflammatory properties. In animal studies, iNO decreased early lung inflammation and oxidant stress,[42] and improved lung structure in models of CLD.[43] These findings have stimulated the investigation of the potential benefit of iNO in reducing the risk or severity of CLD in premature infants.

Interpreting the results of RCTs that examined the efficacy of iNO in the prevention of CLD of these trials is challenging because of variability in study design, most notably variable postnatal age of enrollment and baseline risk of CLD. Eleven RCTs of iNO therapy in preterm infants were included in a Cochrane review[44]. To account for variation in study design, the authors divided the trials into three categories based on entry criteria: 1) enrollment during the first three postnatal days based on oxygenation criteria, 2) enrollment of all intubated infants[45 46], and 3) enrollment after the third postnatal day based on increased risk of CLD.[47 48] Only analyses of these subgroups were performed.

Trials of early treatment of infants enrolled based on oxygenation criteria demonstrated no significant effect of iNO on mortality or CLD. Studies of iNO in intubated infants demonstrated a marginally significant reduction in the combined outcome of death or CLD (RR 0.91; 95% CI 0.84, 0.99). Late treatment based on the risk of CLD demonstrated no reduction in death or CLD. However, one of the larger trials which enrolled intubated infants during the second postnatal week demonstrated a reduction in CLD (50.7% in the iNO group compared to 56.9% in the placebo group) but not death (5.4% vs. 6.3%).[50]

Conclusion—Evidence does not support a clear role for iNO for the prevention of CLD. It is possible that certain populations defined by postnatal age and baseline risk may benefit, but identifying these populations is not possible at this time.

Superoxide dismutase

Superoxide dismutase (SOD) is an enzyme that catalyzes the free oxygen radical superoxide (O_2^-) into oxygen and hydrogen peroxide. Superoxide is toxic and promotes oxidative damage in the lungs. [49] In a piglet model of acute lung injury caused by hyperoxia and barotrauma, intratracheal administration of SOD improved lung compliance, and decreased neutrophil chemotactic activity, total cell counts, and elastase activity recovered from tracheal aspirates.[49]

SOD has been investigated in two RCTs to assess the effect of SOD in preventing CLD and there was no reduction in CLD.[50 51] However, one year follow-up in one trial demonstrated that SOD might reduce the use of treatments with medications such as inhaled corticosteroids and/or albuterol used to treat asthma.[52]

Conclusion—Evidence does not support the use of SOD for the prevention of CLD.

Glutathione

Lung inflammation during mechanical ventilation, particularly with coincidental exposure to high fractions of inspired oxygen, results in the generation of reactive oxygen species and proinflammatory cytokines.[53] These mediators may damage cells of the lungs and can impair pulmonary development. Glutathione is an antioxidant that may inhibit some of these changes. Quantities of glutathione are relatively deficient in preterm infants, and further deficiency may occur because of limited availability of its precursor amino acid, cysteine.[54] Supplementation of glutathione has been suggested as a strategy for minimizing the effects of oxidatiove injury. Because glutathione does not readily cross cell membranes and cysteine is unstable in solution, investigators have examined the ability of N-acetylcysteine, a precursor to cysteine, to prevent CLD. In a multicenter RCT of 391 ELBW infants no difference in CLD or death was observed between infants randomized to receive N-acetylcysteine compared to placebo (51% vs. 49%).[55] Levels of cysteine and glutathione were actually lower among infants in the treatment group on days 3 and 7 of the study. This finding may have resulted from the early administration of parenteral nutrition supplemented with cysteine to both groups of infants.

Conclusion—Evidence does not support treatment with glutathione or its precursors for the prevention of CLD.

OTHER MEDICATIONS

Vitamin A

Vitamin A derivatives define a group of fat soluble compounds called retinoids. These compounds appear to play an important role in lung disease because they are critical in the regulation and promotion of growth and differentiation of lung epithelial cells, particularly during repair following lung injury.[56] In animals, a deficiency of vitamin A results in abnormal lung growth following prolonged exposure to hyperoxia.[57] Preterm infants have low vitamin A levels at birth, and low levels of vitamin A are associated with an increased risk of CLD.[58] Therefore, vitamin A supplementation was developed as a strategy for preventing CLD.

In a Cochrane review, eight studies that examined the efficacy of vitamin A supplementation in the prevention of CLD were identified. In ELBW infants, supplementation reduced the incidence of CLD, defined as receipt of oxygen at 36 weeks PMA (RR 0.87, CI 0.77, 0.98), with a number needed to treat of 13 (95% CI; 7, 100).[59] In the largest study in the review, among infants birth weight <1000 g, death or CLD was lower in the vitamin A group compared to a placebo group (55% vs. 62% percent; RR, 0.89; 95 CI, 0.80 to 0.99).[60] Neurodevelopment at 18 to 22 months of age was not different between groups.[61]

Conclusion—Evidence supports the use of vitamin A supplementation in infants with birth weights <1000 g and meeting other eligibility requirements of the RCTs for the prevention of CLD.

H2 blockers: cimetidine

Cimetidine is an H_2 blocker that also inhibits cytochrome P450. Because upregulation of cytochrome P450 may be important during lung injury, its inhibition may protective. However, an RCT evaluating a 10 day infusion of cimetidine beginning in the first 24 hours after birth in infants with birth weights <1250 g demonstrated no reduction in death or CLD at 36 weeks PMA.[62] No significant differences were identified for other earlier markers of

pulmonary disease. The study was stopped after enrollment of 84 patients because of a significant increase in death or severe intraventricular hemorrhage among infants receiving cimetidine.

Conclusion—Evidence does not support treatment with cimetidine for the prevention of CLD.

Treatment of Ureaplamsa with Macrolides

Although there is an association between colonization of the respiratory tract with *Ureaplasma* and the development of CLD, a causal link between colonization and the disease remains uncertain. In addition, treatments that both eradicate colonization and reduce CLD remain elusive.[63] For example, treatment of infants colonized with *Ureaplasma* with erythromycin does not appear to reduce the incidence of CLD.[64] Treatment with other macrolides, such as azithromycin, have been investigated because these drugs also have anti-inflammatory properties. However, in a small, single-center pilot study, azithromycin therapy reduced the incidence of treatment with dexamethasone, but did not reduce the incidence of CLD.[65]

Conclusion—Evidence does not support treatment of colonization of the respiratory tract with Ureaplasma for the prevention of CLD. However, because of the strong association between colonization and CLD, strategies to prevent or treat colonization warrant further investigation.

VENTILATORY STRATEGIES

Permissive Hypercapnea

Mechanical ventilation, although necessary for survival for many preterm infants, injures lung tissue and is a risk factor for the development of CLD.[66] After retrospective studies indicated that higher levels of CO_2 in the first few days of life were associated with lower risk of CLD, [67 68] several investigators prospectively studied the practice of "permissive hypercapnea".[69–71] The largest of these trials randomized 220 infants to a target PCO_2 > 52 mm Hg (minimal ventilation) or < 48 mm Hg (routine care).[70] No difference in the incidence of CLD was observed, possibly because the separation of PCO_2 between groups was only 4.0 ± 1.3 mmHg. A similar finding of a small difference in PCO_2 was demonstrated in a subsequent study.[69] A larger difference in PCO_2 might have demonstrated a difference in outcome. Although the practice of permissive hypercapnea has been widely adopted, its contribution to reducing the overall burden of CLD is likely to be small if benefits exists because of the pervasive practice and success of avoidance of ventilation.

Conclusions—Evidence is inconclusive that permissive hypercapnea is effective for the prevention of CLD.

High Frequency Ventilation

Many clinicians use some form of high frequency ventilation (HFV), in lieu of conventional mechanical (tidal) ventilation (CMV), in selected infants under the assumption that HFV is less likely to induce lung injury. The mechanisms by which HFV might reduce lung injury thereby decreasing the incidence of CLD include: 1) reducing regional lung overinflation; 2) minimizing volutrauma; 3) minimizing pressure changes at the alveolar level, and 4) lowering oxygen requirements.[72–74] The initial large RCT comparing one form of HFV, high frequency oscillatory ventilation (HFOV), to CMV was conducted in the pre-surfactant era.[75] This study found no difference in death or CLD between the HFOV and CMV groups, but was criticized because of the manner in which HFOV was employed. A Cochrane

review that includes 11 studies of HFOV compared to CMV, demonstrates a small decrease in the relative risk of death or CLD at 36 weeks in infants treated with HFOV, (RR=0.90, 95% CI 0.83, 0.97).[76] Subsequent studies of HFOV have yielded mixed results.[77 78] Studies of the impact on the incidence of CLD of two other methods of high frequency ventilation, high frequency jet ventilation and the high frequency flow interrupter, are inconclusive.[71 79–81]

Conclusion—Current evidence does not support the routine use of HFV for the prevention of CLD.

Continuous Positive Airway Pressure

The use of nasal continuous positive airway pressure (CPAP) appears to be a successful strategy for avoiding the need for mechanical ventilation in some infants, with the presumptive benefit of decreasing the risk of CLD.[82 83] In an observational cohort study, an association between the early use of nasal CPAP and decreased risk of CLD was reported[84]. However, to date, a reduction in CLD has not been demonstrated in RCTs of early CPAP compared to conventional ventilation. For example, in an RCT of 104 infants born <28 weeks gestation, infants receiving nasal CPAP in the delivery room had a rate of CLD (29.4%) comparable to those treated with mechanical ventilation (27.9%), and more infants treated with CPAP died (27% vs. 13%). [85] More recently, a larger RCT comparing the initiation of nasal CPAP compared to intubation and mechanical ventilation in the delivery room among 610 infants between 25 and 28 weeks gestation at birth.[82] Although there was a reduction in the combined outcome of death or oxygen requirement 28 days of age among infants treated with early CPAP compared to those who were ventilated (OR; 0.63 [95%CI; 0.46, 0.88]), no difference was observed at 36 weeks PMA. These studies suggest that the benefits reported in observational studies associated with the early CPAP as a strategy for avoiding mechanical ventilation might be a marker for other center specific care practices that have not been elucidated to date. A large trial in the National Institute of Child Health and Human Development Neonatal Research Network comparing the use of nasal CPAP to intubation and surfactant therapy has completed enrollment.[86] Hopefully, the results of this trial will help answer the unresolved questions about this potentially beneficial strategy.

Conclusion—Current evidence from RCTs does not support the routine use of CPAP to avoid mechanical ventilation and to prevent CLD. However, the evidence in support of this strategy from contemporary observational studies is compelling. It is seems likely that the judicious use of CPAP immediately after birth, in lieu of mechanical ventilation or after a brief period of ventilation, in carefully selected patient populations minimizes the likelihood of developing CLD. This potential benefit may be augmented by a brief period of ventilation for surfactant administration (see Surfactant Therapy above). However, the method for selecting the population is not certain at this time.

NUTRITIONAL AND FLUID THERAPIES

Nutritional Support

The provision of the quality and quantity of energy substrates to premature infants may play a role in the development of CLD. Premature infants may be vulnerable to the effects of nutritional deprivation because they are born with lower glycogen stores and body fat compared to term infants. Poor caloric intake during respiratory illness may result in respiratory muscle fatigue and a longer duration of mechanical ventilation.[87] In one case-control study, infants that developed CLD had significantly lower mean energy intakes than matched controls.[88] In an unmasked RCT, 125 infants <1500 g birth weight were allocated to either standard parenteral nutrition (maximum of 2 g/kg/day lipid, 2.5 mg/kg/day amino

acids, 10% dextrose solution, standard enteral feeding schedule) or aggressive nutrition (maximum of 3.5 g/kg/day of lipids, 3.5 g/kg/day amino acids, 15% dextrose solution, aggressive enteral feeding schedule). Infants in the aggressive nutrition cohort received more caloric intake and experienced faster growth. However, pulmonary outcomes including duration of mechanical ventilation, development of CLD (oxygen requirement at 28 days of life), and need of oxygen at term were similar between groups. [89]

Preterm infants are born with less fat and protein stores compared to infants born at term. Lipids are normally administered as part of total parenteral nutrition in the first few postnatal days. Polyunsaturated fatty acids can act as an antioxidant. Thus, in addition to providing additional calories for growth, nutrition in the form of lipids that are high in polyunsaturated fatty acids might protect the lung from oxygen toxicity.[90] In a study examining the potential benefits of early lipid supplementation, 183 ELBW infants were randomized to lipid administration either beginning in the first 12 hours of life or after the 7th day of life, and the primary outcome was death or CLD.[91] The study was stopped because of a significant increase in mortality among the smallest infants (birth weights 600–800 g) in the early lipid group. There was no difference between groups in the entire cohort in the combined outcome of death or CLD.

Conclusion—There does not appear to be a nutritional strategy that decreases the likelihood of developing CLD. A prudent approach would be to avoid malnutrition.

Fluid Restriction and Diuretic Therapy

Excessive lung water may interfere with respiration by impairing lung mechanics, and thus increasing the need for oxygen and ventilatory support. By these mechanisms, excessive lung water may play a role in the development of CLD. Extremely premature infants have a relatively high percentage of body water that is largely in the extracellular fluid compartment.[92] The normal weight loss that occurs in the first few days after birth may not occur if inappropriately large volumes of fluid are administered. Fluid restriction during this critical period of time, therefore, may help prevent CLD. This possibility was examined in a cohort of 1382 ELBW infants. Higher fluid intake and lack of weight loss during the first postnatal week, even after adjustment for factors known to predict CLD, were associated with a higher risk of death and CLD at 36 weeks PMA.[93] A Cochrane review examined restricted versus liberal water intake for preventing morbidity and mortality in preterm infants and included 5 trials.[94] The incidence of PDA and necrotizing enterocolitis was lower in the restricted water intake groups. However, the risk of CLD was not different between groups defined by water intake (RR 0.85, 95% CI 0.63 to 1.14).

Because sodium supplementation favors expansion of the extracellular fluid compartment, early administration of sodium may also adversely affect risk of CLD. Forty-six infants were randomized to either sodium supplementation after 6% weight loss following birth (delayed supplementation) or supplementation beginning on the second day of life (early supplementation). [95] Although there was a lower proportion of infants receiving oxygen at 28 days in the delayed sodium supplementation group, by 36 weeks PMA, there was no difference in death or CLD in the early compared to the delayed group (54% vs 41%; p=0.38).

Because pulmonary edema appears to be a prominent feature of CLD, diuretics are commonly used to improve lung mechanics in infants with established disease. There is far less experience with the use of diuretics early in life for the prevention of CLD. Two Cochrane reviews examine the use of loop diuretics and diuretics acting on the distal renal tubule.[96 97] They include small studies of single dose or short course therapy and only report short-term outcomes including: extubation rates, change in lung compliance, and change in

fraction of inspired oxygen.[98 99] The potential of these drugs for preventing CLD cannot be determined from these studies.

Conclusion—An appropriate fractional loss of weight immediately after birth, compared to persistence of excessive extracellular fluid, appears to decrease the likelihood of CLD. Strategies for the administration of free water and sodium during the first week of life should include this goal. Evidence does not support the use of diuretics to further decrease exrtacellular fluid for the prevention of CLD.

QUALITY IMPROVEMENT TECHNIQUES

There has been considerable recent interest in using quality improvement or implementation science methodologies to reduce morbidities associated with prematurity, including CLD. This interest has been stimulated by the observation that there is great variability in outcomes such as CLD among centers, even after adjustment for confounding risk factors (e.g. birth weight distribution). The assumption is that variability in practice accounts for the differences in outcome, and that uniform application of best practices would improve outcomes in poorly performing centers. Reports of the success of these techniques in reducing CLD have appeared in reports from single centers and use a before-after study design. That is, the incidence of CLD is measured, an intervention or panel of interventions is implemented, and the incidence of CLD is measured again.[100 101] Using a similar, before-after design to compare outcomes in 2001 to 2003, 19 hospitals in the Vermont-Oxford Network reported a higher incidence of survival without CLD after initiation of a package of potentially better practices (63.4% vs. 53.6%; OR 1.86; CI: 1.41–2.46).[102] Hospitals used conventional ventilation, postnatal steroids, and supplemental oxygen less frequently, increased the use of nasal CPAP, and reduced the median time to first surfactant dose from 22 to 10 minutes after delivery after initiation of quality improvement techniques. In a study using a cluster, randomized, controlled design, seven intervention centers received quality improvement training including potentially better practices. The outcomes after this intervention were compared to outcomes in seven control centers.[103] Intervention centers decreased the time of delivery of the first surfactant dose (from 51 minutes to 31 minutes), increased the use of nasal CPAP on the first day (from 16.9% to 24.2%), and decreased the duration of mechanical ventilation in the first week of life (from 4.0 ± 2.7 days to 3.5 ± 2.8 days). However, despite successful implementation of quality improvement techniques and changes in these short-term outcomes, the rate of CLD was similar between the intervention and the control centers (38.5% vs. 36.1%).

Conclusion

Incorporation of quality improvement methodology into clinical practice has vast potential for improving outcomes and will unquestionably impact outcomes in neonatal medicine. However, the paucity of evidenced-based practices for the prevention of CLD makes the development of bundles of best practices, and therefore the application of quality improvement methodology, difficult. Whether the utilization of these strategies can reduce the incidence of CLD is as yet uncertain.

CONCLUSIONS

A variety of treatments have been used to prevent CLD, but only two medicinal therapies, vitamin A supplementation and treatment with systemic corticosteroids, have proven efficacy based on RCTs. Although not used specifically for the prevention of CLD, the treatment of apnea of prematurity with caffeine and the use of aggressive phototherapy in ELBW infants are also associated with reductions in CLD. Individually, these treatments reduce risk by 7% to 11%. Unfortunately, treatment with systemic corticosteroids

(particularly dexamethasone), although effective in reducing the risk of CLD, is associated with increased rates of neurodevelopmental impairment. The benefits of treatment with systemic corticosteroids may outweigh the risks in infants with high baseline risk of CLD. The use of CPAP in selected populations of infants, in lieu of mechanical ventilation, may also decrease the incidence of CLD, but further data is needed to define this population. The use of quality improvement methodologies has potential for reducing CLD, but will rely upon high quality evidence from RCTs that support bundles of best practices.

Because of the economic impact and long-term consequences of CLD, new preventive therapies are desirable. Future trials that test these therapies should incorporate strategies to systematically quantify the risk of CLD prior to enrollment. To date, a method for predicting CLD with sufficiently high sensitivity and specificity has not been available. A new tool using clinical and demographic variables appears promising.[104] Because of the heterogeneity of the causal pathways that lead to the development of CLD, it is unlikely that a single preventive strategy will have a major impact on the reduction of CLD. Rather, several strategies, with the expectation that each will contribute to a modest reduction in CLD, will need to be tested in RCTs.

Practice Points

- CLD is an important morbidity associated with premature birth.
- The prevention strategies with the highest quality evidence with most favorable benefit/risk ratio include vitamin A and caffeine.
- Corticosteroids reduce the incidence of CLD, but increase the risk of abnormal neurologic examination.

Research Directions

- A simple, clinically relevant predictive model that objectively assesses the risk of CLD needs to be developed.
- Well-powered trials of surfactant therapy with brief ventilation and later surfactant therapy with the primary endpoint of CLD are needed.
- An RCT of systemic corticosteroids versus placebo among patients at high risk of chronic lung disease is needed, with appropriate neurodevelopmental follow-up.

References

1. McGuire W, Fowlie P, Soll R. What has the Cochrane collaboration ever done for newborn infants? Arch Dis Child Fetal Neonatal Ed. 2009
2. Gambrill E. Evidence-based clinical practice, [corrected] evidence-based medicine and the Cochrane collaboration. J Behav Ther Exp Psychiatry 1999;30:1–14. [PubMed: 10365860]
3. Soll RF, Morley CJ. Prophylactic versus selective use of surfactant for preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2000:CD000510. [PubMed: 10796379]
4. Soll RF. Synthetic surfactant for respiratory distress syndrome in preterm infants. Cochrane Database Syst Rev 2000:CD001149. [PubMed: 10796417]
5. Soll RF. Prophylactic synthetic surfactant for preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2000:CD001079. [PubMed: 10796410]
6. Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2000:CD000511. [PubMed: 10796380]
7. Stevens TP, Harrington EW, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database Syst Rev 2007:CD003063. [PubMed: 17943779]

8. Verder H, Albertsen P, Ebbesen F, et al. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. Pediatrics 1999;103:E24. [PubMed: 9925870]
9. Verder H, Robertson B, Greisen G, et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. Danish-Swedish Multicenter Study Group. N Engl J Med 1994;331:1051–5. [PubMed: 8090164]
10. Reininger A, Khalak R, Kendig JW, et al. Surfactant administration by transient intubation in infants 29 to 35 weeks' gestation with respiratory distress syndrome decreases the likelihood of later mechanical ventilation: a randomized controlled trial. J Perinatol 2005;25:703–8. [PubMed: 16163369]
11. Stevens TP, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs selective surfactant and continued mechanical ventilation for preterm infants with or at risk for RDS. Cochrane Database Syst Rev 2002:CD003063. [PubMed: 12076469]
12. Rojas MA, Lozano JM, Rojas MX, et al. Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized, controlled trial. Pediatrics 2009;123:137–42. [PubMed: 19117872]
13. Merrill JD, Ballard RA, Cnaan A, et al. Dysfunction of pulmonary surfactant in chronically ventilated premature infants. Pediatr Res 2004;56:918–26. [PubMed: 15496605]
14. Laughon M, Bose C, Moya F, et al. A pilot randomized, controlled trial of later treatment with a Peptide-containing, synthetic surfactant for the prevention of bronchopulmonary dysplasia. Pediatrics 2009;123:89–96. [PubMed: 19117865]
15. Marshall DD, Kotelchuck M, Young TE, et al. Risk factors for chronic lung disease in the surfactant era: a North Carolina population-based study of very low birth weight infants. North Carolina Neonatologists Association. Pediatrics 1999;104:1345–50. [PubMed: 10585987]
16. Rojas MA, Gonzalez A, Bancalari E, et al. Changing trends in the epidemiology and pathogenesis of neonatal chronic lung disease. J Pediatr 1995;126:605–10. [PubMed: 7699543]
17. Stefano JL, Abbasi S, Pearlman SA, et al. Closure of the ductus arteriosus with indomethacin in ventilated neonates with respiratory distress syndrome. Effects of pulmonary compliance and ventilation. Am Rev Respir Dis 1991;143:236–9. [PubMed: 1990934]
18. Yeh TF, Luken JA, Thalji A, et al. Intravenous indomethacin therapy in premature infants with persistent ductus arteriosus--a double-blind controlled study. J Pediatr 1981;98:137–45. [PubMed: 7005415]
19. Van Marter LJ, Pagano M, Allred EN, et al. Rate of bronchopulmonary dysplasia as a function of neonatal intensive care practices. Journal of Pediatrics 1992;120:938–46. [PubMed: 1593356]
20. Clyman RI. Recommendations for the postnatal use of indomethacin: an analysis of four separate treatment strategies. J Pediatr 1996;128:601–7. [PubMed: 8627430]
21. Fowlie PW. Intravenous indomethacin for preventing mortality and morbidity in very low birth weight infants. Cochrane Database Syst Rev 2000:CD000174. [PubMed: 10796168]
22. Cooke L, Steer P, Woodgate P. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev 2003:CD003745. [PubMed: 12804488]
23. Schmidt B, Davis P, Moddemann D, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med 2001;344:1966–72. [PubMed: 11430325]
24. Knight DB. The treatment of patent ductus arteriosus in preterm infants. A review and overview of randomized trials. Semin Neonatol 2001;6:63–73. [PubMed: 11162286]
25. Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2008:CD003481. [PubMed: 18254020]
26. Cassady G, Crouse DT, Kirklin JW, et al. A randomized, controlled trial of very early prophylactic ligation of the ductus arteriosus in babies who weighed 1000 g or less at birth. N Engl J Med 1989;320:1511–6. [PubMed: 2498657]
27. Clyman R, Cassady G, Kirklin JK, et al. The role of patent ductus arteriosus ligation in bronchopulmonary dysplasia: reexamining a randomized controlled trial. J Pediatr 2009;154:873–6. [PubMed: 19324366]

28. Schmidt B, Roberts RS, Davis P, et al. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med 2007;357:1893–902. [PubMed: 17989382]
29. Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. N Engl J Med 2006;354:2112–21. [PubMed: 16707748]
30. Stocker R, Glazer AN, Ames BN. Antioxidant activity of albumin-bound bilirubin. Proc Natl Acad Sci U S A 1987;84:5918–22. [PubMed: 3475708]
31. Fardy CH, Silverman M. Antioxidants in neonatal lung disease. Arch Dis Child Fetal Neonatal Ed 1995;73:F112–7. [PubMed: 7583597]
32. Schrod L, von Stockhausen HB. Serum bilirubin and development of chronic lung disease in very low birth weight infants. Eur J Pediatr 1999;158:169–70. [PubMed: 10048618]
33. Morris BH, Oh W, Tyson JE, et al. Aggressive vs. conservative phototherapy for infants with extremely low birth weight. N Engl J Med 2008;359:1885–96. [PubMed: 18971491]
34. Bancalari E. Corticosteroids and neonatal chronic lung disease. Eur J Pediatr 1998;157 (Suppl 1):S31–7. [PubMed: 9462905]
35. Halliday HL, Ehrenkranz RA, Doyle LW. Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Cochrane Database Syst Rev 2009:CD001146. [PubMed: 19160190]
36. Halliday HL, Ehrenkranz RA, Doyle LW. Late (>7 days) postnatal corticosteroids for chronic lung disease in preterm infants. Cochrane Database Syst Rev 2009:CD001145. [PubMed: 19160189]
37. Doyle LW, Halliday HL, Ehrenkranz RA, et al. Impact of postnatal systemic corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk for chronic lung disease. Pediatrics 2005;115:655–61. [PubMed: 15741368]
38. Ober C, Hoffjan S. Asthma genetics 2006: the long and winding road to gene discovery. Genes Immun 2006;7:95–100. [PubMed: 16395390]
39. Shah V, Ohlsson A, Halliday HL, Dunn MS. Early administration of inhaled corticosteroids for preventing chronic lung disease in ventilated very low birth weight preterm neonates. Cochrane Database Syst Rev 2007:CD001969. [PubMed: 17943764]
40. Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database Syst Rev 2006:CD000399. [PubMed: 17054129]
41. Abman SH, Kinsella JP, Schaffer MS, Wilkening RB. Inhaled nitric oxide in the management of a premature newborn with severe respiratory distress and pulmonary hypertension. Pediatrics 1993;92:606–9. [PubMed: 8414836]
42. Kinsella JP, Ivy DD, Abman SH. Inhaled nitric oxide improves gas exchange and lowers pulmonary vascular resistance in severe experimental hyaline membrane disease. Pediatr Res 1994;36:402–8. [PubMed: 7808839]
43. McCurnin DC, Pierce RA, Chang LY, et al. Inhaled NO improves early pulmonary function and modifies lung growth and elastin deposition in a baboon model of neonatal chronic lung disease. Am J Physiol Lung Cell Mol Physiol 2005;288:L450–9. [PubMed: 15591412]
44. Barrington KJ, Finer NN. Inhaled nitric oxide for respiratory failure in preterm infants. Cochrane Database Syst Rev 2007:CD000509. [PubMed: 17636641]
45. Schreiber MD, Gin-Mestan K, Marks JD, et al. Inhaled nitric oxide in premature infants with the respiratory distress syndrome. N Engl J Med 2003;349:2099–107. [PubMed: 14645637]
46. Kinsella JP, Cutter GR, Walsh WF, et al. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med 2006;355:354–64. [PubMed: 16870914]
47. Subhedar NV, Ryan SW, Shaw NJ. Open randomised controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants. Arch Dis Child Fetal Neonatal Ed 1997;77:F185–90. [PubMed: 9462187]
48. Ballard RA, Truog WE, Cnaan A, et al. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. N Engl J Med 2006;355:343–53. [PubMed: 16870913]
49. Davis JM, Rosenfeld WN, Sanders RJ, Gonenne A. Prophylactic effects of recombinant human superoxide dismutase in neonatal lung injury. J Appl Physiol 1993;74:2234–41. [PubMed: 8335553]

50. Rosenfeld W, Evans H, Concepcion L, et al. Prevention of bronchopulmonary dysplasia by administration of bovine superoxide dismutase in preterm infants with respiratory distress syndrome. J Pediatr 1984;105:781–5. [PubMed: 6502311]
51. Davis JM, Rosenfeld WN, Richter SE, et al. Safety and pharmacokinetics of multiple doses of recombinant human CuZn superoxide dismutase administered intratracheally to premature neonates with respiratory distress syndrome. Pediatrics 1997;100:24–30. [PubMed: 9200356]
52. Davis JM, Parad RB, Michele T, et al. Pulmonary outcome at 1 year corrected age in premature infants treated at birth with recombinant human CuZn superoxide dismutase. Pediatrics 2003;111:469–76. [PubMed: 12612223]
53. Speer CP. New insights into the pathogenesis of pulmonary inflammation in preterm infants. Biol Neonate 2001;79:205–9. [PubMed: 11275652]
54. Ahola T, Levonen AL, Fellman V, Lapatto R. Thiol metabolism in preterm infants during the first week of life. Scand J Clin Lab Invest 2004;64:649–58. [PubMed: 15513322]
55. Ahola T, Lapatto R, Raivio KO, et al. N-acetylcysteine does not prevent bronchopulmonary dysplasia in immature infants: a randomized controlled trial. J Pediatr 2003;143:713–9. [PubMed: 14657813]
56. Veness-Meehan KA. Effects of retinol deficiency and hyperoxia on collagen gene expression in rat lung. Exp Lung Res 1997;23:569–81. [PubMed: 9358237]
57. Veness-Meehan KA, Bottone FG Jr, Stiles AD. Effects of retinoic acid on airspace development and lung collagen in hyperoxia-exposed newborn rats. Pediatr Res 2000;48:434–44. [PubMed: 11004232]
58. Kennedy KA. Epidemiology of acute and chronic lung injury. Semin Perinatol 1993;17:247–52. [PubMed: 8140438]
59. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. Cochrane Database Syst Rev 2007:CD000501. [PubMed: 17943744]
60. Tyson JE, Wright LL, Oh W, et al. Vitamin A supplementation for extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. N Engl J Med 1999;340:1962–8. [PubMed: 10379020]
61. Ambalavanan N, Tyson JE, Kennedy KA, et al. Vitamin A supplementation for extremely low birth weight infants: outcome at 18 to 22 months. Pediatrics 2005;115:e249–54. [PubMed: 15713907]
62. Cotton RB, Hazinski TA, Morrow JD, et al. Cimetidine does not prevent lung injury in newborn premature infants. Pediatr Res 2006;59:795–800. [PubMed: 16641218]
63. Schelonka RL, Katz B, Waites KB, Benjamin DK Jr. Critical appraisal of the role of Ureaplasma in the development of bronchopulmonary dysplasia with metaanalytic techniques. Pediatr Infect Dis J 2005;24:1033–9. [PubMed: 16371861]
64. Mabanta CG, Pryhuber GS, Weinberg GA, Phelps DL. Erythromycin for the prevention of chronic lung disease in intubated preterm infants at risk for, or colonized or infected with Ureaplasma urealyticum. Cochrane Database Syst Rev 2003:CD003744. [PubMed: 14583992]
65. Ballard HO, Anstead MI, Shook LA. Azithromycin in the extremely low birth weight infant for the prevention of bronchopulmonary dysplasia: a pilot study. Respir Res 2007;8:41. [PubMed: 17550598]
66. Jobe AH, Ikegami M. Mechanisms initiating lung injury in the preterm. Early Hum Dev 1998;53:81–94. [PubMed: 10193929]
67. Kraybill EN, Runyan DK, Bose CL, Khan JH. Risk factors for chronic lung disease in infants with birth weights of 751 to 1000 grams. J Pediatr 1989;115:115–20. [PubMed: 2500509]
68. Garland JS, Buck RK, Allred EN, Leviton A. Hypocarbia before surfactant therapy appears to increase bronchopulmonary dysplasia risk in infants with respiratory distress syndrome. Arch Pediatr Adolesc Med 1995;149:617–22. [PubMed: 7767415]
69. Mariani G, Cifuentes J, Carlo WA. Randomized trial of permissive hypercapnia in preterm infants. Pediatrics 1999;104:1082–8. [PubMed: 10545551]
70. Carlo WA, Stark AR, Wright LL, et al. Minimal ventilation to prevent bronchopulmonary dysplasia in extremely-low-birth-weight infants. J Pediatr 2002;141:370–4. [PubMed: 12219057]

71. Thome U, Kossel H, Lipowsky G, et al. Randomized comparison of high-frequency ventilation with high-rate intermittent positive pressure ventilation in preterm infants with respiratory failure. J Pediatr 1999;135:39–46. [PubMed: 10393602]
72. Clark RH, Gerstmann DR, Null DM Jr, deLemos RA. Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory distress syndrome. Pediatrics 1992;89:5–12. [PubMed: 1728021]
73. Ogawa Y, Miyasaka K, Kawano T, et al. A multicenter randomized trial of high frequency oscillatory ventilation as compared with conventional mechanical ventilation in preterm infants with respiratory failure. Early Hum Dev 1993;32:1–10. [PubMed: 8462430]
74. Frantz ID 3rd, Close RH. Alveolar pressure swings during high frequency ventilation in rabbits. Pediatr Res 1985;19:162–6. [PubMed: 3982871]
75. The HIFI Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. N Engl J Med 1989;320:88–93. [PubMed: 2643039]
76. Henderson-Smart DJ, Cools F, Bhuta T, Offringa M. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. Cochrane Database Syst Rev 2007:CD000104. [PubMed: 17636590]
77. Courtney SE, Durand DJ, Asselin JM, et al. High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. N Engl J Med 2002;347:643–52. [PubMed: 12200551]
78. Johnson AH, Peacock JL, Greenough A, et al. High-frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity. N Engl J Med 2002;347:633–42. [PubMed: 12200550]
79. Keszler M, Modanlou HD, Brudno DS, et al. Multicenter controlled clinical trial of high-frequency jet ventilation in preterm infants with uncomplicated respiratory distress syndrome. Pediatrics 1997;100:593–9. [PubMed: 9310511]
80. Wiswell TE, Graziani LJ, Kornhauser MS, et al. High-frequency jet ventilation in the early management of respiratory distress syndrome is associated with a greater risk for adverse outcomes. Pediatrics 1996;98:1035–43. [PubMed: 8951251]
81. Craft AP, Bhandari V, Finer NN. The sy-fi study: a randomized prospective trial of synchronized intermittent mandatory ventilation versus a high-frequency flow interrupter in infants less than 1000 g. J Perinatol 2003;23:14–9. [PubMed: 12556921]
82. Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 2008;358:700–8. [PubMed: 18272893]
83. Davis PG, Henderson-Smart DJ. Nasal continuous positive airways pressure immediately after extubation for preventing morbidity in preterm infants. Cochrane Database Syst Rev 2003:CD000143. [PubMed: 12804388]
84. Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotrauma and oxygen toxicity explain interhospital variation in rates of chronic lung disease? The Neonatology Committee for the Developmental Network. Pediatrics 2000;105:1194–201. [PubMed: 10835057]
85. Finer NN, Carlo WA, Duara S, et al. Delivery room continuous positive airway pressure/positive end-expiratory pressure in extremely low birth weight infants: a feasibility trial. Pediatrics 2004;114:651–7. [PubMed: 15342835]
86. Clinicaltrials.gov, 2009.
87. Frank L, Sosenko IR. Undernutrition as a major contributing factor in the pathogenesis of bronchopulmonary dysplasia. Am Rev Respir Dis 1988;138:725–9. [PubMed: 3059876]
88. Wilson DC, McClure G, Halliday HL, et al. Nutrition and bronchopulmonary dysplasia. Arch Dis Child 1991;66:37–8. [PubMed: 1996890]
89. Wilson DC, Cairns P, Halliday HL, et al. Randomised controlled trial of an aggressive nutritional regimen in sick very low birthweight infants. Arch Dis Child Fetal Neonatal Ed 1997;77:F4–11. [PubMed: 9279175]
90. Sosenko IR, Innis SM, Frank L. Polyunsaturated fatty acids and protection of newborn rats from oxygen toxicity. J Pediatr 1988;112:630–7. [PubMed: 3351690]

91. Sosenko IR, Rodriguez-Pierce M, Bancalari E. Effect of early initiation of intravenous lipid administration on the incidence and severity of chronic lung disease in premature infants. J Pediatr 1993;123:975–82. [PubMed: 8229533]
92. Friis-Hansen B. Body water compartments in children: changes during growth and related changes in body composition. Pediatrics 1961;28:169–81. [PubMed: 13702099]
93. Oh W, Poindexter BB, Perritt R, et al. Association between fluid intake and weight loss during the first ten days of life and risk of bronchopulmonary dysplasia in extremely low birth weight infants. J Pediatr 2005;147:786–90. [PubMed: 16356432]
94. Bell EF, Acarregui MJ. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2008:CD000503. [PubMed: 18253981]
95. Hartnoll G, Betremieux P, Modi N. Randomised controlled trial of postnatal sodium supplementation on oxygen dependency and body weight in 25–30 week gestational age infants. Arch Dis Child Fetal Neonatal Ed 2000;82:F19–23. [PubMed: 10634836]
96. Brion LP, Primhak RA, Ambrosio-Perez I. Diuretics acting on the distal renal tubule for preterm infants with (or developing) chronic lung disease. Cochrane Database Syst Rev 2002:CD001817. [PubMed: 11869608]
97. Brion LP, Primhak RA. Intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease. Cochrane Database Syst Rev 2002:CD001453. [PubMed: 11869600]
98. Segar JL, Chemtob S, Bell EF. Changes in body water compartments with diuretic therapy in infants with chronic lung disease. Early Hum Dev 1997;48:99–107. [PubMed: 9131311]
99. Hoffman DJ, Gerdes JS, Abbasi S. Pulmonary function and electrolyte balance following spironolactone treatment in preterm infants with chronic lung disease: a double-blind, placebo-controlled, randomized trial. J Perinatol 2000;20:41–5. [PubMed: 10693099]
100. Kaempf JW, Campbell B, Sklar RS, et al. Implementing potentially better practices to improve neonatal outcomes after reducing postnatal dexamethasone use in infants born between 501 and 1250 grams. Pediatrics 2003;111:e534–41. [PubMed: 12671173]
101. Birenbaum HJ, Dentry A, Cirelli J, et al. Reduction in the incidence of chronic lung disease in very low birth weight infants: results of a quality improvement process in a tertiary level neonatal intensive care unit. Pediatrics 2009;123:44–50. [PubMed: 19117859]
102. Payne NR, LaCorte M, Karna P, et al. Reduction of bronchopulmonary dysplasia after participation in the Breathsavers Group of the Vermont Oxford Network Neonatal Intensive Care Quality Improvement Collaborative. Pediatrics 2006;118 (Suppl 2):S73–7. [PubMed: 17079626]
103. Walsh M, Laptook A, Kazzi SN, et al. A cluster-randomized trial of benchmarking and multimodal quality improvement to improve rates of survival free of bronchopulmonary dysplasia for infants with birth weights of less than 1250 grams. Pediatrics 2007;119:876–90. [PubMed: 17473087]
104. Laughon MM, Langer J, Wilson-Costello D, et al. Predictive models for bronchopulmonary dysplasia by postnatal day in premature infants. ePAS 2009:3450.7.