REVIEW ARTICLE

Changes in the Pathogenesis and Prevention of Chronic Lung Disease of Prematurity

Eduardo Bancalari, M.D.[1]

ABSTRACT

With the increasing survival of extremely premature infants there is a large number of them who are developing chronic lung disease (CLD), but the severity of the lung damage is considerably less than that observed in the classic form of bronchopulmonary dysplasia (BPD). Because many of these infants have only a mild initial respiratory distress and therefore do not receive aggressive ventilation, it is clear that factors other than oxygen toxicity and barotrauma are involved in the pathogenesis of this new milder type of CLD. CLD results from the interaction of multiple factors that can injure the immature lung. For this reason the prevention must be based on the elimination of all the factors implicated in its pathogenesis. Clinical and epidemiological data strongly suggest that infections, either prenatal or nosocomial, and the presence of a patent ductus arteriosus (PDA) play a major role in the development of CLD in these infants. For this reason, efforts to prevent CLD in extremely low birth weight infants should include an aggressive approach to the prevention and treatment of prenatal and neonatal infections and an early closure of the PDA.

KEYWORDS: Prematurity, chronic lung disease, bronchopulmonary dysplasia, lung injury, mechanical ventilation, patent ductus arteriosus, inflammation

Chronic Lung Disease (CLD) persists as one of the major complications in premature infants who require prolonged mechanical ventilation. Moreover, the increasing survival of very immature infants in recent years has produced an increase in the number of infants at risk for developing this complication.[1] The classic form of bronchopulmonary dysplasia (BPD) was described

American Journal of Perinatology, Volume 18, Number 1, 2001. Reprint requests: Dr. Bancalari, Department of Pediatrics, Division of Neonatology, University of Miami School of Medicine, P.O. Box 016960 (R-131), Miami, FL 33101. [1]Department of Pediatrics, Division of Neonatology, University of Miami School of Medicine, Miami, Florida. 0735-1631,p;2001,18,01,001,010,ftx,en;ajp35830x.

originally by Northway and colleagues in 1967[2] and was more common prior to the introduction of antenatal steroids and postnatal surfactant therapy. This form is usually seen after severe respiratory failure due to pneumonia or respiratory distress syndrome (RDS). These infants require mechanical ventilation with high airway pressure and inspired oxygen concentration during the first days of life, and frequently their course is complicated by pulmonary interstitial emphysema. This complication further compromises gas exchange requiring increases in ventilatory support and inspired oxygen concentration, which further aggravate the lung damage.[3,4] Other complications, such as persistent patent ductus arteriosus (PDA) with associated left ventricular failure and pulmonary edema, as well as nosocomial infections frequently develop in these patients and contribute to the progression in severity of their lung damage.[5]

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

Once severe lung damage has developed, these infants require mechanical ventilation and increased inspired oxygen concentration for several weeks, months, or sometimes years. Infants with more severe lung damage may die of progressive respiratory failure. Mortality rates of approximately 30 to 40% have been reported in infants with severe CLD, and most of them occur during the first year of life secondary to respiratory failure, intercurrent infections, or intractable cor pulmonale.[6]

Follow-up studies in infants with severe CLD have shown that pulmonary function may remain abnormal for many years, even though the infants may be asymptomatic.[7] A high incidence of obstructive airway disease has been observed at 8 years of age in a small group of survivors with BPD. Northway and associates[8] have reevaluated pulmonary function in their original cohort of infants with severe BPD reported in 1967. At an age ranging between 14 and 23 years, these adolescents and young adults still exhibited evidence of pulmonary dysfunction characterized by airway obstruction, airway hyper reactivity, and hyperinflation.

Infants with severe CLD also have more neurodevelopmental sequelae when compared with control groups, and they exhibit impaired growth curves.[9,10] Although data from long-term studies is scant, it is apparent that neurodevelopmental prognosis not only depends on the severity of the CLD, but on the presence of other risk factors for developmental delay that occur frequently in infants with CLD, such as intracranial hemorrhage, hearing impairment, and retinopathy of prematurity. Infants with severe CLD have also been reported to have an increased risk for sudden infant death, but the evidence for this is not conclusive.[11–13]

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

CLINICAL PRESENTATION OF THE NEW CLD

The majority of small premature infants who develop CLD at present have a mild initial respiratory course and require prolonged ventilatory support for management of apnea and poor respiratory effort.[14] These infants represent more than two third of all patients diagnosed with CLD in our institution. In contrast to infants with severe CLD, initially these infants require mechanical ventilation with low pressures and oxygen concentration, and therefore their exposure to the effects of barotrauma and oxygen toxicity is minimal. These in-

fants require low or moderate initial concentration of oxygen for treatment of mild RDS that usually responds favorably to exogenous surfactant. This is often followed by a few days with minimal or no supplemental oxygen need ("honeymoon"). Many of them, however, have a progressive deterioration in their lung function over time, and their ventilatory and oxygen requirements increase, accompanied by signs of respiratory failure (tachypnea, retractions, etc.). This deterioration is frequently associated with bacterial or viral infections or heart failure secondary to a PDA. In these patients, the functional and roentgenographic lung changes are usually mild, sometimes showing only diffuse haziness that persists over time, without the coarse changes of nonuniform inflation and cystic nature that is observed in the classic severe form of CLD.

PATHOGENESIS OF THE NEW CLD

The major factors implicated in the pathogenesis of the classic severe form of BPD are thought to be barotrauma and oxygen toxicity. As mentioned before, most infants who develop this form of lung damage have severe initial respiratory failure and therefore are exposed to high positive airway pressures and inspired oxygen concentrations. Today, with the increased use of antenatal steroids and the administration of exogenous surfactant, the initial respiratory course is usually mild and, therefore, infants are exposed to much lower airway pressures and oxygen concentrations. Still, many of them gradually develop increasing oxygen requirements and show radiographic changes compatible with CLD that persist for weeks or months. Although it is possible that these low levels of airway pressure and oxygen exposure may be sufficient to damage the immature lung, it is likely that other factors play a more important role in the development of the lung damage observed in these infants.[15]

Increasing evidence has accumulated recently suggesting that inflammation plays a major role in the pathogenesis of CLD.[16] This inflammatory response can be triggered by a number of factors including ventilation with excessive tidal volumes, free oxygen radicals, increased pulmonary blood flow due to a PDA, and a variety of perinatal infections.[17] The role of prenatal infections has been suggested by publications showing an increased risk for CLD in infants born to mothers with evidence of chorioamnionitis.[18,19] Several inflammatory cytokines were found in higher concentrations in fetal cord blood and in the amniotic fluid of mothers who delivered infants who developed CLD in comparison with those who gave birth to infants who recovered without CLD.[20,21] In addition, several publications have suggested a higher risk of CLD in infants whose airways are colonized with ureaplasma urealyticum at birth, but these data are confounded by higher colonization rates at lower gestational ages.[22–24]

A significant increase in inflammatory cells, eicosanoids, and various cytokines has been reported in the airways of infants who subsequently develop CLD.[25,26] This increase in cytokines concentration has been demonstrated from the first days after birth supporting the contention that at least in some infants the inflammatory process starts before birth and is secondary to an infection of the amniotic cavity and the fetal lung. Among the markers of inflammation that have been found in high concentrations in tracheobronchial secretions of infants who develop CLD are neutrophils, macrophages, leukotrienes, platelet-activating factor (PAF), IL6, IL8, and tumor necrosis factor (TNF).

Evidence of pulmonary alveolar macrophage (PAM) activation has been reported in infants who subsequently developed CLD. These activated PAM'S have been suggested as source of neutrophil chemoattractants, especially when exposed to hyperoxia.[27,28] Neonates who develop CLD also have elevated concentration of fibronectin in lung lavage fluid.[29] This large molecular weight protein is released from PAM, epithelial and endothelial cells, and fibroblasts and is associated with the development of pulmonary fibrosis.

An increase in elastase and an imbalance between elastase and α proteinase inhibitor (PI) in the lung has also been mentioned as an important mechanism for the development of neonatal lung injury.[30–32] Urine excretion of elastic degradation products is greater in neonates who develop CLD than in controls.[33] This is of particular relevance in light of recent evidence of a marked reduction in alveolar septation in lungs of infants who died with severe CLD.

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

Searching for an explanation for the interaction between neonatal infection and PDA, we observed that the presence of a systemic infection in the premature infant adversely affects permanent closure of the ductus, often inducing ductal opening after the first week of life and failure to respond to medical treatment with indomethacin.[34] A likely explanation for this interaction is the elevated serum levels of prostaglandins and tumor necrosis factor (TNF) observed in infants with infections. In addition, infants with serious infections frequently have complications that prevent or delay the medical or surgical treatment of the PDA. As a result, the ductus remains open for prolonged periods of time, maintaining an increased pulmonary blood flow, high capillary pressure, and increased lung fluid.

PREVENTION OF THE NEW CLD

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

Acceleration of Lung Maturation

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

Perinatal Infections

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

Exogenous Surfactant

The introduction of surfactant replacement in infants with HMD has also improved substantially the respiratory course in these infants.[37] Because of this, it is seldom necessary to use high airway pres-

sures and oxygen concentrations during mechanical ventilation. As a result of this, the incidence of lung damage due to barotrauma is infrequent today. Simultaneously, the use of surfactant has improved the survival of extremely low-birth-weight (ELBW) infants and this has increased the number of infants who are at risk for developing CLD masking the beneficial effect on the overall incidence of CLD.

Gentle Ventilation

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

PDA Closure

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

Fluid Intake

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

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

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

Nutrition

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

Vitamin A plays an important role in the preservation of airway epithelium and alveolar septation. Small preterm infants are frequently vitamin A deficient and the supplementation of sufficient Vitamin A is difficult to achieve because of

the inactivation induced by light and the adhesion to the plastic of the infusion lines.[58–60]

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

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

Corticosteroids

Because of the strong evidence that inflammation plays an important role in the pathogenesis of CLD, there is great interest in the use of exogenous corticosteroids during the early states of the disease to reduce its progression.[63–65] Many reports have shown a rapid improvement in lung function after the administration of steroids, facilitating weaning from oxygen and the ventilator when compared with control infants who received placebo.[66] The optimal age of treatment, dose schedule, and duration of therapy have not been established and long-term outcome has not always improved in treated infants.[67] The possible mechanisms that explain the beneficial effect of steroids in CLD are numerous. Steroids can enhance production of surfactant and antioxidant enzymes, decrease bronchospasm, decrease pulmonary and bronchial edema and fibrosis, improve Vitamin A status, and decrease the response of inflammatory cells and mediators in the injured lung.[68,69] Possible complication of prolonged steroidal therapy include masking the signs of infection, arterial hypertension, hyperglycemia, increased proteolysis, adrenocortical suppression, somatic and lung growth suppression, and hypertrophic myocardiopathy.[70–74] Of greater concern is the fact that long-term follow-up studies suggest that infants who received prolonged steroid therapy have worse neurological outcome than control infants.[75–77] Because of the seriousness of some of these complications, until more information on efficacy and safety is available, the use of systemic steroids should be considered experimental and be limited to those infants who show clear evidence of progressive pulmonary damage and remain oxygen and ventilator dependent. The dose and duration of therapy should be limited to the minimum necessary to achieve the desired effects.[78]

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

REFERENCES

1. Avery ME, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics 1987;79:26
2. Northway WH Jr, et al. Pulmonary disease following respirator therapy of hyaline membrane disease: bronchopulmonary dysplasia. N Engl J Med 1967;276:357
3. Bancalari E, et al. Bronchopulmonary dysplasia. Pediatr Clin North Am 1986;33:1
4. Bancalari E, et al. Bronchopulmonary dysplasia: clinical presentationl J Pediatr 1979;95:819
5. Melnick G, et al. Normal pulmonary vascular resistance and left ventricular hypertrophy in young infants with bronchopulmonary dysplasia: an echocardiographic and pathologic study. Pediatrics 1980;66:589
6. Groothius JR, et al. Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. Pediatrics 1988;82:199
7. Blayney M, et al. Bronchopulmonary dysplasia: improvement in lung function between 7 and 10 years of age. J Pediatr 1991;118:201
8. Northway WH, et al. Late pulmonary sequelae of bronchopulmonary dysplasia. N Engl J Med 1990;323:1793
9. Bregman J, Farrell EE. Neurodevelopmental outcome in infants with bronchopulmonary dysplasia. Clin Perinatol 1992;19:673–694

10. Markestad T, et al. Growth and development in children recovering from bronchopulmonary dysplasia. Pediatrics 1986;77:345
11. Abman SH, et al. Late sudden unexpected deaths in hospitalized infants with bronchopulmonary dysplasia. Am J Dis Child 1989;143:815
12. Gray PH, et al. Are infants with bronchopulmonary dysplasia at risk for sudden infant death syndrome? Pediatrics 1994;93:774
13. Werthammer J, et al. Sudden infant death syndrome in infants with bronchopulmonary dysplasia. Pediatric 1982;69: 301
14. Rojas MA, Gonzalez A, Bancalari E, et al. Changing trends in the epidemiology and pathogenesis of neonatal chronic lung disease. J Pediatr 1995;126:605–601
15. Marshall DD, Kotelchuck M, Young TE, Bose CL, Kruyer L, O'Shea M, and the North Carolina Neonatologist Association. Risk factors for chronic lung disease in the surfactant era: a North Carolina population-based study of very low birth weight infants. Pediatrics 1999;104:1345–1350
16. Pierce MR, Bancalari E. The role of inflammation in the pathogenesis of bronchopulmonary dysplasia. Pediatr Pulmonol 1995;19:371–378
17. Couroucli XI, Welty SE, Ramsay PL, et al. Detection of microorganisms in tracheal aspirates of preterm infants by polymerase chain reaction: association of adenovirus infection with bronchopulmonary dysplasia. Pediatr Res 2000; 47:225–232
18. Matsuda T, Nakajima T, Hattori S, et al. Necrotizing funisitis: clinical significance and association with chronic lung disease in premature infants. Am J Obstet Gynecol 1997;177:1402–1407
19. Watterberg KL, Demers LM, Scott SM, Murphy S. Chorioamniotis and early lung inflammation in infants in whom bronchopulmonary dysplasia develops. Pediatrics 1996;97:210–215
20. Yoon BH, Romero R, Jun JK, et al. Amniotic fluid cytokines (interleukin-6, tumor necrosis factor-á, interleukin-1â, and interleukin-8) and the risk for the development of bronchopulmonary dysplasia. Am J Obstet Gynecol 1997; 177:825–830
21. Yoon BH, Romero R, Kim KS, et al. A systemic fetal inflammatory response and the development of bronchopulmonary dysplasia. Am J Obstet Gynecol 1999;181: 773–779
22. Cassell GH, Crouse DT, Cannup KC, Waites KB, Rudd PT, Stagno S. Association of Ureaplasma urealyticum infection of the lower respiratory tract with chronic lung disease and death in very low birth weight infants. Lancet 1988;2:240–244
23. Sanchez PJ, Regan JA. Ureaplasma urealyticum colonization and chronic lung disease in low birth weight infants. Pediatr Infect Dis J 1988;7:542–546
24. Wang EL, Ohlsson A, and Kellner JD. Association of ureaplasma urealyticum colonization with chronic lung disease of prematurity: results of meta-analysis. J Pediatr 1995;127:640–644
25. Groneck P, Gotze-Speer B, Oppermann M, et al. Association of pulmonary inflammation and increased microvascular permeability during the development of bronchopulmonary dysplasia: a sequential analysis of inflammatory mediators in respiratory fluids of high-risk preterm neonates. Pediatrics 1994;93:712–781
26. Mirro R, Armstead W, Leffler C. Increased airway leukotriene levels in infants with severe bronchopulmonary dysplasia. Am J Dis Child 1990;144:160–161
27. Brus F, Oeveren W, Okken A, et al. Activation of circulating polymorphonuclear leukocytes in preterm infants with severe idiopathic respiratory distress syndrome. Pediatr Res 1996;456–463
28. Carlton DP, Albertine KH, Cho SC, et al. Role of neutrophils in lung vascular injury and edema after premature birth in lambs. J Appl Physiol 1997;83:1307–1317
29. Gerdes JS, Yoder MC, Douglas SD, Paul M, Harris MC, Polin RA. Tracheal lavage and plasma fibronectin: relationship to respiratory distress syndrome and development of bronchopulmonary dysplasia. J Pediatr 1986;108:601–606
30. Ogden BE, Murphy SA, Saunders GC, Pathak D, Johnson JD. Neonatal lung neutrophils and elastase/proteinase inhibitor imbalance. Am Rev Respir Dis 1984;130:817–821
31. Walti H, Tordet C, Gerbaut L, et al. Persistent elastase/proteinase inhibitor imbalance during prolonged ventilation of infants with BPD: evidence for the role of nosocomial infections. Pediatr Res 1989;26:351–355
32. Watterberg KL, Carmichael DF, Gerdes JS, et al. Secretory leukocyte protease inhibitor and lung inflammation in developing bronchopulmonary dysplasia. J Pediatr 1994;125: 264–269
33. Bruce MC, Wedig KE, Jentoft N, et al. Altered urinary excretion of elastin cross-links in premature infants who develop bronchopulmonary dysplasia. Am Rev Resp Dis 1985;131:568–572
34. Gonzalez A, Sosenko IRS, Chandar J, et al. Influence of infection on patent ductus arteriosus and chronic lung disease in premature infants weighting 1000 grams or less. J Pediatr 1996;128:470–478
35. Varsila E, Hallman M, Venge P, et al. Closure of patent ductus arteriosus decreases pulmonary Myeloperoxidase in premature infants with respiratory distress syndrome. Biol Neonate 1995;67:167–171
36. Van Marter LJ, et al. Maternal glucocorticoid therapy and reduced risk of bronchopulmonary dysplasia, Pediatrics 1990;86:331
37. Collaborative European Multicenter Study Group. Surfactant replacement therapy for severe neonatal respiratory distress syndrome: an international randomized clinical trial. Pediatrics 1990;82:683–690
38. Albertine KH, Jones GP, Starcher BC, et al. Chronic lung injury in preterm lambs. Disordered respiratory tract development. Am J Respir Crit Care Med 1999;159:945–958

39. Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. Am J Respir Crit Care Med 1998;157:294–323
40. Gerstmann DR, deLemos RA, Coalson JJ, Clark RH, Wiswell TE, Winter DC, Kuehl TJ, Meredith KS, Null DM Jr. Influence of ventilatory technique on pulmonary baro injury in baboons with hyaline membrane disease. Pediatr Pulmonol 1988;5:82–91
41. Bjorklund LJ, Ingimarsson J, Curstedt T, et al. Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lambs. Pediatr Res 1997;42:348–355
42. Wada K, Jobe AH, Ikegami M. Tidal volume effects on surfactant treatment responses with the initiation of ventilation in preterm lambs. J Appl Physiol 1997;83:1054–1061
43. Jackson JC, et al. Reduction in lung injury after combined surfactant and high-frequency ventilation. Am J Resp Crit Care Med 1994;150:534
44. 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
45. Thome U, Kossel H, Lopowsky 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
46. Gerhardt T, Bancalari E. Lung compliance in newborns with patent ductus arteriosus before and after surgical ligation. Biol Neonate 1980;38:96–105
47. Cotton RB, Stahlman MT, Bender HW, Graham TP, Catterton WZ, Kovar I. Randomized trial of early closure of symptomatic patent ductus arteriosus in small preterm infants. J Pediatr 1978;93:647–651
48. Brown ER, et al. Bronchopulmonary dysplasia possible relationship to pulmonary edema, J Pediatr 1978;92:982
49. Bell EF, et al. Effect of fluid administration on the development of symptomatic patent ductus arteriosus and congestive heart failure in premature infants. N Engl J Med 1980;392:598
50. Tammela OKT, et al. Fluid restriction for preventing bronchopulmonary dysplasia? Reduced fluid intake during the first weeks of life improves the outcome of low-birthweight infants. Acta Paediatr 1992;81:201
51. Van Marter LJ, et al. Hydration during the first days of life and the risk of bronchopulmonary dysplasia in low birth weight infants, J Pediatr 1990;116:942
52. Albersheim SG, et al. Randomized, double-blind, controlled trial of long-term diuretic therapy for bronchopulmonary dysplasia. J Pediatr 1989;115:615
53. Engelhardt B, et al. Short- and long-term effects of furosemide on lung function in infants with bronchopulmonary dysplasia. J Pediatr 1986;109:1034
54. Kao LC, et al. Furosemide acutely decreases airways resistance in chronic bronchopulmonary dysplasia, J Pediatr 1983;103:624
55. Kao LC, et al. Randomized trial of long-term diuretic therapy for infants with oxygen- dependent bronchopulmonary dysplasia. J Pediatr 1994;124:772
56. Berner ME, et al. Furosemide reduces lung fluid filtration in lambs with lung microvascular injury from air embolic. J Appl Physiol 1989;67:1990
57. Frank L, Groseclose EE. Oxygen toxicity in newborns: the adverse effects of under nutrition. J Appl Physiol 1982;53: 1248–1255
58. Hustead VA, Gutcher GR, Anderson SA, Zachman RD. Relationship of vitamin A (retinol) status to lung disease in the preterm infant. J Pediatr 1984;105:610–615
59. Shenai JP, Chytil F, Stahlman MT. Vitamin A status of neonates with bronchopulmonary dysplasia. Pediatr Res 1985;19:185–189
60. Shenai JP, Kennedy KA, Chytil F, Stahlman MT. Clinical trial of vitamin A supplementation in infants susceptible to bronchopulmonary dysplasia. J Pediatr 1987;111:269–277
61. Shenai JP. Vitamin A supplementation in very low birth weight neonates: rational and evidence. Pediatrics 1999; 104:1369–1374
62. Tyson JE, Wright LL, Oh W, Kennedy KA, Mele L, Ehrenkranz RA, Stoll BJ, Lemons JA, Stevenson DK, Bauer CR, Korones SB, Fanaroff AA, and the National Institute of Child Health and Human Development Neonatal Research Network. Vitamin A supplementation for extremely-low-birth-weight infants. N Engl J Med 1999; 340:1962–1968
63. Bancalari E. Corticosteroids and neonatal chronic lung disease. Eur J Pediatr 1998;157:S31–S37
64. Co E, Chari G, McCulloch K, Vidyasagar D. Dexamethasone treatment suppresses collagen synthesis in infants with bronchopulmonary dysplasia. Pediatr Pulmonol 1993; 16:36–40
65. Collaborative Dexamethasone Trial Group. Dexamethasone therapy in neonatal chronic lung disease: an international placebo-controlled trial. Pediatrics 1991;88:421–427
66. Avery GB, Fletcher AB, Kaplan M, Brudno DS. Controlled trial of dexamethasone in respirator-dependent infants with bronchopulmonary dysplasia. Pediatrics 1985; 75:106–111
67. Bhuta T, Ohlsson A. Systematic review and meta-analysis of early postnatal dexamethasone for prevention of chronic lung disease. Arch Dis Child Fetal Neonatal 1998;79:F26–33
68. Georgieff MK, Mammel MC, Mills MM, Gunter EW, Johnson DE, Thompson TR. Effect of postnatal steroid administration on serum vitamin A concentrations in newborn infants with respiratory compromise. J Pediatr 1989; 114:301–304
69. Groneck P, Reuss D, Götze-Speer B, Speer CP. Effects of dexamethasone on chemotactic activity and inflammatory mediators in tracheobronchial aspirates of preterm infants at risk for chronic lung disease. J Pediatr 1993;122:938–944
70. Ellington B, McBride JT, Stokes DC. Effects of corticosteroids on postnatal lung and airway growth in the ferret. J Appl Physiol 1990;68:2029–2033

71. Papile LA, Tyson JE, Stoll BJ, et al. A multicenter trial of two dexamethasone regimens in ventilator-dependent premature infants. N Engl J Med 1998;338:1112
72. Tsai F-J, Tsai C-H, Wu S-F, Liu Y-H, Yeh T-F. Catabolic effect in premature infants with early dexamethasone treatment. Acta Paediatr 1996;85:1487–1490
73. Tschanz SA, Damke BM, Burri PH. Influence of postnatally administered glucocorticoids on rat lung growth. Biol Neonate 1995;68:229–245
74. Werner JC, et al. Hypertrophic cardiomyopathy associated with dexamethasone therapy for bronchopulmonary dysplasia. J Pediatr 1992;120:286
75. O'Shea TM, Kothadia JM, Klinepeter KL, Goldstein DJ, Jackson B, Dillard RG. Follow-up of preterm infants treated with dexamethasone for chronic lung disease. Am J Dis Child 1993;147:658–661
76. O'Shea TM, Kothadia JM, Klinepeter KL, et al. Randomized placebo-controlled trial of a 42-day tapering course of dexamethasone to reduce the duration of ventilator dependency in very low birth weight infants: outcome of study participants at 1-year adjusted age. Pediatrics 1999;104: 15–21
77. Yeh TF, Lin YJ, Huang CC, Chen YJ, Lin CH, Lin HC. Early dexamethasone therapy in preterm infants: a follow-up study. Pediatrics 1998;101:E7
78. Brozanski BS, Jones JG, Gilmour CH, et al. Effect of pulse dexamethasone therapy on the incidence and severity of chronic lung disease in the very low birth weight infant. J Pediatr 1995;126:769–776
79. Cloutier MM, McLellan N. Nebulized steroid therapy in bronchopulmonary dysplasia. Pediatr Pulmonol 1993;15: 111–116
80. LaForce WR, Brudno DS. Controlled trial of beclomethasone dipropionate by nebulization in oxygen- and ventilator-dependent infants. J Pediatr 1993;122:285–288
81. Cole CH, Colton T, Shah BL, et al. Early inhaled glucocorticoid therapy to prevent bronchopulmonary dysplasia. N Engl J Med 1999;340:1005–1010