

NEONATOLOGY TODAY

News and Information for BC/BE Neonatologists and Perinatologists

Volume 5 / Issue 5

April 2010

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NEONATOLOGY TODAY

Editorial and Subscription Offices
16 Cove Rd, Ste. 200

Westerly, RI 02891 USA

www.NeonatologyToday.net

Neonatology Today (NT) is a monthly newsletter for BC/BE neonatologists and perinatologists that provides timely news and information regarding the care of newborns and the diagnosis and treatment of premature and/or sick infants.

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Pharmacological Treatment and Prevention of Chronic Lung Disease in Preterm Infants

By Manhal Khilfeh, MD, MPH; Vish Agrawal, MD; and Tsu F. Yeh, MD

Bronchopulmonary dysplasia (BPD) is an important cause of mortality and morbidity in premature infants. Pathogenesis of BPD is not known, inflammation appears to play the central role. Many factors including: prematurity, Respiratory Distress Syndrome, mechanical ventilation, oxygen exposure, nutrition, inflammation and infections may contribute to the development of BPD. Genetic susceptibility may also play a role in BPD. Studies of multiple births and BPD show that genetic factors have an important role in developing BPD. BPD in one twin was a high predictor of BPD in the other twin. Genetic susceptibility may be influenced by the expression of the genes that are critical for surfactant synthesis, vascular development and regulation of inflammation. Many genes suspected of developing BPD have been studied but with no conclusive results.^{1,2}

The classic BPD or the old BPD is characterized by bronchial and bronchiolar mucosal metaplasia and hypertrophy, interstitial edema, an increase in fibrous tissue with focal thickness of basement membrane, peribronchial muscular hypertrophy³, vascular medial muscular hypertrophy, a decrease in the branching of pulmonary vessels and a decrease in alveolar number.⁴ The most obvious abnormality is tissue destruction and fibrosis.

In the new BPD there is a decrease in the number of alveoli with an increase in alveolar diameter and disruption of the collagen around the saccules. The most obvious abnormality in

the lungs of infants with the new BPD is the arrest of alveolarization. In animal models, over-expression of pro-inflammatory cytokines such as TNF- α , IL-6, IL-8, IL-1, IL-13 during a period of alveolarization causes an increase in the size of alveoli and a decrease in their number. Hypoxia, hyperoxia and ventilation can also impair alveolarization. Antenatal, post-natal corticosteroids and deficit in nutrition can cause lung damage and make the lungs more sensitive to oxidant damage.⁵

Bronchodilators

Bronchodilators have been used in the management of infants with BPD for a long time. The rationale for using bronchodilators in infants with BPD includes: peribronchial smooth muscle hypertrophy,⁶ airway reactivity,⁷ airway hyperactivity, and response to bronchodilators in older children with BPD⁸ and family history of severe asthma was more likely associated with premature infants with BPD.⁹ Abnormality of airway structure and function persist during long-term follow-up, which leads to recurrent respiratory hospitalizations, exercise intolerance, abnormal respiratory functions and increased airway resistance in infants with BPD.¹⁰

β 2 Agonists

Mechanism of action: β 2 agonists act by direct relaxation of the bronchial smooth muscles by activation of G γ adenyl cyclase cyclic AMP. This consequently reduces smooth muscle tone, increases the conductance of Ca²⁺ leading to smooth muscle relaxation. Stimulation of β -agonists receptors inhibits the function of

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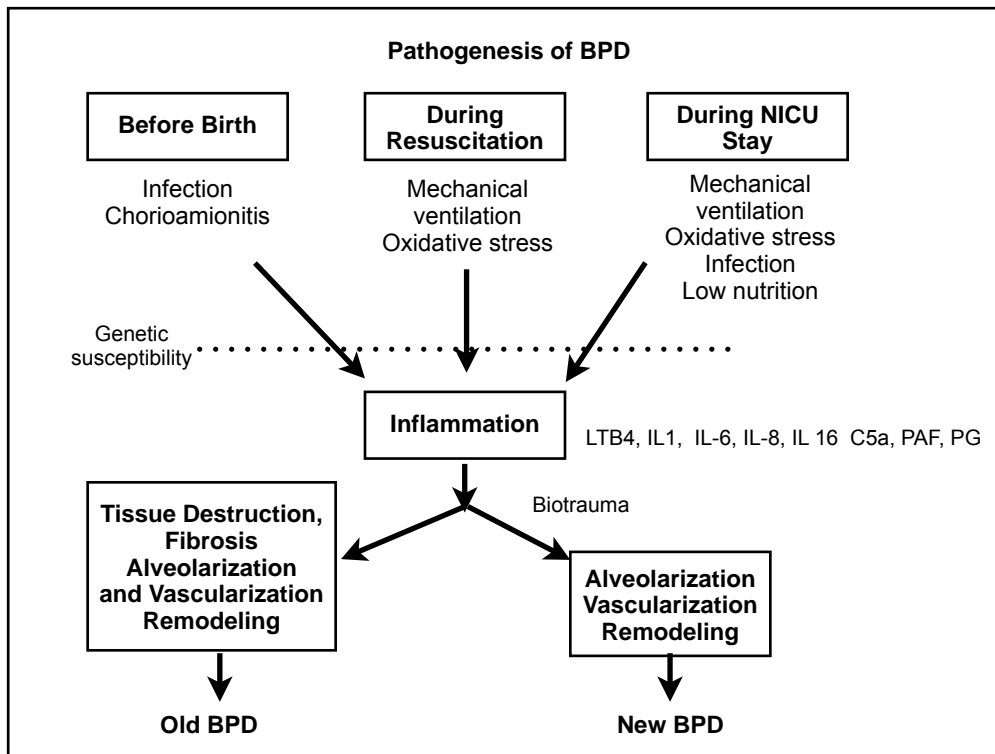
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Bronchodilators			
Drug	Trade Name	Preparation	Doses
Albuterol	Proventil Ventolin	Inhalation solution MDI, 90 mcg/puff Oral	0.1-0.5 mg/kg every 2-6 hours 1-2 Puff every 4-6 hours 0.1-0.3 mg/kg every 8 hours
Levalbuterol	Xopenex	Inhalation solution MDI 45 mcg/puff	0.31 mg every 8 hours 1-2 Puffs every 4-6 hours
Terbutaline	Brethaire	Inhalation solution MDI 0.2 mg/puff Oral	0.1-0.3 mg/kg every 2-6 hours 1-2 puffs every 4-6 hours 0.05-0.15 mg/kg every 8-12 hours
Metaproterenol	Alupent	Inhalation solution MDI 0.65 mg/puff	0.25-0.5 mg/kg every 2-4 hours 1-2 puff every 4-6 hours
Pirbuterol	Maxair	MDI 200 mcg/puff	1-2 puff every 4-6 hours Children over 12 years old

Anticholinergics			
Drug	Trade Name	Preparation	Doses
Atropine		Inhalation solution	0.05 mg/kg every 6-8 hrs
Ipratropium	Atrovent	Inhalation solution MDI 17 mcg/buff	75-175 mcg every 6-8 hrs 2-4 puffs every 6-8 hrs
Tiotropium	Spiriva	Inhalation, capsules contain 18 mcg dry powder formulation	18 mcg once a day for adults (not used in children)

numerous inflammatory cells, including: mast cells, eosinophils, neutrophils and lymphocytes through cascade that inhibits the release of inflammatory mediators and cytokines.¹¹

Pharmacology: Short-acting β 2 agonist include albuterol, levalbuterol, metaproterenol, terbutaline and pirbuterol. Albuterol, metaproterenol and terbutaline are available in oral form, but due to increased side effects,

inhalation is preferred. By inhalation treatment, the onset of action occurs within 1-5 minutes and the effects last 2-6 hours.¹¹

Long acting β 2 agonists such as salmeterol (Serevent) and formoterol (Foradil) have very high selectivity for β 2 receptors. They are not commonly used in infants.

Adverse effects: Adverse effects depend on dose, selectivity, and route of administration.

Tachycardia, palpitation, cardiac arrhythmia, tremor, CNS stimulation occur due to hyper-excitability. Other effects are increased serum glucose and decreased serum potassium. Long-term use of agonists can cause desensitization. B receptors in bronchial smooth muscles are usually resistant to desensitization but receptors on mast cells and lymphocytes are rapidly desensitized.¹¹

Studies: β -agonists decrease airway resistance, increase tidal volume, increase airway compliance and improvement in lung mechanics in infants with BPD.^{7, 12, 13, 14, 15, 16} In a study by De Boeck K, et al,¹⁷ salbutamol and ipratropium were used in 52 patients at 1 years of age, who had been ventilated after birth. The bronchodilatory effect was not uniform, and patients had different response. The study concluded that routine use of bronchodilators seemed unnecessary. The Cochrane database of systematic reviews concluded that there is no evidence at the present time that bronchodilators are useful in the treatment or prevention of BPD in preterm infants.¹⁸

Anticholinergics

Mechanism of action: Muscarinic M3 receptor is the cholinergic receptor that results in bronchial smooth muscle contraction. Anticholinergic agents inhibit bronchoconstriction and mucus secretion. Ipratropium blocks all 5 muscarinic receptors resulting in a decrease in the formation of cyclic guanosine monophosphate (cGMP). Bronchodilation effect by anticholinergic is usually less intense and slower than the effect of adrenergic drugs.^{11, 19}

Pharmacology: Atropine is absorbed through the gastrointestinal tract and from the mucous membranes; it crosses the blood brain barrier and is excreted in the urine. Serum half-life is 3 hours in adults and longer in children. Ipratropium is a non-selective muscarinic antagonist. It does not diffuse into the blood or cross the blood-brain barrier from an inhaled dose, thereby preventing systemic and central nerve system side-effects. Ipratropium is considered a short-acting bronchodilator. Its peak effect is 1-2 hours, and duration of its action is 4-6 hours.^{11, 19}

Adverse effects: Dose dependent adverse effects are dry mouth and skin, tachycardia, problems with swallowing and micturition, flushing of skin and mental changes.^{11, 19}

Studies: When ipratropium was combined with β 2 agonist, its action was prolonged and it was more effective.^{19, 20} In infants with BPD, atropine sulfate in a dose 0.05 mg increased dynamic compliance.²¹ Ipratropium in ventilator-dependent neonates with BPD showed decrease in airway resistance and

Methylated xanthines				
Drug	Loading Dose	Maintenance Dose	Route	
Caffeine citrate	20-25 mg/kg	5-10 mg/kg every 24hours	IV/PO	Wild therapeutic range
Aminophylline	5-8 mg/kg	1.5-3 mg/kg/day divided every 8-12hours	IV/PO	Monitor levels
Theophylline	5-8 mg/kg	3-6mg/kg/day divided every 6-8 hours	PO	Monitor levels

These doses are used for management of apnea of prematurity. Changing aminophylline from IV to PO increase the dose by 20%. No need to adjust theophylline.

Diuretics				
Drug	Site of Action	Route	Onset	Dose
Furosemide	Loop diuretic	IV PO	15-30 min 30-60 min	1 mg/kg/dose 1-3 mg/kg/dose
Hydrochlorothiazide	Distal tubule	PO	1-2 hrs	2-4 mg/kg/day
Spironolactone	Aldosterone antagonist	PO	3-5 days	1.5-3 mg/kg/day

increase in lung compliance.²² A Significant effect of ipratropium was seen at a dose of 175 mcg, causing decreased resistance and increased compliance. The effect was also seen with ipratropium and salbutamol but was prolonged.²³ Synergy effect could not be demonstrated when atropine and metaproterenol were combined.²⁴

Methylated xanthines: Caffeine aminophylline, theophylline and pentoxifylline.

Mechanism of action: These are competitive nonselective phosphodiesterase inhibitors and prevent breakdown of cyclic AMP and cyclic GMP. This leads to raised intracellular cAMP and cGMP. They also inhibit TNF-alpha and leukotriene synthesis,^{11, 25} thereby reducing inflammation and innate immunity. Methylxanthines are nonselective adenosine receptor antagonists. Adenosine can cause broncho-constriction and potentiate immunologically induced mediator release from lung mast cells. Inhibition of this action will cause bronchodilatation.¹¹ Methylxanthines also inhibit sleepiness-inducing adenosine and lead to improved respiratory drive.²⁵ Theobromine, a metabolic product of caffeine and theophylline causes vasodilatation and increases urine volume.¹¹

Pharmacology: Methylxanthines are absorbed rapidly after oral or parenteral administration. Maximum plasma concentration for caffeine is achieved within 1 hour and for theophylline within 2 hours. Serum half-life of methylxanthines is decreased with advance postmenstrual age in preterm infants. The average half life for caffeine is 50 hours and for theophylline is 20-36 hours. Metabolized mainly in the liver, less than 15% of theophylline and 5% of caffeine is recovered from the urine. Metabolism of methylxanthines is affected by liver disease, heart failure and acute pulmonary edema. Cimetidine and erythromycin increase their half-life while

phenytoin and barbiturate increase clearance.¹¹

Adverse effects: Toxicity with theophylline is more common than with caffeine. Side effects are usually associated with plasma level over 20 ug/ml: nausea, vomiting, headache, diarrhea, tachycardia, irritability. At high levels, the patient may develop hyperglycemia, hypokalemia, hypotension, cardiac arrhythmias, seizure, brain damage and death.¹¹

Studies:

Theophylline: Rooklin et al in 1979 showed that theophylline increased lung compliance and decreased airway resistance in infants less than 30 days old.²⁶ Kao et al showed that oral theophylline improved dynamic compliance, airway resistance, maximal expiratory flow at functional residual capacity and decreased time constant. When diuretics and theophylline were used an additive effect was noted.²⁷

Caffeine: Davis et al demonstrated an improvement in minute ventilation, an increase in tidal volume, a decrease in lung resistance and improved lung compliance one hour following 10 mg/kg of caffeine.²⁸ In a randomized study by B. Schmidt et al, infants who received caffeine were less likely to use oxygen at 36 weeks postmenstrual age. In addition, ventilator use was discontinued one week earlier than infants who received a placebo.^{29, 30} Capers et al, showed that theophylline at a serum levels less than 10 is not beneficial as an aid to wean the ventilator.³¹

Pentoxifylline: Lauterbach R et al, (32) studied 150 low birth weight infants who required oxygen by the fourth day of life. The infants were randomized in three groups: placebo, intravenous 0.25 mg/kg dexamethasone every 12 hours on three consecutive days and nebulized pentoxifylline

every 6 hours on three consecutive day in a dose of 20 mg/kg when infants who were breathing spontaneously or 10 mg/kg when they needed ventilatory support. Authors concluded that nebulized pentoxifylline reduces the risk of BPD and may be a potential alternative to steroids in the prevention BPD.

Diuretics

Infants with chronic lung disease tend to retain interstitial fluid which results in increased respiratory distress, increase in oxygen requirement, increase in ventilator settings, hypoxemia and hypercarbia. Diuretics mobilize fluid, improve lung compliance and decrease resistance.³³

Furosemide

Furosemide is the most commonly used diuretic. It is a potent and rapid acting loop diuretic. It can be used orally and intravenously. The main benefit of the intravenous route is a quick response.

Mechanism of Action: At the ascending loop of Henle, furosemide inhibits active reabsorption of chloride resulting in lower sodium and water reabsorption. It also acts against antidiuretic hormones, and increases urine aldosterone excretion. Furosemide decreases left ventricular filling pressure by increasing venous capacitance. Furosemide helps in chronic lung disease by both diuretic and vasculature effects.

Adverse effects: Main adverse effects of chronic furosemide therapy are hypercalcemia, nephrocalcinosis and hypochloremia. Electrolytes should be monitored carefully. Ototoxicity is related to plasma concentration and is usually reversible after cessation of therapy. Other side effects include: osteopenia, cholelithiasis, displacement of bilirubin and hyperparathyroidism.

According to Cochrane review in preterm infants < 3 weeks of age with BPD, intravenous furosemide administration has either inconsistent effects or no detectable effect. In infants less than 3 weeks of age with BPD, a single intravenous dose of 1 mg/kg of furosemide transiently improves pulmonary mechanics. Chronic enteral or intravenous furosemide administration improves both oxygenation and pulmonary mechanics. The Cochrane review concluded that there is little evidence to support any benefit of furosemide administration with respect to ventilatory support, length of hospital stay, survival or long-term outcome. Accordingly, routine or sustained uses of systemic loop diuretics in infants with BPD cannot be recommended.^{33, 34, 35, 36, 37}

Inhaled furosemide has been shown to transiently improve pulmonary function. No

long-term outcomes have been studied. More trials are needed before this delivery method can be recommended for routine use.³⁷

Thiazide Diuretics

Thiazides work by inhibiting sodium reabsorption in the distal tubule. In contrast to furosemide, thiazides decrease calcium excretion.

Potassium Sparing Diuretic

Spironolactone is a competitive antagonist of aldosterone. It is a weak diuretic and is usually given in combination with thiazides.

There are very few randomized control trials. By Cochrane reviewer's opinion, in infants less than 3 weeks of age with BPD, chronic administration of thiazide and spironolactone improves lung compliance at four weeks of treatment and reduces need for furosemide. Only one study showed long-term benefits such as decreased rates of death and artificial ventilation.^{38, 39, 40, 41, 42}

Corticosteroids

As anti-inflammatory agents used widely in treatment of BPD, their action is mediated by annexin-1 synthesis. Corticosteroids inhibit two main inflammatory products prostaglandins and leukotrienes. Through suppression of cyclo-oxygenase I and II, corticosteroids potentiate the anti-inflammatory effect.⁴³ Through decrease of inflammatory mediators such as IL1, α 1 protease inhibitors, LTB4 corticosteroids reduce pulmonary edema.⁴⁴ Steroids enhance surfactant production and stimulate antioxidant production.

Side effects of systemic corticosteroids administration include: hypertension, growth suppression, glucose intolerance, alkalosis, pituitary-adrenal suppression, increase risk for gastrointestinal bleeding and perforation, vomiting, increase risk for osteopenia and pathological fracture, immune suppression and increase risk of neurodevelopment dysfunction.⁴⁵ For details of postnatal use of corticosteroid therapy, the readers are referred to: *Neonatology Today* Vol 4 Issue 11.

Inhaled Nitric Oxide (INO)

INO decreases pulmonary vascular resistance and improves oxygenation. It is proposed that INO will improve oxygenation, improve ventilation and will decrease respiratory support. Side effects include methemoglobinemia and direct pulmonary injury if excessive INO is used

Studies on INO were done with different doses, started at different ages, different durations of treatment, and in infants whose characteristics were different among the

studies. INO was approved by FDA to term and near-term infants.⁴⁶ AAP Committee on Fetus and Newborn recommended that centers that provide INO therapy should provide comprehensive long-term medical and neurodevelopment follow-up and should establish prospective data collection for treatment time, course, toxic effects, treatment failure, use of alternative therapies, and outcomes.⁴⁶

A systematic review which included 11 studies⁴⁷ failed to show a significant benefit of INO on BPD. Cochrane database for systematic review by Keith J Barrington in 2006 concluded: INO as rescue therapy for the very ill ventilated preterm infant does not appear to be effective, and may increase the risk of severe IVH.⁴⁸ Later use of INO to prevent BPD also does not appear to be effective. Early routine use of INO in mildly sick preterm infants may decrease serious brain injury, and may improve survival without BPD. Further studies are needed.

Antioxidants

Free radical and oxidant stress cause damage to DNA, cell membrane, protein and lipids. Free radicals are produced by many mechanisms such as mitochondrial electron transport chain, prostaglandin metabolism, ischemia-reperfusion, hypoxia, neutrophil and macrophage activations, and endothelial cell hypoxanthine-xanthine oxidation. There is a balance between free radical production and clearing by the antioxidant system. The antioxidant defense system includes enzymatic components such as Co-Zn superoxide dismutase (SOD) glutathione peroxidase, and a non-enzymatic components such as glutathione, selenium, zinc, vitamin E and vitamin C. Preterm infants have an immature antioxidant defense system, and are highly exposed to oxidant stress, therefore prone to get tissue damage.⁴⁹ Many antioxidant agents have been tried to treat or prevent BPD in newborn. These include:

Vitamin E: Tocopherol is a fat-soluble, antioxidant and it decreases reactive oxygen species. The American Academy of Pediatrics Committee on Nutrition has recommended daily supplementation of 5-25 IU of vitamin E in preterm infants. Supplementing very low birth weight infants with vitamin E as an antioxidant agent has been proposed for preventing or limiting retinopathy of prematurity, intracranial hemorrhage, and chronic lung disease. In clinical trials, vitamin E supplementation did not affect the incidence of BPD. Vitamin E supplementation significantly increased the risk for necrotizing enterocolitis and sepsis.⁵⁰

Superoxide dismutase: Intra-tracheal administration of CuZn SOD in preterm infants did not reduce BPD.⁵¹ It decreased the need for asthma medications, emergency depart-

ment visits and hospitalizations during the one year follow-up.⁵² Rosenfeld et al showed that radiologic evidence, clinical signs of BPD and days of CPAP were less in patients treated with SOD, and no side effects were observed.⁵³ Cochrane database concluded that there is insufficient evidence that superoxide dismutase is efficient in preventing chronic lung disease of prematurity, but it is well-tolerated, and has no serious adverse effects.⁵⁴

N acetyl cysteine (NAC): NAC is a precursor of cysteine, which is essential in Glutathione synthesis. Glutathione is a non-enzymatic antioxidant. NAC treatment in preterm infants did not prevent BPD or death,⁵⁵ and did not improve lung function at discharge from the hospital.⁵⁶

Allopurinol: Allopurinol is inhibitor of xanthine oxidase, an enzyme which generates superoxide radicals. It did not decrease BPD in preterm infants of 24-32 weeks' gestation.⁵⁷

Melatonin: Melatonin is a hormone that is found in all biological organisms, and is a potent free radical scavenger. Melatonin treatment reduced the proinflammatory cytokines (IL-6, IL-8 and tumor necrosis factor (TNF)-alpha), and improved the clinical outcome in mechanically ventilated newborns with respiratory distress.⁵⁸

Other Pharmacological Agents Used in Some Studies

Vitamin A: Vitamin A is very important for the health of epithelial tissues. It reduces ciliary loss, and is associated with increased alveoli. In animals studies, vitamin A deficiency has been associated with necrotizing tracheobronchiolitis and squamous metaplasia the changes akin to BPD. Very low birth weight infants are known to have low vitamin levels.

There have been several studies looking at vitamin A in the prevention of BPD. The largest study by Tyson et al showed significant decrease (from 62% to 55%) in combined outcome of death or chronic lung disease.⁵⁹ Meta-analysis also revealed similar results.⁶⁰ A follow-up study did not show any untoward outcome at 18 to 22 months of age.⁶¹ Many units routinely use vitamin A for prevention of BPD. Five thousand IU of Vitamin A has to be given by tri-weekly intramuscular injections for four weeks. In one study it was given by oral route.⁶² Intravenous emulsion preparation needs to be studied by randomized control trials.

Cimetidine: In animal studies, lung injury as result of induction of cytochrome P450 by oxygen exposure may result in the release of free radical oxidants and arachidonic acid metabolites, that can be re-

duced by cimetidine. In study by Cotton et al of infants weighing less than 1250 grams who were mechanically ventilated and required oxygen, Cimetidine had no significant effect on the severity of respiratory insufficiency at 10 day postnatal age, and did not affect the tracheal aspirate levels of inflammatory markers or arachidonic acid metabolites.⁶³

Azithromycin: A macrolid antibiotic, azithromycin, acts as a free radical scavenger, inhibits cytokines, and inhibits neutrophil chemotaxis. In a study by Ballard HO et al on extremely premature infants requiring mechanical ventilation, azithromycin did not affect mortality, incidence of BPD and days on ventilator.⁶⁴

Alpha-1 protease inhibitor (A1PI): Matrix Metalloproteinase is a member of a family of extracellular enzymes that are essential in proteolysis activity against extra cellular matrix proteins such as collagen, elastic lamina and fibronectin. These enzymes are produced by variety of cells such as fibroblasts, osteoblasts, macrophages, monocytes and neutrophils. These enzymes are essential in growth, tissue remodeling, angiogenesis and wound healing. If the balance between activation and inhibition of this enzymes is disturbed, many pathological conditions can occur such as bronchopulmonary dysplasia.⁶⁵ In a study by Stiskal JA et al, the incidence of CLD in survivors was lower in infants treated with intravenous A1PI as compared with a placebo group, but the difference was not statistically significant. The incidence of pulmonary hemorrhage was lower in the treated group.⁶⁶

Thyroxine, did not reduce the incidence of BPD.⁶⁷ Oestradiol and progesterone hormonal replacements were studied in 83 infants, but did not show decrease in incidence of BPD.⁶⁸

Conclusions

In the past two decades, there were many medications being used for the treatment or prevention of BPD. Most of the results were derived from the Cochrane database analysis. Many of these analyses, however, are not conclusive and sometimes are difficult to interpret, because each of the clinical trials was designed differently, not only in terms of time in which the therapy was initiated, but also in terms of dosage and dura-

tion of therapy. Nevertheless, the information is valid for reference; but in many occasions, management decisions may have to be made based on individual clinical experiences.

Based on current published literature and our own experiences, we would like to make the following conclusions:

1. Appropriate respiratory care is still the most promising and safest way to treat and prevent BPD. In this regard, training more nurses and letting them use one type of respirator and/or CPAP is essential to avoid lung injury and prolonged intubation.
2. Diuretics, bronchodilators and methylxanthines can be used as adjunctive therapy if needed.
3. Systemic dexamethasone therapy should be reserved only for those infants who are in intractable respiratory failure, expected to have poor neurodevelopment outcome and/or who would otherwise die without therapy. A short course of 0.1-0.2 mg/kg /dose every 12 hours for 3-5 days may be beneficial.
4. Vitamin A, Hydrocortisone, SOD, inhaled NO and intratracheal instillation of budesonide using surfactant as vehicle all need more studies and/or longer follow-up.
5. More studies of liquid ventilation in animals and human neonates.

Reference

1. Bhanadari V and Gruen J The Genomics of Broncho-pulmonary dysplasia. NeoReview 2007; 8 (8)
2. Parker RA, Lindstrom DP, Cotton RB. Evidence from twin study implies possible genetic susceptibility to bronchopulmonary dysplasia. Semin perinatol 1996; 20 (3) 206-9.
3. Stocker JT. Pathologic features of long-standing "healed" bronchopulmonary dysplasia: a study of 28 3- to 40-month-old infants. Hum Pathol. 1986;17(9):943-61.
4. JD'Angio CT, Maniscalco WM. The role of vascular growth factors in hyperoxia-induced injury to the developing lung. Front Biosci. 2002 1;7:d1609-23.
5. Alan Jobe , The new BPD NeoReview 2006 10 (17) e531-45.
6. Bonikos DS, Bensch KG, Northway WH Jr, Edwards DK bronchopulmonary dysplasia: the pulmonary pathology sequel

- of necrotizing bronchitis and pulmonary fibrosis. Hum Pathol 1976 7(6):643-66.
7. Motoyama EK, Fort MD, Klesh KW, Mutich RL, Guthrie RD. Early onset of airway reactivity in premature infants with BPD. Am Rev Respir dis 1987 jul 136 (1) 50-7.
8. De Boeck K, Smith J, Van Lierde S, Devlieger H. Response to Bronchodilators in clinically stable 1-year old patients with bronchopulmonary dysplasia. Eur J Pediatr 1998 157 (1): 75-9.
9. Nickerson BG, Taussig LM. Family history of asthma in infants and children with BPD . Pediatrics 1980; 65 (6):1140-4.
10. Gerhardt T, Hehre D, Feller R, Reifenberg L, Bancalari E. et al. Serial determination of pulmonary function in infants with chronic lung disease. J Pediatr 1987; 110 (3):448-56.
11. Laurence L Brunton et al. The Pharmacology basis of Therapeutics. 11th edition Page 720-730.
12. Kao LC, Warburton D, Platzker AC, Keens TG. Effect of Isoproterenol inhalation on airway resistance in chronic bronchopulmonary dysplasia. Pediatrics 1984; 73 (4):509-14.
13. Sosulski R, Abbasi S, Bhutani VK, Fox WW. Physiologic effects of terbutaline on pulmonary function of infants with Bronchopulmonary dysplasia. Pediatr pulmonol 1986; 2 (5): 269-73.
14. Rotschild A, Solimano A, Puterman M, Smyth J, Sharma A, Albersheim S. Increased compliance in response to salbutamol in preterm infants with developing bronchopulmonary dysplasia. J pediatr 1989 115 (6):984-91.
15. Kirpalani H, Koren G, Schmidt B, Tan Y, Santos R, Soldin S. Respiratory response and pharmacokinetics of intravenous salbutamol in infants with bronchopulmonary dysplasia. Crit care Med 1990 18 (12): 1374-7.
16. Stefano JL, Bhutani VK, Fox WW. A randomized Placebo- controlled study to evaluate the effects of oral albuterol on pulmonary mechanics in ventilator- dependent infants at risk of developing bronchopulmonary dysplasia. Pediatr pulmonol 1991; 10 (3):183-90.
17. De Boeck K, Smith J, Van Lierde S, Devlieger H. Response to Bronchodilators in clinically stable 1-year old patients with bronchopulmonary dysplasia. Eur J Pediatr 1998 157 (1): 75-9.
18. Ng G. Bronchodilators for the prevention and treatment of CLD in preterm infants

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- Cochrane Database of systematic reviews as up to date 21 July 2009.
19. Cross NJ, Skorodin MS. Anticholinergic, antimuscarinic bronchodilators Am rev respir dis 1984; 129 (5):856-70.
 20. Lin MT, Lee-Hong E, Collins-Williams C. A clinical trail of the bronchodilator effect of SCH 1000 aerosol in asthmatic children. Ann Allergy 1978; 40(5)326-32.
 21. Logvinoff MM, Lemen RJ, Taussig LM, Lamont BA. Bronchodilators and diuretics in children with bronchopulmonary dysplasia. Pediatr Pulmonol 1985; 1 (4): 198-203.
 22. Wilkie RA, Bryan MH. Effect of bronchodilators on airway resistance in ventilator-dependent neonate with chronic lung disease J pediatr 1987 111(2) 278-282.
 23. Brundage KL, Mohsini KG, Froese AB, Fisher JT. Bronchodilator response to Ipratropium bromide in infants with bronchopulmonary dysplasia. Am rev respir dis 1990; 142 (5):1137-42.
 24. Kao LC, Durand DJ, Nickerson BG. Effect of inhaled metaproterenol and atropine on pulmonary mechanics of infants with bronchopulmonary dysplasia. Pediatr Pulmonol 1989 6 (2) 74-80.
 25. Peters-Golden M, Canetti C, Mancuso P, Coffey MJ. (2005). "Leukotrienes: underappreciated mediators of innate immune responses." J Immunol. 174 (2): 589-94.
 26. Rooklin AR, Moomjian AS, Shutack JG, Schwartz JG, Fox WW. Theophylline therapy in bronchopulmonary dysplasia J pediatr 1979; 95 (5 pt2): 882-8.
 27. Kao LC, Durand DJ, Phillips BL, Nickerson BG. Oral theophylline and diuretics improve pulmonary mechanics in infants with bronchopulmonary dysplasia. J pediatr 1987; 111 (3): 493-544.
 28. Davis JM, Bhutani VK, Stefano JL, Fox WW, Spitzer AR. Changes in pulmonary mechanics following caffeine administration in infants with bronchopulmonary dysplasia. Pediatr Pulmonol 1989;6 (1) 49-52.
 29. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W. Caffeine therapy for apnea of prematurity. N Engl J Med 2006; 354 (20): 2112-21.
 30. Schmit B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W. Long-Term effects of Caffeine Therapy for Apnea of Prematurity. N Engl J Med 2007 357 (19) 1893-902.
 31. Capers CC, Ward ES, Murphy JE, Job ML, Land PA. Use of theophylline in neonate as an aid to ventilator weaning. Ther Drug Monit 1992; 14 (6):471-4.
 32. Lauterbach R, Szymura-Oleksiak J, Pawlik D, Warchol J, Lisowska-Miszczuk I, Rytlewski K. Nebulized pentoxifylline for prevention of bronchopulmonary dysplasia in very low birth weight infants: a pilot clinical study. J Matern Fetal Neonatal Med. 2006;19(7):433-8.
 33. McCann EM, Lewis K, Deming DD, Donovan MJ, Brady JP. Controlled trial of furosemide therapy in infants with chronic lung disease. Journal of Pediatrics 1985;106:957-62.
 34. Kao LC, Durand DJ, McCrear RC, Birch M, Powers RJ, Nickerson BG. Randomized trial of long-term diuretic therapy for infants with oxygen-dependent bronchopulmonary dysplasia. J Pediatr. 1994;124(5 Pt 1):772-81.
 35. Reiter PD, Makhlof R, Stiles AD. Comparison of 6-hour infusion versus bolus furosemide in premature infants. Pharmacotherapy - The Journal of Human Pharmacology and Drug Therapy 1998;18:63-8.
 36. Rush MG, Engelhardt B, Parker RA, Hazinski TA. Double-blind, placebo-controlled trial of alternate-day furosemide therapy in infants with chronic bronchopulmonary dysplasia. Journal of Pediatrics 1990;117:112-8.
 37. Brion LP, Primhak RA, Yong W. Aerosolized diuretics for preterm infants with (or developing) chronic lung disease. Cochrane Database Syst Rev. 2006 Jul 19;3:CD001694. Review.
 38. 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;(1):CD001817. Review.
 39. Engelhardt B, Blalock WA, DonLevy S, Rush M, Hazinski TA. Effect of spironolactone-hydrochlorothiazide on lung function in infants with chronic bronchopulmonary dysplasia. J Pediatr. 1989 ;114(4 Pt 1):619-24.
 40. 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(1):41-5.
 41. Kao LC, Durand DJ, McCrear RC, Birch M, Powers RJ, Nickerson BG. Randomized trial of long-term diuretic therapy for infants with oxygen-dependent bronchopulmonary dysplasia. J Pediatr. 1994 ;124(5 Pt 1):772-81.
 42. Segar JL, Chemtob S, Bell EF. Changes in body water compartments with diuretic therapy in infants with chronic lung disease. Early Hum Dev. 1997 25;48(1-2):99-107.
 43. Rhen T, Cidlowski J. Anti-inflammatory action of glucocorticoids: new mechanisms for old drugs. N Eng J Med 2005 353:1421-31.
 44. Groner P, Resuss D, Gotze-Speer B, Speer C.P. The effects of Dexamethasone on Chemotactic activity and inflammatory mediators in tracheobroncheal aspirates of preterm at risk of chronic lung disease. J pediatr 1993 122; 938-944.
 45. Yeh TF, Lin YJ, Lin HC et AL. Outcome at school age after postnatal dexamethasone therapy for lung disease of prematurity. N Eng J med; 2004 350: 1304-13.
 46. Committee on Fetus and Newborn Policy Statement, American Academy of Pediatrics use of inhaled nitric oxide. Pediatrics, 2000 ;106 344-45.
 47. Barrington KJ, Finer NN. Inhaled Nitric Oxide for Preterm Infants: A Systematic Review Pediatrics 2007;120;1088-1099.
 48. Barrington KJ, Finer NN. Inhaled nitric oxide for respiratory failure in preterm infants, Cochrane database for systematic review 2006.
 49. Thibeault DW. The precarious antioxidant defenses of the preterm infant. Am J Perinatol 2000;17 (4) 167-81.
 50. Brion LP. Vitamin E supplementation for prevention of morbidity and mortality in preterm infants Cochrane systematic review 2003.
 51. Davis JM, Rosenfeld WN, Richter SE, Parad MR, Gewolb IH, Spitzer AR, Carlo WA, Couser RJ, Price A, Flaster E, Kassem N, Edwards L, Tierney J, Horowitz S. Safety and pharmacokinetics of multiple doses of recombinant human CuZn superoxide dismutase administered intratracheally to premature neonates with respiratory distress syndrome. Pediatrics 1997;100 (1):24-30.
 52. Davis JM, Parad RB, Michele T, Allred E, Price A, Rosenfeld W. Pulmonary outcome at 1 year corrected age in premature infants treated at birth with recombinant human CuZn superoxide dismutase. Pediatrics. 2003 Mar;111(3):469-76.
 53. Rosenfeld W, Evans H, Concepcion L, Jhaveri R, Schaeffer H, Friedman A. Prevention of bronchopulmonary dys-



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- plasia by administration of bovine superoxide dismutase in preterm infants with respiratory distress syndrome. *J Pediatr* 1984;105 (5):781-5.
54. Suresh GK, et al. Superoxide dismutase for preventing chronic lung disease in mechanically ventilated preterm infants. *Cochrane Database Syst Rev*. 2001.
 55. Ahola T, Lapatto R, Raivio KO, Selander B, Stigson L, Jonsson B, Jonsbo F, Esberg G, Stövring S, Kjartansson S, Stiris T, Lossius K, Virkola K, Fellman V. N-acetylcysteine does not prevent bronchopulmonary dysplasia in immature infants: a randomized controlled trial. *J Pediatr*. 2003;143(6): 713-9.
 56. Sandberg K, Fellman V, Stigson L, Thiringer K, Hjalmarson O. N-acetylcysteine administration during the first week of life does not improve lung function in extremely low birth weight infants. *Biol Neonate*. 2004;86(4):275-9.
 57. Russell GA, Cooke RW. Randomised controlled trial of allopurinol prophylaxis in very preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 1995 J;73(1) F27-31.
 58. Gitto E, Reiter RJ, Sabatino G, Buonocore G, Romeo C, Gitto P, Buggé C, Trimarchi G, Barberi I. Correlation among cytokines, bronchopulmonary dysplasia and modality of ventilation in preterm newborns: improvement with melatonin treatment. *J Pineal Res*. 2005 Oct;39(3):287-93.
 59. Tyson JE, Wright LL, Oh W, Kennedy KA, Mele L, Ehrenkranz RA et al. Vitamin A supplementation for extremely-low-birth-weight infants. *New England Journal of Medicine* 1999;340:1962-8.
 60. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD00050. DOI: 10.1002/14651858.CD000501.pub2.
 61. Ambalavanan N, Tyson JE, Kennedy KA, Hansen NI, Vohr BR, Wright LL, Carlo WA; National Institute of Child Health and Human Development Neonatal Research Network. Vitamin A supplementation for extremely low birth weight infants: outcome at 18 to 22 months. *Pediatrics* 2005;115:e249-54.
 62. Wardle SP, Hughes A, Chen S, Shaw NJ. Randomised controlled trial of oral vitamin A supplementation in preterm infants to prevent chronic lung disease. *Archives of Disease in Childhood Fetal Neonatal Edition* 2001;84:F9-F13.
 63. Cotton RB. Cimetidine does not prevent lung injury in newborn premature infants. *Pediatr Res*. 2006 Jun;59(6):795-800. Epub 2006 Apr 26.
 64. Ballard HO, Anstead MI, Shook LA.(abstract) Azithromycin in the extremely low birth weight infant for the prevention of bronchopulmonary dysplasia: a pilot study. *Respir Res*. 2007 June5;8:41.
 65. Murphy G, Docherty AJP. The matrix metalloproteinases and their inhibitors. *Am j Respir Cell Mol Biol* 1992; 7(2):120-125.
 66. Stiskal JA, Dunn MS, Shennan AT, O'Brien KK, Kelly EN, Koppel RI, Cox DW, Ito S, Chappel SL, Rabinovitch M. Alpha1-Proteinase inhibitor therapy for the prevention of chronic lung disease of prematurity: a randomized, control trial. *Pediatrics*. 1998 101(Pt 1):89-94.
 67. Smith LM, Leake RD et al Postnatal thyroxin supplementation in infants less than 32 weeks gestation: effects of pulmonary Morbidity *J perinatol* 200;20:427-31.
 68. Trotter A, Maier L et al. Effect of oestradiol and progesterone replacement on BPD in extremely preterm infants. *Arch Dis Chil, Fetal Neonatal* 2007;92 F94-8.

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Acknowledgement: This paper is supported in part from grant NHRI-EX98-9818PI, Taiwan.

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Global Neonatology Today: A Monthly Column

By Dharmapuri Vidyasagar, MD, FAAP, FCCM

Tracking the progress of Millennium Development Goals (MDG)

The progress in achieving goals of MDG are being closely monitored world-wide. There is intense effort by governments and NGOs (non-governmental organizations) around the world to meet the MDGs by the target date of 2015. There is a MDG clock ticking (www.un.org/millenniumgoals/). Although there is noticeable progress in some countries, others are lagging behind. Let us see how the progress is being made.

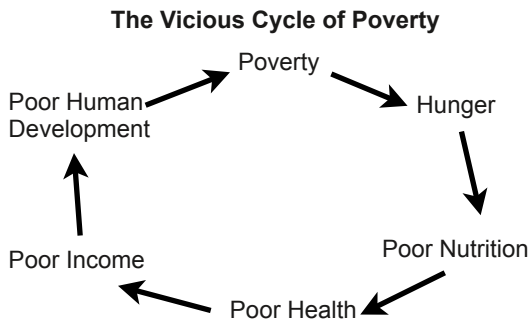
MDG GOAL # 1:

The MDG #1 goal calls for eradicating extreme poverty with the proportion of people whose income is less than \$1/day by year 2015. It also aims at increasing employment for women and young people, and reduction of hunger by 50%.

Why is this goal important?

Poverty affects human health many ways. Poverty is proxy to poor nutrition. Poor nutrition affects health. Poor nutrition combined with poverty leads to poor human development. Hunger is the extreme manifestation of poverty, and poverty affects the most vulnerable populations - women and children. Over one billion people in the world are estimated to suffer from hunger. Worldwide every day, 16,000 children die of hunger-related problems (One death every five seconds).

To improve the health of women and children, the vicious cycle (see below) of poverty and hunger must be interrupted.



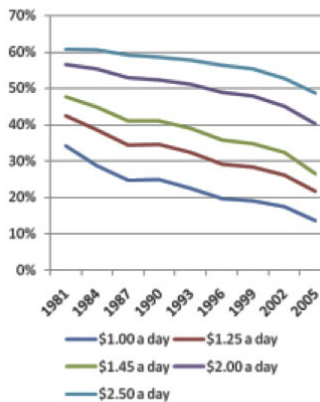
How is poverty defined?

In 1990, the poverty line was set at earning <\$1/day. It was estimated that global population over over two billion lived below this poverty line. The World Bank, based on the data of 2005, re-calibrated poverty line to those who earn <\$1.25/day. This translates to less than what we in the developed countries spend on a cup of regular coffee!

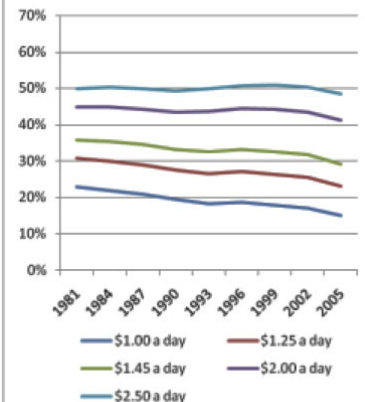
What are the global trends of poverty?

It's now estimated that there are more poor and extremely poor people, and that the incidence of poverty reaches further into middle-income countries. By the new measurements, 1.4 billion people are living in ex-

Poverty levels over time world population (%)



Poverty levels over time excluding China



Source: World Bank Development Indicators 2008

treme poverty. More than one-quarter of the population of developing countries live in poverty. But there is a silver lining: some countries have reduced poverty in their population. In 1990, at the beginning of the period tracked by the MDG, 42% of the people in developing countries lived on less than \$1.25 a day. Over the next 15 years, global poverty fell by an average of one percentage point per year. The poverty rates have fallen fastest in East Asia. China accounts for greatest reduction, where poverty has fallen from 85% to 16%, affecting 600 million people. It is estimated that excluding China, global poverty dropped by only 10%. The graph above (left panel) shows the percent of world population, by different levels of earning, from \$1.25 to \$10/day. From 1981 to 2005, there has been a steady drop in each category. The largest drop is seen in the population earning <\$1. However, when data from China is excluded, there is little change in poverty reduction (right panel) in any category, suggesting much more needs to be done in other regions of the world. For example, India, another country with a population of one billion, has yet to make major progress. Fifty-four percent of Indian households live on income of <\$1 and 77 % live on <\$2. African countries also need to make progress if we are to reach the first MDG Goal by 2015.

The Clock is ticking!

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The information included here is based upon multiple published and website sources, including: WHO, UNICEF and World Bank Reports.



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FocusROP: A Solution to Retinopathy of Prematurity (ROP) Management

By Lawrence Y. Ho, MD; Lisa J. Faia MD; and Michael T. Trese, MD

Retinopathy of prematurity (ROP) management has progressed greatly over the last decade and a half, now yielding an anatomic success rate of greater than 98%.¹⁻³ Much of this success, however, is based on the timely and accurate screening of infants at risk for retinopathy of prematurity. It has become a great problem in the United States to find doctors who are trained and willing to screen for retinopathy of prematurity and insurance companies that are willing to insure those who do the ROP screening.⁴ For the past two decades, screening for retinopathy of prematurity has been documented by drawings in the infant's medical record. These handwritten drawings are used in addition to the physician's memory to gauge any change between previous and current examinations. In addition, even though they did not make the original drawings, different subsequent examiners may, with much difficulty, attempt to interpret the previous examiner nota-

“Retinopathy of prematurity (ROP) management has progressed greatly over the last decade and a half now yielding an anatomic success rate of greater than 98%.¹⁻³ Much of this success, however, is based on the timely and accurate screening of infants at risk for retinopathy of prematurity”



Figure 1. The homepage of the FocusROP website is shown.

tions. This form of documentation is imprecise to say the least and, in some areas, inaccurate, and is not compatible with electronic medical records. For several years, it has been possible to use photography to document much of the infant's retina.⁵ We know from current management of diabetic retinopathy and macular degeneration, as well as other retinal diseases, that photographic documentation is far superior to any physician drawing.⁶⁻⁸

Given the very high success rates that are possible with the proper management of ROP, a new approach to screening in order to try and reduce misrepresentation and misinterpretation of data is extremely important. The medical malpractice awards in retinopathy of prematurity have captured the attention of doctors, hospitals, the American Academy of Ophthalmology, peer-reviewed journals, and insurance companies.⁹⁻¹¹ All of these groups are looking for a mechanism to provide the best possible care for each infant, while providing protection for the doctors and hospitals who administer that care. In order to supply this care, there must be a thoroughly reviewed ROP screening system that is reproducible and well documented. This system can supply a safety net for ROP management - a safety net that benefits the infant, the physician, and the hospital, as

well as insurance companies. The system should have three core components: (1) hospital participation, (2) photographic documentation with appropriate image management, and (3) parental participation. Two of these components are discussed in this paper.

Hospital Participation

In order to maintain a hospital's neonatal intensive care unit (NICU), the hospital must provide appropriate ROP screening. Currently hospitals request ophthalmologists on their staff to screen infants, usually via a bedside examination. These ophthalmologists may be from any specialty within ophthalmology and may or may not have acquired the necessary experience in regards to retinopathy of prematurity. The analogy of any ophthalmologist performing ROP screening is not dissimilar to the analogy of any radiologist performing mammography. A radiologist must be certified every few years in order to perform mammography.¹² The ophthalmologist who currently performs ROP screening may or may not be familiar with the most up-to-date ROP information. The hospital should demand that the ophthalmologist involved in ROP screening for their NICU demonstrate that they have the appropriate skill set necessary to perform ROP screening.



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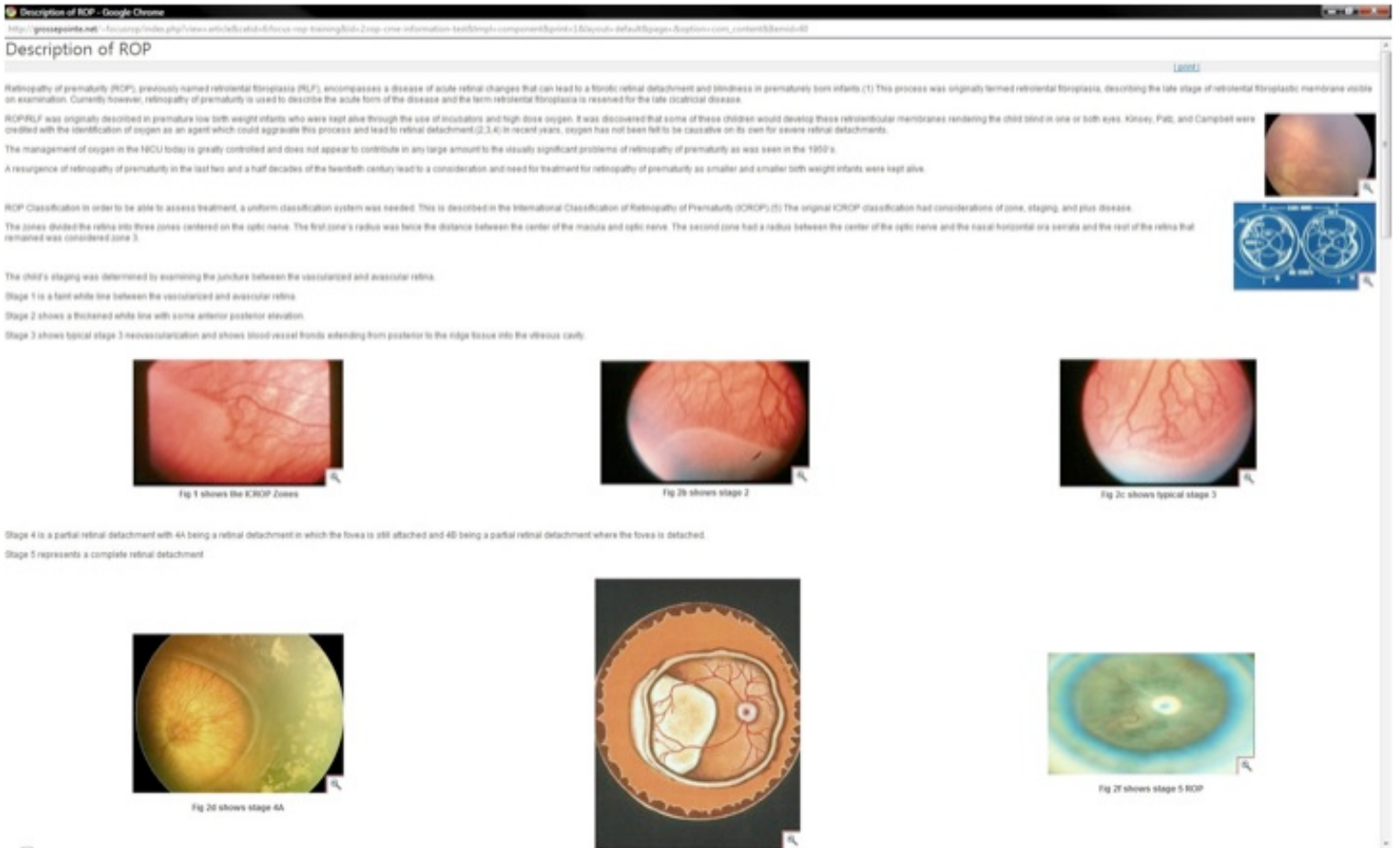


Figure 2. The education module of the FocusROP website is shown which provides free didactic material about ROP management.

In order to aid the screening ophthalmologist, the hospital must supply the necessary equipment for documentation. The best documentation for ROP screening is undoubtedly photography. Photography requires personnel capable of capturing adequate images for interpretation. The preferred personnel are the NICU nurses who are already comfortable handling these fragile neonates. In addition, the hospital must supply equipment that allows the uploading of these digital images to a secure website on the internet for viewing.

Finally, the parents should be required to sign a document before hospital discharge stating that they realize that their infant can become blind from ROP if follow-up visits are missed. Also, the hospital should make the first follow-up appointment for the infants.

Photographic Remote Image-Managing System

FocusROP is a remote image-managing software program located on the website www.focusrop.com as shown in Figure 1. It is HIPPA compliant, and allows the secure transfer of images from the NICU to a primary certified FocusROP reader.¹³ This reader has undergone an educational program as shown in Figure 2, and certification examination as shown in Figure 3 through the website to assure that they are familiar with the most up-to-date ROP information. This certification is done every two years to keep the examiner current. Training and certification are also necessary for the nursing staff obtaining and uploading the images. The software program allows the primary reader, who is notified by text message as shown in Fig-

ure 4 that images are available for reading. The reader then is able to securely enter the website as shown in Figure 5 and use an algorithm contained within the software program combined with recommendations based on the most up-to-date ROP studies to process the images as shown in Figure 6. These recommendations couple both photographic documentation, as well as bedside examination, to achieve the highest level of ROP care. This image-management program allows the reader to return a report to the hospital that provides photographically the circumstances of each eye and recommendations for the subsequent examinations. The reader cannot change the recommendations of the algorithm mentioned above, which is important in the safety net. Inappropriately long periods of time between examinations in the NICU and delay in examinations after

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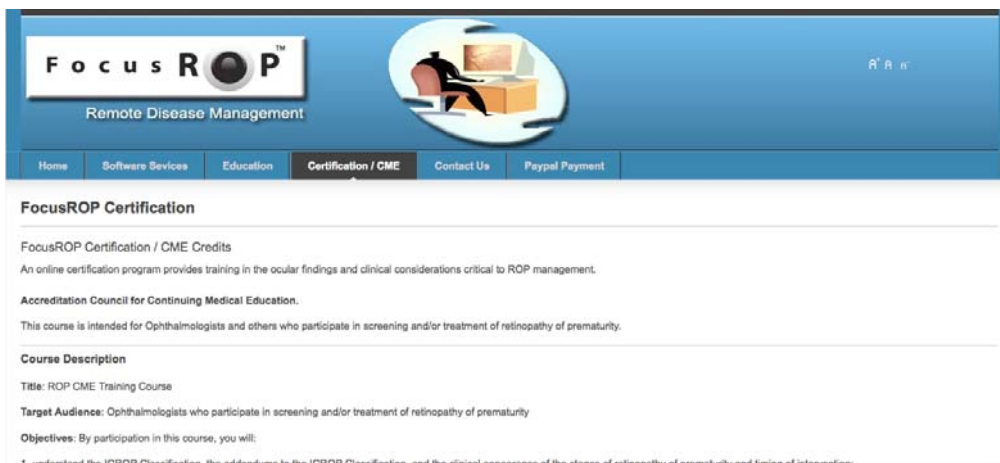


Figure 3. The reader certification module of the FocusROP website is shown which has an online examination which provides three hours of CME credits.



Figure 4. Sample of a text message sent to the certified reader when images are available for reading.

transfer of care from the NICU may lead to future litigation and can be avoided with this program.^{11,14} The images can also be compared side-by-side to previous examinations. This allows absolute documentation of interval change and provides the infant with the most up-to-date examination schedule. In addition, this report can be printed or seamlessly entered into an electronic medical record and is stored in an off-site image area available for 22 years. The algorithm never tells the doctor/reader that treatment is necessary as the decision for treatment is left to the doctor's best judgment. The program instead mandates a bedside examination. In addition, if the primary reader has a challenging case, there is a mechanism for them to seek the advice of an expert of their own designation. All of the participants, the NICU, the primary reader, and the expert reader are notified by text message of the available images to be read or that they have been read. The readings can be performed and returned to the hospital in several hours time even from any device connected to the Internet as shown in Figure 7. This speed and efficiency is important due to the potential rapid progression of retinopathy of prematurity.¹⁵ The images that are captured at the bedside can be helpful in terms of NICU personnel and house staff education, as well as parental understanding of the severity of retinopathy of prematurity and the need for treatment or frequent follow-up care.

Using these core components, a safety net for ROP management can be achieved, leading to a system in which no infant falls



Figure 5. The secure login section of the FocusROP website is shown.

through the cracks, missing the opportunities of treatment that can yield extremely highly successful anatomic results.

References

1. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the Early Treatment for Retinopathy of Prematurity Randomized Trial. *Arch Ophthalmol* 2003;121:1684-94.
2. Capone A Jr, Trese MT. Lens-sparing vitreous surgery for tractional stage 4A retinopathy of prematurity retinal detachments. *Ophthalmology* 2001;108:2068-70.
3. Prenner JL, Capone A Jr, Trese MT. Visual outcomes after lens-sparing vitrectomy for stage 4A retinopathy of prematurity. *Ophthalmology* 2004;111:2271-2273.

“Using these core components, a safety net for ROP management can be achieved, leading to a system in which no infant falls through the cracks, missing the opportunities of treatment that can yield extremely highly successful anatomic results.”



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Browse patients Interpretation: MRN 157

Patient Interpretation

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Patient Information

Demographic Information

MRN	First Name	Last Name	DOB (mm/dd/yyyy)	01/01/2009
Hosp MRN	Clinic	Clinic Code	Gender	Male
Ethnicity				

Medical Information

Date of photograph (mm/dd/yyyy)	01/13/2009	Gestational age (in weeks)	34	Post menstrual age (in weeks)	32	Comments
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Right External Right Temp Report Details - Right Eye

Ext.	Post Pole	High Stage	Low Zone
Pupil size adequate <input checked="" type="checkbox"/>	Normal <input checked="" type="checkbox"/>	No ROP <input type="checkbox"/>	Zone 1 <input type="checkbox"/>
Rubecosis <input type="checkbox"/>	Pre-plus <input type="checkbox"/>	S1 <input type="checkbox"/>	Zone 2 <input checked="" type="checkbox"/>
Indet. <input type="checkbox"/>	Plus <input type="checkbox"/>	S2 <input checked="" type="checkbox"/>	Zone 3 <input type="checkbox"/>
	Vasoconst. <input type="checkbox"/>	S3 Flat <input type="checkbox"/>	Zone indet. <input type="checkbox"/>
	Vitreous Haze <input type="checkbox"/>	S3 Typical <input type="checkbox"/>	
	Indet. <input type="checkbox"/>	Stage Indet. <input type="checkbox"/>	
		Stage 4/5 <input type="checkbox"/>	

Right Eye Comments

Ext: Pupils size adequate; Rubecosis NOT present;
 Post: Posterior pole normal in appearance;
 Temp: Stage 2 present in one or more quadrant(s); Zone 2 noted in one or more photograph(s);
 Nas: No ROP; Zone 2 noted in one or more photograph(s);
 Sup: No ROP; Zone 2 noted in one or more photograph(s);
 Inf: No ROP; Zone 2 noted in one or more photograph(s);

Left External Left Posterior Pole Report Details - Left Eye

Ext.	Post Pole	High Stage	Low Zone
Pupil size adequate <input checked="" type="checkbox"/>	Normal <input checked="" type="checkbox"/>	No ROP <input type="checkbox"/>	Zone 1 <input type="checkbox"/>
Rubecosis <input type="checkbox"/>	Pre-plus <input type="checkbox"/>	S1 <input type="checkbox"/>	Zone 2 <input checked="" type="checkbox"/>
Indet. <input type="checkbox"/>	Plus <input type="checkbox"/>	S2 <input checked="" type="checkbox"/>	Zone 3 <input type="checkbox"/>
	Vasoconst. <input type="checkbox"/>	S3 Flat <input type="checkbox"/>	Zone indet. <input type="checkbox"/>
	Vitreous Haze <input type="checkbox"/>	S3 Typical <input type="checkbox"/>	
	Indet. <input type="checkbox"/>	Stage Indet. <input type="checkbox"/>	
		Stage 4/5 <input type="checkbox"/>	

Figure 6. This example of the report sent to the hospital can be printed or entered into an electronic medical record.

- Survey: physicians being driven away from ROP treatment. Ocular Surgery News Website. <http://www.osnsupersite.com/view.aspx?id=18018>. Accessed November 23, 2009.
- The Photographic Screening for Retinopathy of Prematurity Cooperative Group. The photographic screening for retinopathy of prematurity study: primary outcomes. *Retina* 2008; 28:S47-S54.
- Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study: Age-Related Eye Disease Study Report Number 3. Age-Related Eye Disease Study Research Group. *Ophthalmology* 2000;107(12):2224-32.
- Azen SP, Irvine AR, Davis MD, et al. The validity and reliability of photographic documentation of proliferative vitreoretinopathy. *Ophthalmology* 1989;96(3):352-7.
- Pugh JA, Jacobson JM, Van Heuven WA, Watters JA, Tuley MR, Lairson DR, Lormor RJ, Kapadia AS, Velez R. Screening for diabetic retinopathy. The wide-angle retinal camera. *Diabetes Care*. 1993;16(6):889-95.
- Demorest BH. Retinopathy of prematurity requires diligent follow-up care. *Surv Ophthalmol*. 1996;41(2):175-178.
- Reynolds JD. Malpractice and the quality of care in retinopathy of prematurity (an American Ophth105:461-480.
- Day S, Menke AM, Abbott RL. Retinopathy of Prematurity Malpractice Claims The Ophthalmic Mutual Insurance Company Experience. *Arch Ophthalmol*. 2009;127(6):794-798.
- The Mammography Quality Standards Act of 1992, Public Law No. 102-539.
- Focus ROP- Case a wide safety net for retinopathy of prematurity (ROP). Focus ROP Website. www.focusrop.com. Accessed November 23, 2009.
- Arahamian AD, Coats DK, Paysse EA, Brady-McCreery K. Compliance with outpatient follow-up recommendations for infants at risk for retinopathy of prematurity. *J AAPOS*. 2000;4(5):282-286.

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Figure 7. The certified reader can access the images available for reading on a computer or cellular phone connected to the Internet.

15. International Committee for the Classification of Retinopathy of Prematurity, The International Classification of Retinopathy of Prematurity revisited, Arch Ophthalmol 2005;123:991-999.

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NEONATOLOGY TODAY

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