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Pulmonary Disease (Chronic Lung Disease) in Infants; Overview of Proper Management

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Abstract: **More than 30% of preterm children born before 30 weeks' gestational age establish neonatal Chronic lung disease (CLD), also called bronchopulmonary dysplasia (BPD), a disease with significant morbidity and mortality. In this review paper the main aim was to discuss and overview the recent advances in treatment approaches for the prevention and management of chronic lung disease (CLD) in infant, by other words bronchopulmonary dysplasia (BPD), and discuss approaches with future potential. This review is based on published meta-analyses, randomized controlled trials (RCTs), systematic reviews, individual clinical studies, but only studies which were related to Chronic lung disease (CLD), and mostly the management therapy of this condition in infancy, this was done by performing an electronic search among the databases; PubMed, and Embase, through the period until December 2016, we Included all relevant articles and restricted our search to English published articles with human, and animal subjects. Numerous therapy techniques for CLD have been assessed in well-conducted medical trials and meta-analyses. Although for a few of these therapies conclusive proof of efficacy is doing not have there are numerous continuous areas of research study that show potential.**

Keywords: **Chronic lung disease (CLD), Broncho Pulmonary Dysplasia (BPD), Randomized Controlled Trials (RCTs).**

1. INTRODUCTION

Infants born too soon regularly establish respiratory failure secondary to structural and biochemical immaturity of their lungs and inadequate breathing drive [(1)]. more than 30% of preterm children born before 30 weeks' gestational age establish neonatal Chronic lung disease (CLD), also called bronchopulmonary dysplasia (BPD), a disease with significant morbidity and mortality [(1,2,3,4)]. Infants with BPD are at increased risk for long-term hospitalization, persistent breathing disorders in early infancy, and life-long effects from impaired lung and neurologic development [(5,6,7,8)]. Impacted infants might remain O2 dependent for months, and although few remain O2 reliant beyond 2 years of age [(4, 9)], respiratory signs reflecting disturbed lung development are often obvious for several years [(5, 9)].

There is now growing acknowledgment that infants with chronic lung disease after early birth have a different medical course and pathology than had actually been recorded prior to surfactants were utilized. [(10,11,12,13)]. The timeless progressive stages with popular fibroproliferation that initially characterized BPD are normally less striking now, and the disease is now primarily specified by a disruption of distal lung development, and has been termed the "new bronchopulmonary dysplasia" [(14)] (**Table 1**), [(12)] (**Figure 1**) [(15)]. Unlike the original kind of the disease, this "brand-new" type typically establishes in preterm babies who might have needed little or no ventilatory assistance, and have actually had low inspired oxygen concentrations throughout the early postnatal days [(10,11)].

BPD or prematurity changes lung aging and whether this results in early lung function decline or increases the risk for adult lung diseases such as COPD is an ongoing discussion [(8)]. Mechanical ventilation (MV) and O^2- abundant gas are life-saving treatments, these therapies likewise promote lung injury. Thus, throughout the past twenty years, advances in medical therapy have greatly enhanced the survival of early infants. Using antenatal steroids to speed up lung maturation, the development of surfactant replacement treatment for acute breathing failure, the organization of lung protective strategies of ventilation, and an optimization of dietary assistance have actually contributed to a total decline in the mortality of Very Low Birth Weight (VLBW) infants [(9,10,12)].

Table 1: Difference in pathological features of the "old" and "new" bronchopulmonary dysplasia [12]

Pre-surfactant ("old")	Post-surfactant ("new")
Alternating atelectasis with hyperinflation	Less regional heterogeneity of lung disease
Severe airway epithelial lesions (eg, hyperplasia, squamous metaplasia)	Rare airway epithelial lesions
Marked airway smooth muscle hyperplasia	Mild airway smooth muscle thickening
Extensive, diffuse fibroproliferation	Rare fibroproliferation changes
Hypertensive remodelling of pulmonary arteries	Fewer arteries but "dysmorphic"
Decreased alveolarisation and surface area	Fewer, larger and simplified alveoli

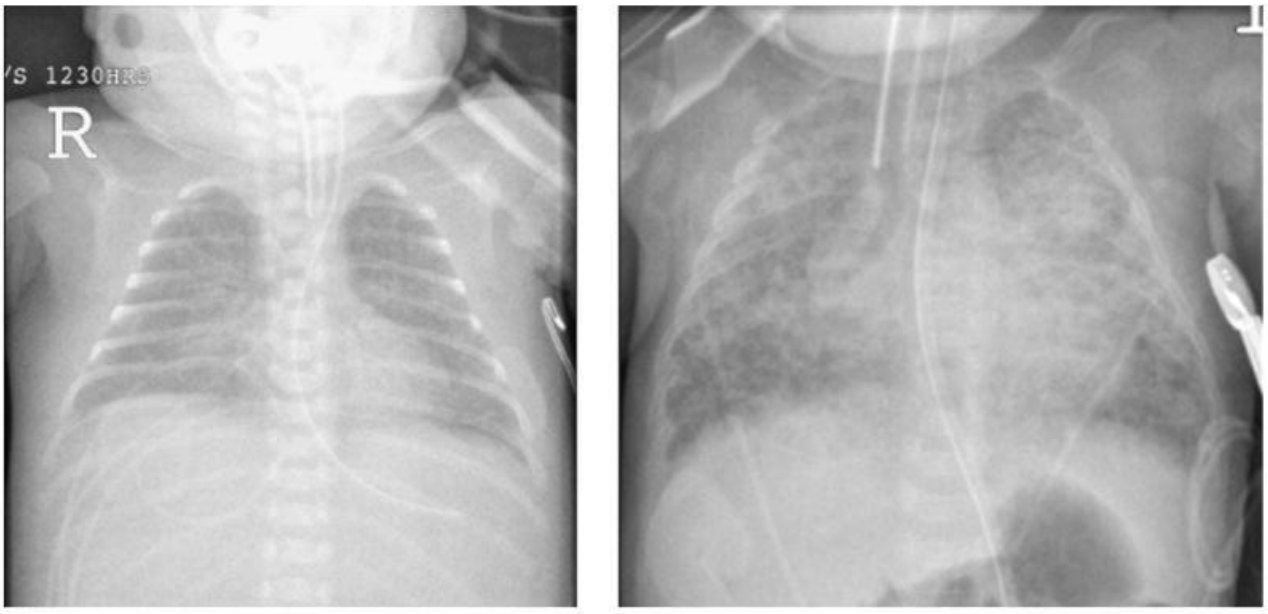

Figure1: *Left:* Chest x-ray showing early bronchopulmonary dysplasia with showing small hazy lung fields. *Right:* Chest x-ray showing established BPD with widespread interstitial shadows in both lung fields, consistent with fibrosis. The demineralization of the ribs is consistent with osteopenia of prematurity, a frequent association of bronchopulmonary dysplasia. [15]

In this review paper the main aim was to discuss and overview the recent advances in treatment approaches for the prevention and management of Chronic lung disease (CLD) in infant, by other words bronchopulmonary dysplasia (BPD), and discuss approaches with future potential.

2. METHODS

This review is based on published meta-analyses, randomized controlled trials (RCTs), systematic reviews, individual clinical studies, but only studies which were related to Chronic lung disease (CLD), and mostly the management therapy of this condition in infancy, this was done by performing an electronic search among the databases; PubMed, and Embase, through the period until December 2016, we Included all relevant articles and restricted our search to English published articles with human, and animal subjects.

3. RESULTS & DISCUSSION

Management therapy of Chronic Lung Disease in infants:

It is very important to treat correctible consider infants with CLD and pulmonary high blood pressure. Ventilation techniques to prevent ongoing lung injury, and the maintenance of arterial pH and oxygen saturations near normal [9,10], to avoid vasoconstriction from hypoxia or acidosis, are both crucial. The treatment of reflux, monitoring and early treatment of infections, immunotherapy against viral infections and management of other issues of prematurity consisting of sepsis and necrotizing enterocolitis are key [10].

Steroid therapy:

The use of antenatal steroids in mothers at high risk of providing a premature infant lowers the occurrence of neonatal death and breathing distress syndrome by 50%, however even in combination with postnatal surfactant, cannot minimize the occurrence of BPD. Exogenous surfactant therapy reduces the rate of death from BPD, however does not prevent the disease; probably, this could be due to the increased survival of extremely immature infants at high risk of BPD [(16)]. The association of barotrauma or volutrauma with BPD has caused using strategies such as permissive hypercapnia [(16)] to keep lung injury to a minimum. Recent proof recommends some advantage to volume guarantee as a ventilator mode for preventing BPD and reducing inflammation related to mechanical ventilation [(17,18)]. Even more big randomized trials will be had to validate this finding. Although no perfect ventilation mode has up until now emerged, it is clear from physiological research studies that tidal volumes and motivated oxygen concentrations ought to be kept as low as possible to avoid oxygen, hypocarbia, and volutrauma toxicity, and lung recruitment methods should be used.

An alternative approach to reduce BPD has been to avoid intubation and mechanical ventilation using early nasal continuous favorable pressure (CPAP). A study comparing the results of premature infants weighing 500-1500 g at birth who were dealt with in either Boston or New York, USA, reported that the occurrence of BPD was much greater in Boston (22%) than in New York (4%), and the increased risk of the disease was connected with early endotracheal intubation and mechanical ventilation [(19)]. Lots of centers now decrease their use of mechanical ventilation, preferring nasal constant positive pressure with or without exogenous surfactant, and report low occurrences of BPD in high-risk infants. Big regulated medical trials, nevertheless, have not yet had the ability to replicate the single center experience. The COIN trial randomized 610 infants who were born at 25-to-28-weeks' gestation to CPAP or intubation and ventilation at 5 minutes after birth and discovered early nasal CPAP did not substantially decrease the rate of death or bronchopulmonary dysplasia, as compared with intubation [(20)]. This study again showed the effectiveness of surfactant in decreasing airleak, as CPAP was connected with substantially increased risk of pneumothorax. Another current study randomized 1316 infants to intubation and surfactant treatment (within 1 hour after birth) or to CPAP treatment started in the delivery room, with subsequent use of a protocol-driven minimal ventilation technique and also found no difference in the main result of death or bronchopulmonary dysplasia as defined by the requirement for supplemental oxygen at 36 weeks [(21)]. Based upon these findings warn need to be taken in picking a population that might gain from this method and adverse events, such as hemodynamic instability and necrotizing enterocolitis, ought to be thoroughly kept an eye on.

A meta-analysis of 7 randomized trials reveals that systemic supplements with vitamin A in enough quantities to develop regular serum retinol concentrations decreases oxygen reliance at 36 weeks' post-menstrual age [(22)], but does not change long term outcomes. Vitamin A levels, however, should be carefully monitored and while advantageous in the short-term, the lack of tested beneficial long-term results on pulmonary and neurological result has restricted use of this treatment.

Inhaled steroids have also been examined in an effort to optimize the benefits of corticosteroids and lessen unacceptable systemic negative effects. The trials did not demonstrate considerable modification on the BPD rate at 28 days or 36 weeks' postmenstrual age (PMA) regardless of whether the treatment was provided early (<7 days) or late (>7 days). In addition, breathed in steroids have actually been found to offer no advantage over systemic steroid therapy [(23,24)] Major interest in inhaled corticosteroids consisted of the kind of steroids, dose, the potential for systemic absorption, and unpredictability regarding drug shipment. a multicenter randomized controlled clinical trial is underway in Europe (NEuroSIS) aimed to examine whether early administration of inhaled budesonide in preterm infants minimizes the occurrence of BPD. The research study consists of short-term and long term outcomes [(25)] There is also a stage 2 clinical trial underway examining inhaled beclomethasone in infants with the medical diagnosis of BPD to assess effect on exacerbations [(26)] Inhaled corticosteroids continue to provide promise in the avoidance and management of BPD, and bigger randomized, placebo-controlled trials are needed to establish their effectiveness and security.

Systemic corticosteroids for CLD:

The Cochrane meta-analysis review [(27)] of twenty-eight clinical trials of early systemic steroids exposed that they assisted in extubating and decreased the occurrence of BPD. Adverse effects such as hyperglycemia, intestinal perforation, high blood pressure, infection, steroid-induced cardiomyopathy and long-term neurodevelopmental results including cerebral palsy complicated the treatment [(27)]. Another Cochrane meta-analysis evaluated the use of steroids at > 7 days in nineteen RCTs. They likewise noted that steroid treatment was related to reductions in extubation faliure as well as BPD. The patterns to a boost in cerebral palsy or unusual neurological assessment in the steroid groups were partially balanced out by a trend towards reduced death. The combined rate of death or cerebral palsy was not considerably various in between

steroid and control groups [28]. Both the late and early steroid trials generally utilized dexamethasone at high doses (> 0.5-1 mg/kg/day). Given the offered proof, the European Association of Perinatal Medicine, the American Academy of Pediatrics and the Canadian Pediatric Society have actually advised against the early use of dexamethasone in the very first week of life and have actually concluded that there is insufficient evidence to recommend regular use of systemic dexamethasone after seven days of life [29]. Later use of dexamethasone is currently undertaken with caution and reserved for patients with BPD in whom weaning from high ventilator settings and oxygen assistance is not successful or their respiratory status is rapidly deteriorating.

Current studies [22-33] have tried to assess the function of steroids aside from dexamethasone. Hydrocortisone prophylaxis for early adrenal insufficiency to prevent BPD was analyzed [30] in a study of preterm infants weighing <1 kg and being mechanically aerated. The infants were randomized to get placebo or hydrocortisone, 1 mg/kg/day for 12 days then 0.5 mg/kg/day for 3 days. No significant differences in survival rates in between the two groups were found, however, amongst infants exposed to chorioamnionitis, the ones treated with hydrocortisone had considerably lower mortality and improved survival without BPD [31,32].

Corticosteroid treatment, although directed at decreasing the lung inflammation seen in infants with evolving or developed BPD, is maybe the most controversial location of care. Clinical research studies have actually consistently revealed that steroids acutely enhance lung mechanics and gas exchange, and lower inflammatory cells and their items in tracheal samples of patients with BPD [33,34]. A meta-analysis of randomized trials shows that corticosteroids reduce chronic oxygen dependence at 28 days, and 36 weeks' post-menstrual age, if offered systemically in the very first 96 h, [35] however there are important concerns regarding increased mortality and negative effects on head development, neurodevelopmental outcomes, and lung structure [35]. The routine early use of high-dose steroids in premature newborns is highly discouraged, as reflected in editorials from the American Academy of Pediatrics and others [36,37]. The negative findings, however, are normally based on information from research studies that have used high dosages of dexamethasone began in the very first few days of life and administered for extended periods. Numerous concerns continue regarding the risk-benefit relation in the use of other steroids for shorter study periods. As a result, some centers recommend use of steroids outside the very first week of life at lower dosages and for shorter durations (5-7 days) in ventilator-dependent infants with serious, consistent lung disease. Due to the observed negative effects of dexamethasone, postnatal steroid administration utilizing hydrocortisone has actually been studied for the avoidance of BPD. While no research study has actually shown clear advantage with hydrocortisone administration, the direction of effect favors hydrocortisone in all studies and in the biggest research study to date, for infants exposed prenatally to chorioamnionitis, hydrocortisone substantially reduced mortality and increased survival without BPD [38]. No unfavorable brief or long term impacts have actually been demonstrated with hydrocortisone usage in any research studies. For infants with recognized BPD and ventilator reliant chronic lung disease, hydrocortisone administered at a dosage of 5 mg/kg per day, tapered over 3 weeks was as efficient as dexamathasone for weaning infants from the ventilator and decreasing additional oxygen therapy, with fewer short and no long term negative effects [39]. The possible beneficial impacts of hydrocortisone therapy need to be weighed versus the increased incidence of gastrointestinal perforation, especially with concomitant use of indomethacin [38]. To prevent the negative impacts connected with systemic administration, steroids have also been given by inhalation, but no crucial benefits have been noted with this method. The significant impact of breathed in betamethasone in a multicentre randomised trial was to decrease the perceived need for using systemic steroids [40,41,42]. A more recent analysis demonstrated an increased rate of effective extubation with 1-4 weeks of breathed in steroid use, without a decrease in the occurrence of BPD [43].

Bronchodilators for the prevention and treatment of chronic lung disease:

Bronchodilators may be suggested in BPD due to increased respiratory tract resistance, smooth muscle hypertrophy and hyperreactivity. The two most extensively used bronchodilators are salbutamol and ipratoprium. Short-term research studies demonstrated increased respiratory compliance and reduced resistance after bronchodilator treatment in infants with recognized and evolving BPD [44]. These medications target essential elements of the disease procedure, studies have shown that actions are frequently transient and variable. In conclusion, based on current proof, routine use of bronchodilators for prevention of BPD cannot be advised. Lung vasodilators Pulmonary high blood pressure is increasingly recognized as a problem of early birth and BPD. BPD-associated lung high blood pressure is approximated to happen in 30-45% of infants with moderate to severe BPD and can add to the severity and determination of BPD symptoms and impose additional morbidity and mortality [45]. Animal studies have actually shown that breathed in nitric oxide (iNO) lowers lung inflammation, enhances surfactant function and promotes lung and alveolar growth, suggesting

that iNO may be beneficial to treat or avoid BPD [46]. The role of nitric oxide (NO) in preterm infants regarding survival and rate of BPD is controversial. Early use of low-dose iNO in extremely early infants did not enhance survival without BPD or brain injury, and is thus unsuccessful [47]. Early rescue treatment (< 3 days) with iNO, based on oxygenation criteria, did not seem to impact death or BPD rates. Later treatment (> 3 days) based on the risk of BPD showed no effect on the combined result of death or BPD. Early regular use for intubated, slightly ill preterm infants showed only a little decrease in the incidence of the combined result of death or BPD [48].

The research study [49] included in this review showed no evidence that salbutamol lowered mortality or CLD at 28 days in preterm infants at risk of establishing CLD. This research study did not report results for CLD at 36 weeks' postmenstrual age, which is typically regarded as the more important outcome with regards to CLD. The research study did not demonstrate earlier weaning from breathing support with salbutamol or the duration of oxygen supplements. The research study showed that salbutamol does not affect need for intravenous dexamethasone or sepsis compared to placebo. [49].

4. CONCLUSION

Numerous therapy techniques for CLD have been assessed in well-conducted medical trials and meta-analyses. Although for a few of these therapies conclusive proof of efficacy is doing not have there are numerous continuous areas of research study that show potential. Our present understanding of the complex and multifactorial pathophysiology of BPD suggests that targeting specific pathways is unlikely to have a considerable influence on outcome.

REFERENCES

[1] Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163:1723–1729.

[2] Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, Wrage LA, Poole K; National Institutes of Child Health and Human Development Neonatal Research Network. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics 2005;116:1353–1360.

[3] Doyle LW, Cheung MM, Ford GW, Olinsky A, Davis NM, Callanan C. Birth weight ,1501 g and respiratory health at age 14. Arch Dis Child 2001;84:40–44.

[4] Greenough A, Alexander J, Burgess S, Chetcuti PA, Cox S, Lenney W, Turnbull F, Shaw NJ, Woods A, Boorman J, et al. Home oxygen status and rehospitalisation and primary care requirements of infants with chronic lung disease. Arch Dis Child 2002;86:40–43.

[5] Gross SJ, Iannuzzi DM, Kveselis DA, Anbar RD. Effect of preterm birth on pulmonary function at school age: a prospective controlled study. J Pediatr 1998;133:188–192.

[6] Doyle LW, Halliday HL, Ehrenkranz RA, Davis PG, Sinclair JC. Impact of postnatal systemic corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk for chronic lung disease. Pediatrics 2005;115:655–661.

[7] Skidmore MD, Rivers A, Hack M. Increased risk of cerebral palsy among very low-birthweight infants with chronic lung disease. Dev Med Child Neurol 1990;32:325–332.

[8] Baraldi E, Filippone M. Chronic lung disease after premature birth. N Engl J Med 2007;357:1946–1955.

[9] Greenough A, Alexander J, Burgess S, Bytham J, Chetcuti PA, Hagan J, Lenney W, Melville S, Shaw NJ, Boorman J, et al. Preschool healthcare utilisation related to home oxygen status. Arch Dis Child Fetal Neonatal Ed 2006;91:F337–F341.

[10] Rojas MA, Gonzalez A, Bancalari E, et al. Changing trends in the epidemiology and pathogenesis of neonatal chronic lung disease. J Pediatr. 1995 Apr;126(4):605–10.

[11] Charafeddine L, D'Angio CT, Phelps DL. Aytypical chronic lung disease patterns in neonates. Pediatrics. 1999;103:759–60.

[12] Hussain AN, Siddiqui NH, Stocker JT. Pathology of arrested acinar development in postsurfactant bronchopulmonary dysplasia. Hum Pathol. 1998;29:710–17.

[13] Coalson JJ. Pathology of chronic lung disease of early infancy. New York: Marcel Dekker; 2000. pp. 85–124.

[14] Jobe AH. The new bronchopulmonary dysplasia: an arrest of lung development. Pediatr Res. 1999;46:641–43.

[15] Gien J, Kinsella JP. Pathogenesis and Treatment of Bronchopulmonary Dysplasia. *Current opinion in pediatrics*. 2011;23(3):305-313. doi:10.1097/MOP.0b013e328346577f.

[16] Woodgate PG, Davies MW. Permissive hypercapnia for the prevention of mortality and morbidity in mechanically ventilated newborn infants. Cochrane Database Syst Rev. 2001;2 CD002061.

[17] Lista G, Colnaghi M, Castoldi F, et al. Impact of targeted-volume ventilation on lung inflammatory response in preterm infants with respiratory distress syndrome (RDS) Pediatr Pulmonol. 2004 Jun;37(6):510–4.

[18] 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;347:643–652.

[19] 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.

[20] Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med. 2008 Feb 14;358(7):700–8.

[21] Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010 May 27;362(21):1970–9. This study confirms finding from prior studies that early CPAP when compared with intubation and surfactant administration does not decrease the incidence of BPD.

[22] Darlow BA, Graham PJ. Vitamin A supplementation for preventing morbidity and mortality in very low birthweight infants. Cochrane Database Syst Rev. 2002;4 CD000501.

[23] Shah SS, Ohlsson A, Halliday H, Shah VS. Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants. Cochrane database of systematic reviews (Online) 2003:CD002057.

[24] Shah SS, Ohlsson A, Halliday H, Shah VS. Inhaled versus systemic corticosteroids for preventing chronic lung disease in ventilated very low birth weight preterm neonates. Cochrane database of systematic reviews (Online) 2003:CD002058.

[25] Bassler D, et al. The Neonatal European Study of Inhaled Steroids (NEUROSIS): an eu-funded international randomised controlled trial in preterm infants. Neonatology. 2010;97:52–55.

[26] Inhaled Extra-fine Hydrofluoalkane-beclomethasone (QVAR) in Premature Infants With Bronchopulmonary Dysplasia (BPD).

[27] Halliday HL, Ehrenkranz RA, Doyle LW. Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Cochrane database of systematic reviews (Online) 2010:CD001146.

[28] Halliday HL, Ehrenkranz RA, Doyle LW. Moderately early (7-14 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Cochrane database of systematic reviews (Online) 2003:CD001144.

[29] Halliday HL, Ehrenkranz RA, Doyle LW. Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants. Cochrane database of systematic reviews (Online) 2003:CD001145.

[30] Halliday HL, Ehrenkranz RA, Doyle LW. Late (>7 days) postnatal corticosteroids for chronic lung disease in preterm infants. Cochrane database of systematic reviews (Online) 2009:CD001145.

[31] Watterberg KL. Policy statement--postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia. Pediatrics. 2010;126:800–808.

[32] Watterberg KL, et al. Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. Pediatrics. 2004;114:1649–1657.

[33] Yoder MC, Chua R, Tepper R. Effect of dexamethasone on pulmonary inflammation and pulmonary function of ventilator dependent infants with bronchopulmonary dysplasia. Am Rev Respir Dis. 1991;143:1044–48.

[34] Halliday HL. Clinical trials of postnatal corticosteroids; inhaled and systemic. Biol Neonate. 1999;76:29–40.

[35] Tschanz SA, Damke BM, Burri PH. Influence of postnatally administered glucocorticoids on rat lung growth. Biol Neonate. 1995;68:229–45.

[36] Committee on fetus and newborn. Postnatal corticosteroids to treat or prevent chronic lung disease in premature infants. Pediatrics. 2002;109:330–38.

[37] Doyle LW, Halliday HL, Ehrenkranz RA, et al. Impact of postnatal corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk for chronic lung disease. Pediatrics. 2005;115:655–61.

[38] Watterberg KL, Gerdes JS, Cole CH, et al. Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. Pediatrics. 2004;114(6):1649–1657.

[39] Rademaker KJ, Uiterwaal CS, Groenendaal F, et al. Neonatal hydrocortisone treatment: neurodevelopmental outcome and MRI at school age in preterm-born children. J Pediatr. 2007;150(4):351–357.

[40] Lister P, Iles R, Shaw B, Cucharme F. Inhaled steroids for neonatal chronic lung disease. Cochrane Database Syst Rev. 1999;4 CD002311.

[41] Shah V, Ohlsson A, Halliday HL, et al. Early administration of inhaled corticosteroids for preventing chronic lung disease in ventilated very low birthweight neonates. Cochrane Database Syst Rev. 2000;1 CD001969.

[42] Cole CH, Colton T, Shah BL, et al. Early inhaled glucocorticoid therapy to prevent bronchopulmonary dysplasia. N Engl J Med. 1999;340:1005–10.

[43] Lister P, Iles R, Shaw BNj, et al. Inhaled steroids for neonatal chronic lung disease. Cochrane Database Syst Rev. 2010 Jan;20(1) CD002311.

[44] Ng GY, da Silva O, Ohlsson A. Bronchodilators for the prevention and treatment of chronic lung disease in preterm infants. Cochrane Database Syst Rev. 2001;(3):CD003214.

[45] Kim GB. Pulmonary hypertension in infants with bronchopulmonary dysplasia. Korean J Pediatr. 2010;53:688-93.

[46] Ballard PL, Gonzalez LW, Godirez RI, Godinez MH, Savani RC, McCurnin DC, Gibson LL, Yoder BA, Kerecman JD, Grubb PH, Shaul PW. Surfactant composition and function in a primate model of infant chronic lung disease: effects of inhaled nitric oxide. Pediatr Res. 2006;59(1):157-62.

[47] Mercier JC, Hummler H, Durrmeyer X, Sanchez-Luna M, Carnielli V, Field D, Greenough A, Van Overmeire B, Jonsson B, Hallman M, Baldassarre J; EUNO Study Group. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. Lancet. 2010;376(9738): 346-54.

[48] Barrington KJ, Finer NN. Inhaled nitric oxide for respiratory failure in preterm infants. Cochrane Database Syst Rev 2007;(3):CD000509.

[49] Denjean A, Paris-Llado J, Zupan V, Debillon T, Kieffer F, Magny J-F, et al.Inhaled salbutamol and beclomethasone for preventing bronchopulmonary dysplasia: a randomised double-blind study. European Journal of Pediatrics 1998; 157:926–31.