

# NEONATOLOGY TODAY

News and Information for BC/BE Neonatologists and Perinatologists

Volume 4 / Issue 11  
November 2009

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## NEONATOLOGY TODAY

Editorial and Subscription Offices  
16 Cove Rd, Ste. 200  
Westerly, RI 02891 USA  
[www.NeonatologyToday.net](http://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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## Postnatal Corticosteroid to Prevent or Treat Chronic Lung Disease in Preterm Infants

By Shou-Yien Wu, MD; Tessy Joseph, MD; Medha Kamat, MD; Suma Pyati, MD; and Tsu-Fuh Yeh, MD

Bronchopulmonary Dysplasia (BPD) is a pathological diagnosis, as a result of lung injury caused by either oxygen or mechanical ventilation in premature infants with Respiratory Distress Syndrome (RDS). The "classic" or "old" BPD described by Northway four decades ago occurred in relatively large premature infants (birth weight 1500-2000 g) and occurs less nowadays. Instead a new type of chronic lung disease (CLD), often described as new "BPD" has emerged. The so called "new BPD" occurs in very immature infants who initially may have

RDS or have minimal or even absent signs of RDS and subsequently develop oxygen and ventilator dependency over the first several weeks of life. The diagnosis of so called "new BPD" was also redefined. A workshop organized by NICHD/NHLBI/ORD in 2000 set diagnostic criteria based on the clinical findings (Table 1)<sup>1</sup> BPD now is defined only clinically as the need for supplemental O<sub>2</sub> for at least 28 days after birth, and its severity is graded according to respiratory support at near term. With the advance of neonatal care, more tiny infants who previously would have died now survive and remain oxygen /ventilator dependent at 28 days of age. Rate of severe BPD increases inversely with gestation age at 20% among 27 weeks to 44% at 24 weeks or less.<sup>2</sup>

Table-1. Definition of Bronchopulmonary Dysplasia: Diagnostic Criteria

| Gestation Age                                      | <32 Weeks   | ≥32 Weeks   |
|--|---|---|
| Time point of assessment                           | 36 wk PMA or discharge to home, whichever comes first   | > 28 d but < 56 d postnatal age or discharge to home, whichever comes first                                     |
| Treatment with oxygen > 21% for at least 28 d plus |   |   |
| Mild BPD   | Breathing room air at 36 wk PMA or discharge, whichever comes first   | Breathing room air at 56 d postnatal age or discharge, whichever comes first                                    |
| Moderate BPD                                       | Need for <30% oxygen at 36 PMA or discharge, whichever comes first  | Need for <30% oxygen at 56 d postnatal age or whichever comes first   |
| Severe BPD   | Need for ≥30% oxygen and /or positive pressure, (PPV or NCPAP) at 36 wk PMA or discharge, whichever comes first | Need for ≥30% oxygen and /or positive pressure, (PPV or NCPAP) at 36 wk PMA or discharge, whichever comes first |

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Severe BPD may be associated with long term pulmonary morbidity and poor neurodevelopmental outcome. Corticosteroids, in particular dexamethasone, was shown to improve pulmonary function in preterm infants with RDS and was being widely used in NICU until several long-term follow-up studies showed the concern of its adverse effects on later neurodevelopmental outcome. The American Academy of Pediatrics and the Canadian Pediatric Society do not recommend routine use of systemic dexamethasone for prevention or treatment of CLD in preterm infants,<sup>3</sup> however, a recent survey indicated that the use of steroid remains relatively common among the tiniest babies who have severe BPD and ventilator dependency.<sup>4</sup>

### Pathology and Pathogenesis of Bronchopulmonary Dysplasia

There are two different pathological differences between “old” BPD and “new” BPD. The characteristic morphology in “old” BPD is intense inflammation, alveolar fibroproliferation, bronchoalveolar smooth muscle hyperplasia, epithelial cell metaplasia and inhibition of distal lung formation.<sup>5</sup> In contrast, the morphology of “new” BPD is diffusely reduced alveolar development with fewer and larger alveoli, decreased microvascular development, less fibrosis and more uniform inflation.<sup>6,7</sup> The relationship between these two pathological findings is not clear.

The etiology of BPD is multifactorial. Traditionally, lung immaturity, respiratory distress, oxygen toxicity, and mechanical ventilation are considered the major pathogenetic factors in developing BPD. These factors still play an important role in the evolution of new BPD. Inflammation may play a major role in the development of BPD. Inflammatory reaction may be triggered by factors including infection before or after birth, oxygen free radicals, barotraumas or volutrauma from mechanical ventilation, and pulmonary edema. Neutrophils and macrophages are recruited in the airway and pulmonary tissues. The activated neutrophils adhere to the endothelium of the pulmonary vascular system and thus initiate a sequence of pathogenetic events. Infants who subsequently develop BPD are found to have a high concentration of pro-

inflammatory and chemotactic factors in the tracheobronchial aspirate such as: leukotriene B<sub>4</sub>, interleukin-1 $\beta$ , interleukin-8, soluble ICAM-1, anaphylatoxin C5a, platelet aggregation factor and prostaglandin.<sup>8,9</sup> Pulmonary inflammation affects normal alveolization and vascular development; these may further lead to remodeling of developing lungs resulting in BPD. Leukotrienes may remain elevated in BPD infants even at 6 months of age and cause bronchoconstriction, vasoconstriction, edema, neutrophils chemotaxis and mucus production.<sup>10</sup>

### Possible Mechanisms of Action of Glucocorticoid

The pathogenesis of BPD is complex, thus, more than one mechanism is likely responsible for the acute and rapid improvement of pulmonary function seen with steroid therapy. Since inflammation plays a central role for developing BPD, glucocorticoids (GCS) most likely exercise their action through anti-inflammatory effect.

The primary anti-inflammatory effect of GCS is mediated by annexin-1 synthesis. Annexin-1 suppresses phospholipase A<sub>2</sub> expression, thereby blocking eicosanoids (i.e., prostaglandins, thromboxanes, prostacyclins, and leukotriens) and the subsequent leukocyte inflammatory events including adhesion, migration etc. Thus, GCS inhibit two main products of inflammation- prostaglandins and leukotrienes. In addition, GCS also suppress both cyclooxygenase I and II similar to NSAID, potentiating the anti-inflammatory effect.<sup>11</sup>

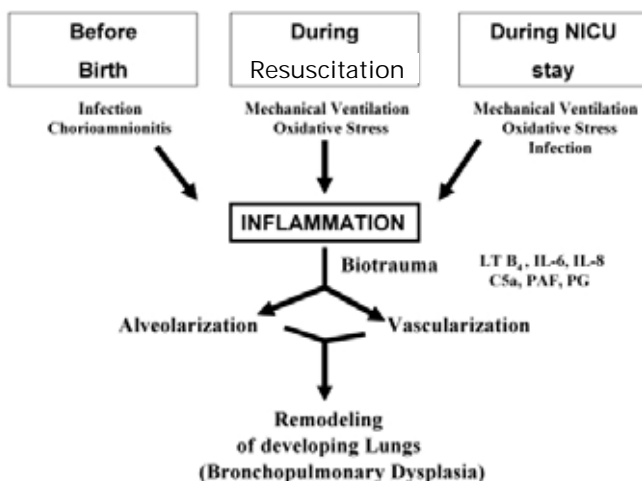
Lung inflammation is down-regulated by dexamethasone therapy. Groneck et al. evaluated the tracheobronchial aspirate from preterm infants at high risk of BPD. The number of neutrophils, and concentrations of LTB<sub>4</sub>, IL-1, elastase- $\alpha$ 1-protease-inhibitor and albumin were decreased after dexamethasone treatment.<sup>12</sup> It indicates that dexamethasone affects the release of inflammatory mediators and neutrophils influx into the airways of preterm infants who require mechanical ventilation and decreases the microvascular permeability. Pulmonary edema is the hallmark of BPD; dexamethasone has been shown to reduce the pulmonary edema in infants with BPD.

GCS block the release of arachidonic acids and its subsequent conversion to eicosanoids. The decreased incidence of PDA after prenatal or postnatal steroid therapy is likely due to the influence of the corticoid effect on the responsiveness of ductal tissue to prostaglandins. Prostaglandin has an important role in maintaining the integrity of gastrointestinal mucosa. The use of steroids may increase the risk of gastrointestinal perforation.

Other mechanisms such as modulating the transcription and posttranscriptional regulation of surfactant component, stimulation of antioxidant production, enhancement of adrenergic activities may also be responsible for the acute and rapid improvement of pulmonary function.<sup>13</sup>

Unfortunately, some of these mechanisms are also involved in physiologic signaling other than inflammatory signaling; the therapeutic effects of GCS in inflammation are often accompanied by clinically significant side effects. Glucocorticoid receptors are present virtually in all cells. Prolonged or high dose GCS therapy causes multiple systemic side effects. There is a consensus that the desired anti-inflammatory effects of GCS are mainly mediated via repression of gene transcription. In contrast, the underlying molecular mechanisms for GC-mediated side effects are complex, and partly understood.

## Pathogenesis of BPD



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## Postnatal Corticosteroid Therapy in Preterm infants

### Choice of glucocorticoids

Dexamethasone is a potent, long-acting steroid with almost exclusive glucocorticoid effect. Compared to hydrocortisone, dexamethasone is 25-50 times more potent. The half-life is 36-54 hours. Dexamethasone has been extensively studied in neonatal medicine and has shown to improve pulmonary function, facilitate extubation and decrease the incidence of BPD.<sup>14-19</sup> However, many associated adverse side effects prevent the routine use of dexamethasone. The short-term side effects include hyperglycemia, hypertension, hypertrophic cardiomyopathy, GI bleeding and perforation. The risk of GI perforation increases with concomitant indomethacin treatment.<sup>20</sup> There is also a concern with the chronic suppression of the hypothalamic-pituitary-adrenal axis,<sup>21, 22</sup> and long-term neurodevelopmental delay.<sup>23, 24</sup>

Hydrocortisone, an endogenous type of glucocorticoid, has 1:1 potency of glucocorticoid and mineralocorticoid effects. The half-life of hydrocortisone is only 8 hours vs. 36-54 hours of dexamethasone. Sick premature infants have relative adrenal insufficiency during acute illness because of developmental immaturity of the hypothalamic-pituitary-adrenal axis suggesting that an early physiological replacement of cortisol may be needed.<sup>25</sup> However, large doses above physiologic levels to achieve the anti-inflammatory action may cause significant mineralocorticoid side effects. Early use of hydrocortisone (<48 hours) was shown to decrease the risk of PDA, but increased survival only in infants exposed to maternal chorioamnionitis or who had low cortisol values.<sup>26, 27</sup>

Betamethasone is a stereoisomer of dexamethasone. They differ only in the orientation of the methyl group at position 16, which is in the  $\alpha$  configuration in dexamethasone and in  $\beta$  configuration in betamethasone. However, this structural difference could be responsible for marked differences in nongenomic effects. Previous antenatal steroid studies have demonstrated that both drugs have the same effects in reducing the risk of IVH, but betamethasone has been shown to be more effective than dexamethasone in reducing the risk of neonatal death and cystic periventricular leukomalacia among very premature infants.<sup>28, 29</sup> The study of be-

tamethasone in postnatal use is limited. A recent study has shown that betamethasone is as effective as dexamethasone in improving pulmonary function, but with fewer adverse effects, such as poor weight gain and hyperglycemia.<sup>30</sup>

Inhaled glucocorticoids have been used in neonates without concomitant systemic side effects. They have been successfully used for years in asthmatic patients, but their effects on mechanically ventilated preterm infants are less impressive. The delivery of inhaled GCS in preterm infants is technically difficult, and its effectiveness has been shown to be limited. Similarly, direct intratracheal instillation of GCS alone has also not been shown to be effective. A topical glucocorticoid aerosol (budesonide, fluticasone or beclomethasone) is administered by metered dose inhaler and spacer directly to the endotracheal tube of intubated infants. In an animal model, delivery of beclomethasone to the lungs of an intubated neonate was only 1-2% of the original aerosolized drug.<sup>31</sup> The inhaled steroid did not decrease the incidence of BPD,<sup>32</sup> but improved blood gas, chest x-ray score, and a decrease in the use of systemic steroids.<sup>32-35</sup>

A recent study from Yeh et al. suggested that intratracheal instillation of budesonide, a strong local GCS, using surfactant as vehicle may effectively deliver the medication to the lung and may decrease the incidence of BPD.<sup>36</sup>

### Timing of postnatal steroid use

It is unclear which potential mechanism of GC plays a major role in premature infants with RDS. Most of the clinical trials only evaluated clinical responses, and did not study mechanisms explaining the beneficial effects. Based on the pathologic and physiologic studies, steroid therapy given at different times may mediate physiologic effect via different mechanisms. Premature infants may develop lung injury shortly after birth and during the first 1-2 weeks after exposure to infection, oxygen or positive pressure ventilation. Therefore, steroid should be given shortly after birth or during the first few weeks to prevent BPD via its anti-inflammatory action. On the other hand, steroid therapy given at 3-6 weeks of life may derive its benefits from the modulation of lung repair. Alternately, steroids given at any age may be effective in infants with BPD by blunting hyper-reactivity and inflammation.

### Dosage and duration of corticosteroids

Any medication with potential side effects should be given at the lowest possible effective dose and for the shortest duration to achieve therapeutic effects and minimize the potential side effects. Most previous studies use a dose of dexamethasone 0.25-0.5 mg/kg/day, which is equivalent to 10 to 20 times of endogenous corticosteroid levels. The duration also varied in each study, ranging from 24 hours to 42 days.

The high dosage and long duration of treatment might be responsible for the delay of brain growth and subsequent poor neurodevelopmental outcomes. A lower-dose, and shorter-duration of dexamethasone may be beneficial and without significant side effects.<sup>37, 38</sup> However, the proper dosage and duration of treatment has not been well defined.

On the other hand, the dosage of hydrocortisone used in the trials aimed to prevent BPD was smaller, ranging from 1-2 mg/kg/d, which is equivalent to 1-2 times the physiological level. Unfortunately, the low-dose replacement showed no reduction of BPD.


### Clinical Trials and Meta-analysis

#### Dexamethasone treatment

Many clinical trials were studied to evaluate the efficacy of dexamethasone on prevention or treatment of BPD. The results of these studies are mixed and somewhat conflicting.

It is difficult to interpret these because each of these studies was designed differently with respect to sample size, timing of initiation, dosage and duration of the therapy. Most studies were performed during the time systemic steroids were commonly used in NICU in treating severe BPD while infants in the placebo groups also received GC after the study period. Thus, the comparison of the long-term outcomes between the treatment group and placebo group might not be accurate.


In recent Cochrane meta-analysis, clinical trials were grouped according to the time when corticosteroids were started: early postnatal <7 days, late postnatal >7 days. Twenty-eight (3740 infants) of early postnatal and nineteen (1345 infants) of late postnatal randomized clinical trials were included for meta-analysis.<sup>39, 40</sup>




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Beneficial effects of treatment such as significant reductions in failure to extubate by 3, 7 or 28 days, CLD at both 28 days and 36 weeks' postmenstrual age (overall and in survivors), need for late rescue treatment with dexamethasone, discharge to home on oxygen therapy, and death or CLD at both 28 days and 36 weeks' postmenstrual age (PMA) were noted in both early and late steroid use. Early corticosteroid use decreased the incidence of PDA, mild and severe ROP. Late but not early treatment was associated with a reduction in neonatal mortality at 28 days. Short-term adverse effects including hyperglycemia, hypertension, and gastrointestinal bleeding were significantly increased in both regimens. Early steroid treatment increased the risk of gastrointestinal perforation, hypertrophic cardiomyopathy and growth failure.

In the early steroid trials, dexamethasone was the drug used in most studies ( $n = 20$ ); only eight studies used hydrocortisone. In subgroup analyses by type of corticosteroid, most of the beneficial and harmful effects were attributable to dexamethasone; hydrocortisone had little effect on any outcomes except for an increase in intestinal perforation and a borderline reduction in PDA.

### Hydrocortisone

Compelling evidence of inflammation in the pathogenesis of BPD and the reports of adverse effects of dexamethasone prompted investigators to look for an alternative treatment for BPD. Watterberg and colleagues randomly assigned ventilated infants to a 15-day replacement therapy of hydrocortisone or placebo within 48 hours of life.<sup>41</sup> Hydrocortisone was given at doses from 1mg/kg/day for 12 days, then 0.5mg/kg/day for 3 days. The study revealed no overall improvement in survival without BPD for hydrocortisone treated infants; however, treated infants exposed to chorioamnionitis had significantly increased survival and survival without BPD. The trial was terminated early because of increased intestinal perforations in the hydrocortisone-treated infants who also received indomethacin. Peltoniemi et al. conducted a 3-center study involving<sup>53</sup> premature infants with respiratory failure. Hydrocortisone was started before 36 hours of age and given for 10 days at doses 0.75-2.0mg /kg/day. The risk of PDA was decreased in the treated group. In infants with cortisol values below the median, hydrocortisone treatment increased survival without BPD. The hydrocortisone-treated infants with serum cortisol concentra-

tions above the median had a high risk of gastrointestinal perforation, especially if they also received indomethacin/ibuprofen treatment.<sup>26</sup>

### Inhaled steroid

In an effort to avoid the side effects of systemic steroids, the efficacy of aerosolized corticosteroid has been studied. The early postnatal administration of inhaled steroid to prevent BPD was studied in a large randomized, multicenter trial.<sup>35</sup> In this study, 253 infants with a gestation age of <33 weeks, a birth weight of <1250g, and who were mechanically ventilated at 3 to 14 days of age, were randomly assigned to inhaled beclomethasone or a placebo for four weeks. The need for supplemental oxygen was similar in the beclomethasone and placebo groups at 28 days of life and 36 weeks postmenstrual age. In this study, beclomethasone therapy did not prevent BPD, however, it significantly reduced the use of systemic glucocorticoid therapy and mechanical ventilation at 28 days of age.

In a small study, fluticasone propionate inhalation was given for 3 weeks to premature infants (less than 32 weeks) with moderate BPD (required fraction of inspired oxygen >0.25 or mechanical ventilation) at 28-60 days. There was no difference between infants treated with inhaled fluticasone vs. placebo in the duration of oxygen therapy or ventilatory support.<sup>33</sup>

Several studies compared the effects of inhaled steroid versus intravenous dexamethasone therapy. Groneck et al. compared the effects of daily inhaled beclomethasone starting on day 3 and for 12 days, with those of IV dexamethasone between 11-13 days of life.<sup>42</sup> Levels of IL-8, elastase  $\alpha$  proteinase inhibitor, free elastase activity and albumin in tracheal aspirates were measured on day 10 and 14 of life. In contrast to systemic dexamethasone treatment, a 12 days course of inhaled beclomethasone did not affect lung inflammation and pulmonary permeability.

Recent Cochrane Review by Shah included 3 studies<sup>43, 44, 45</sup> comparing inhaled vs. systemic steroids administered to ventilator-dependent preterm infants of <32 weeks after two weeks of age for the treatment of evolving CLD. There were no statistically significant differences between groups in either trial for oxygen dependency at 28 days, death by 28 days, or the combined outcome of death or

CLD at 28 days, duration of intubation, or duration of oxygen dependency. The results of this evaluation found no evidence that inhaled steroid provides advantages over systemic steroids in the management of ventilator dependency in preterm infants.

Based on these studies, it remains unclear whether inhaled steroids provide any benefit to infants with BPD. Despite the limited data on the efficacy of inhaled steroids, clinicians continue using inhaled beclomethasone or fluticasone in infants with severe BPD who are ventilator dependent or require supplemental oxygen. Aerosolized drugs may be ineffective in preterm infants as very little drug is delivered to the lung, thereby limiting its effects.

A recent study by Yeh et al.<sup>36</sup> demonstrated that intratracheal instillation of budesonide using surfactant as a vehicle significantly decreased the combined outcome of death and CLD without apparent immediate and long-term adverse effects. Budesonide is a strong topical anti-inflammatory GC. It can be effectively delivered to the lungs and remain in the lungs for sometime after intratracheal instillation. Once absorbed, it can be rapidly metabolized to metabolites of low GC effect. However, before this regimen can be recommended, a large sample trial is needed.

### Neurodevelopmental Outcome After Postnatal Steroid Therapy

Preterm infants with BPD are at increased risk of neurodevelopmental impairment. Multiple factors including episodes of hypoxia, poor growth, infection and postnatal steroids may contribute to this. Follow-up studies of infants exposed to postnatal steroids have raised concerns that postnatal steroids contribute to adverse long-term effects, especially cerebral palsy. Interpretation of the follow-up studies is difficult due to differences in the severity of CLD, sample size, the dose and timing of corticosteroids and the exposure of control group to open-label corticosteroids.

Yeh and colleagues<sup>24</sup> evaluated 146 of 159 survivors who were enrolled in a randomized multicenter trial of early postnatal at school age. In comparison with the control group, the dexamethasone-treated group had significantly high incidence of neuromotor dysfunction; they also had shorter stature, smaller head circumference, poorer motor skills, motor coordination, and visual-motor integration, lower full IQ, verbal IQ and performance IQ.

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O'Shea and colleagues<sup>46</sup> evaluated 95 survivors at 4 to 11 yrs age who were randomly assigned at 15 to 25 days of life to a 42-day tapering course of dexamethasone or placebo. The rates of major neurodevelopmental impairments were 40% for the dexamethasone group and 20% for the placebo group. The higher impairment rate for the dexamethasone group was mainly attributed to a higher prevalence of cerebral palsy. Rates of the composite outcome of death or major neurodevelopmental impairment were 47% and 41%, respectively.

On the other hand, outcome at 2 years of age of infants from the DART study indicated that the low-dose dexamethasone (starting at 0.15mg/kg/day and tapering in 10 days) after the first week of life was not associated with increased risk of CP or the combined outcomes of death or CP.<sup>38</sup> However, this study's results should be interpreted with caution due to early closure of the trial and lower than expected sample size. The neurodevelopmental follow-up results at 7 years for children from the OSECT study also showed no differences among the groups, but many of the enrolled infants did not finish the full course of treatment or received open-label dexamethasone therapy.<sup>47</sup>

Meta-analysis<sup>48</sup> of 20 studies with data on 1721 randomized infants evaluated the relationship between the GC effect on the combined outcome, death or CP, and the risk for CLD. Early group received GCS starting first week and late group received GCS after the first week. Overall, cerebral palsy was more likely to occur in infants who received GC therapy than control infants (15.2% vs. 10.3%). Corticosteroid treatment increased death or CP among infants with low risk (<35%) of CLD, whereas, it decreased death or CP among infants with higher risk (>65%) for CLD.

Follow-up studies of infants exposed to hydrocortisone suggests that hydrocortisone may be associated with a less adverse neurodevelopmental outcome. In a randomized, multicenter trial of early low-dose hydrocortisone vs. placebo to treat adrenal insufficiency in mechanically ventilated ELBW infants, the neurodevelopmental outcome was assessed at 18 to 22 months.<sup>49</sup> There were no differences in the rates of CP, or neurologic impairment. However, in this study, hydrocortisone was used mainly for adrenal insufficiency not for BPD.

## Current Practice

Striking evidence from multiple studies of the adverse effects of dexamethasone and its long-term neurological effects on preterm infants prompted the American Academy of Pediatrics and the Canadian Pediatric Society to strongly discourage the use of corticosteroids to prevent or treat BPD in 2002.<sup>3</sup> The following were the recommendations:

1. On the basis of limited short-term benefits, the absence of long-term benefits, and the number of serious short- and long-term complications, the routine use of systemic dexamethasone for the prevention or treatment of CLD in infants with VLBW is not recommended.
2. Postnatal use of systemic dexamethasone for the prevention or treatment of CLD should be limited to carefully designed randomized double-masked controlled trials. The primary outcome of those trials should be survival without long-term developmental impairments, and the potential confounders of contamination and crossover should be avoided.
3. Long-term neurodevelopment assessment of infants who are or have been subjects in trials of dexamethasone to prevent or treat CLD is strongly encouraged.
4. Clinical trials investigating the use of alternative anti-inflammatory corticosteroids, systemic and inhaled, are required before additional recommendations can be made.
5. Outside the context of randomized, controlled trial, the use of corticosteroids should be limited to exceptional clinical circumstances (e.g. an infant on maximal ventilatory and oxygen support). In those circumstances, parents should be fully informed about the known short- and long-term risks and agree to treatment.

Since the release of this consensus statement, the use of corticosteroids has decreased.<sup>50</sup> There was a concern that the decreased use of postnatal steroid might increase the risk of BPD. In a recent study, Shinwell et al.<sup>51</sup> in Israel found that decreased use of postnatal steroids was associated with a significant increase in the rate of BPD.

The decline in use of dexamethasone after the consensus statement was associated with a concomitant increase in the use hydrocortisone. However, the use of hydrocortisone did

not have any impact on the rate and severity of BPD.<sup>52</sup>

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***“In summary, postnatal corticosteroids continue to be a controversial form of therapy for preterm infants at risk of BPD due to the adverse neurodevelopmental outcome. Routine use to prevent or treat BPD is not recommended.”***

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Our recent survey<sup>4</sup> (2006) on the current opinions of neonatologists in the USA revealed that clinicians continue to use steroids because they are effective in the management of premature infants. We found that 66% of neonatologists used steroids for intractable respiratory failure, and 41% used steroids for infants requiring high ventilatory support. The duration of use was less than a week; and the dosage was smaller.

## Summary

In summary, postnatal corticosteroids continue to be a controversial form of therapy for preterm infants at risk of BPD due to the adverse neurodevelopmental outcome. Routine use to prevent or treat BPD is not recommended. It remains unclear whether a short course of postnatal corticosteroids therapy is beneficial to a subgroup of low birth weight infants who are in intractable respiratory failure and for whom the advantages of steroids may outweigh the risk. Well-designed, randomized controlled trials are needed to find the target population with the greatest benefit/risk ratio, the appropriate form of glucocorticoid, the optimal drug regimen with provisions to evaluate short-term and long-term outcome. Until such data is available, we do not recommend treating infants with BPD with postnatal glucocorticoids outside of a clinical trial. We have to follow the AAP guidelines, limiting the use of corticosteroids to a low dose, short course in infants with severe BPD



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and refractory respiratory failure, and informing the infant's family.

### Acknowledgement

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

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# Bisphenol A in the Neonatal Intensive Care Unit: Exposure and Biological Effects

By Rebecca Roberts, PhD

Bisphenol A (BPA) is an environmental estrogen that is pervasive in our society. A survey by the Centers for Disease Control found that approximately 93% of Americans (age 6 and older) have detectable levels of BPA in their urine, with children displaying the highest levels. Unfortunately, the biological effects of BPA in fetuses and neonates are unclear given the lack of research on these populations. Indeed, the vast majority of studies on the effect of BPA on fetal development as a result of in utero exposure have been carried out in animals. The compound, however, has been found in the bloodstream, placenta, cord blood, and fetal blood of humans at levels that are within the range studied in many of the animal models. Moreover, it can be transmitted into colostrum and breast milk.

BPA is used in the manufacture of polycarbonate, epoxy, and polyesterstyrene resins widely used in food-contact plastics (baby bottles, water bottles, etc.), can linings, and some medical devices (for example, oxygen hoods, dialysis machines, and blood oxygenators). Furthermore, it is found in some polyvinyl chloride (PVC) plastics that can then be used in medical settings, including the neonatal intensive care unit. PVC-containing devices in the NICU may include those associated with feeding such as nasogastric and enteral feeding tubes and intravenous fluid bags, as well as respiratory masks, umbilical catheters, and endotracheal tubes.<sup>1</sup>

BPA exposure affects estrogen signaling in the hormonal system by acting through the estrogen receptor. Many animal studies focus on the effect of BPA exposure during fetal development, when cells and tissues are especially susceptible to hormonal alterations. Not only does BPA disrupt proper functioning of the placenta during gestation, but it also causes many deleterious health effects in offspring exposed in utero, including enlarged prostates, malformed urethra, and a higher risk of prostate cancer in male offspring, as well as genital tract alterations and earlier puberty in female offspring. Exposure also affects brain development, causing behavioral differences between males and females to be diminished in offspring exposed in the uterus.

In 2008 the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (NTP/CERHR) published a Monograph reviewing the current scientific literature (both animal and human studies) and panel findings on BPA.<sup>2</sup> Their focus was on the potential human reproductive and developmental effects of BPA exposure. The NTP/CERHR panel applied a five-level scale of concern ("negligible," "minimal," "some," "concern," and

"serious concern") in order to rate the exposure risk of BPA for various populations. They expressed "some" or "minimal" concern that fetal exposure causes neural, behavioral, and prostate problems, as well as accelerations in puberty. They stated "negligible" concern that BPA would cause birth defects or malformations and, when considering infants and children, "some" concern that neural and behavioral effects may occur and "minimal" concern for accelerations in puberty. For adult populations, only those subgroups exposed to higher levels of BPA, for example through occupational exposure, were highlighted as having "minimal" risk for adverse reproductive effects. Overall, the panel concluded that "the possibility that human development may be altered by bisphenol A at current exposure levels cannot be dismissed."<sup>2</sup>

Given the higher level of concern for fetuses and infants, the fact that children have higher measurable levels of BPA in their systems, that the biological processes involved in their ongoing development are vulnerable to disruption by BPA, and that their ability to metabolically detoxify such contaminants is not yet mature, it is imperative that NICU practitioners be aware of possible BPA exposure of the patients under their care.

To-date, there is only one study investigating the levels of BPA in premature infants. The study by Calafat et al. evaluated the levels of BPA in the urine of premature infants who were housed at two different NICUs in the Boston area for a minimum of three days.<sup>1</sup> The samples were initially taken as part of a study on the effect of exposure to PVC devices containing di(2-ethylhexyl)phthalate (DEHP) in NICUs.<sup>3</sup> For that reason, infants were categorized into low, medium, or high exposure groups according to the intensity of procedures requiring DEHP-containing products that they received. The low-exposure group were those infants that were bottle and/or gavage fed. Medium-exposure infants received CPAP and/or enteral feedings by indwelling gavage tubes and/or intravenous hyperalimentation by indwelling percutaneous intravenous central catheter line, broviac or umbilical catheter. More invasive procedures leading to placement in the high-exposure group included continuous indwelling umbilical vein catheterization, endotracheal intubation, intravenous hyperalimentation, and placement of an indwelling gavage tube. BPA levels were obtained from urine samples.

A positive correlation was found between the exposure level and urine BPA concentrations. Infants in the high-exposure group showed greater than 8-fold higher levels of BPA in their urine compared to the low-exposure group. Interestingly, there was no correlation between BPA levels and time spent in the NICU; however, infants born at 25-27 weeks showed con-

centrations about a magnitude higher than those born at 28-34 weeks gestation.

BPA concentrations in similar exposure groups varied significantly between the institutions studied. Although there is no proof given in the study that this was the route of exposure, those infants in the NICU that more frequently used unsiliconized PVC indwelling endotracheal tubes and a PVC indwelling hemodynamic monitoring UVC for parenteral nutrition had BPA levels that were 16.6 times higher than infants at the other NICU site where these devices were seldom used.<sup>3</sup>

On average, the infants displayed BPA levels that were a magnitude higher than older children in the general population, meaning that these infants have the highest BPA levels of any population.<sup>1,2</sup> Considering that the developmental processes that premature infants are undergoing are those that are most likely to be disrupted by BPA, such exposure levels may result in detrimental health effects.

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# Medical News, Products and Information

## Seizures During Pregnancy Associated with Risk of Preterm and Small Babies

Women with epilepsy who have seizures during pregnancy appear more likely to give birth to pre-term, small or low-birth-weight babies than women without epilepsy, according to a report in the August issue of *Archives of Neurology*, one of the JAMA/Archives journals.

An estimated 0.2%-0.7% of pregnant women have epilepsy, the most common major neurologic complication in pregnancy, according to background information in the article. "While approximately 40% of the 18 million women with epilepsy in the world are of childbearing age, managing maternal epilepsy and monitoring the health of the developing fetus remain some of the most perplexing and engaging issues in the fields of neurology and obstetrics," the authors write.

Yi-Hua Chen, PhD, of Tai Pei Medical University, Taiwan, and colleagues used data from the Taiwan National Health Insurance Research Data set and analyzed records from 1,016 women with epilepsy who gave birth between 2001 and 2003. Of these, 503 had seizures during pregnancy and 513 did not. A control group of 8,128 women who were the same age and gave birth during the same years, but did not have epilepsy or any other chronic disease, were selected for comparison.

Compared to women without epilepsy, women who had seizures during pregnancy had a 1.36-fold greater risk of having a low-birth-weight baby (weighing less than 2,500 grams), a 1.63-fold increased risk of giving birth preterm (before 37 weeks) and a 1.37-fold increased risk of having a baby who was small for gestational age (having a birth weight below the 10th percentile for age). In addition, when compared with women who had epilepsy but did not have seizures, the odds of women who had seizures during pregnancy having a baby who was small for gestational age were 1.34 times greater.

Some previous studies had reported a link between adverse pregnancy outcomes and mothers' epilepsy, but others found no association, the authors note. "Our study further illuminates these conflicting data to suggest that it is the seizures themselves that seem to contribute greatly to the increased risk of infants being delivered preterm, of low birth weight and small for gestational age. For women who remained seizure-free throughout pregnancy, null or mild risk was identified compared with unaffected women."

Several mechanisms might explain the association between seizures and adverse pregnancy outcomes. Trauma caused by a

woman's seizures could rupture fetal membranes, increasing risk of infection and early delivery. Tension and acute injury may result from contractions in the uterus that occur during seizures. However, additional research is needed to understand how seizures interfere with fetal development.

"Neonates born pre-term, of low birth weight and small for gestational age, may be predisposed to diseases during infancy and later life, highlighting the significance of proper intervention strategies for prevention," the authors write. These could include helping women control seizures for a period of time before pregnancy, assisting them in sleeping better, providing education about the risks of seizures while pregnant and teaching improved strategies for coping with stress.

## Maternal Immunity Not All Good for a Fetus

As a fetus does not mount an immune response to maternal proteins that cross the placenta, it has been assumed that a fetus would not reject non-genetically matched blood cells (specifically allogeneic blood cells) if they were transplanted while the fetus was in utero. The hope is that this procedure, which is known as IUHCT, could provide a viable approach for treating congenital blood disorders. However, studies using a mouse model of IUHCT indicate that most fetal recipients of allogeneic blood cells lose their transplanted cells 3-5 weeks after transplantation. Alan Flake and colleagues, at Children's Hospital of Philadelphia, have now identified an immune mechanism responsible for graft failure in this model of IUHCT. Surprisingly, although fetal immune cells eliminated the transplanted allogeneic blood cells, they were triggered to do so by immune molecules known as alloantibodies that they obtained from their mother's breast milk. The maternal alloantibodies were produced in response to IUHCT and so the authors conclude that in the absence of either a maternal immune response or transmission of the maternal alloantibodies to the fetus, transplanted blood cells should not be rejected, leaving open the door for IUHCT as a potential clinical strategy.

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ISSN: 1932-7129 (print); 1932-7137 (online).  
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