

# eNeonatal Review

Jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing

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## NOVEMBER 2005 VOLUME 3, NUMBER 3

### In this issue...

We focus on the use of PNCS — systemic postnatal corticosteroids — and their effects on brain development and neurological outcomes in children born prematurely. The clinical dilemma of "whether, when, and in whom" to use corticosteroids is immediately followed by questions of "which corticosteroid, what dosage and duration". What are the risks, benefits, and tradeoffs of prescribing PNCS when a premature infant requires increasing, prolonged respiratory support?

Fortunately, corticosteroid effect on the immature brain and neuroendocrine system is an active focus of basic, translational, and clinical research, with recent reports offering new insights and lessons from past studies, and with long-term follow-up data providing new information regarding hydrocortisone effect on neurostructure and neurofunction.

In the final analysis, however, advice from the 12<sup>th</sup> century philosopher-physician-scientist, Moses B. Maimonides, is particularly relevant to the postnatal corticosteroid dilemma of today:

"Teach thy tongue to say I do not know, and thou shalt progress."

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**Edward E. Lawson, M.D.**  
Professor

Department of Pediatrics Neonatology  
The Johns Hopkins University  
School of Medicine

**Lawrence M. Noguee, M.D.**  
Associate Professor

Department of Pediatrics Neonatology  
The Johns Hopkins University  
School of Medicine

**Christoph U. Lehmann, M.D.**  
Assistant Professor

Department of Pediatrics,  
Health Information  
Science and Dermatology  
The Johns Hopkins University  
School of Medicine

**Mary Terhaar, RN**  
Assistant Professor

Undergraduate Instruction,  
The Johns Hopkins University  
School of Nursing

**Robert J. Kopic, MSN, RRT, FAARC**  
Director of Clinical Programs

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### This Issue

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### Guest Editor of the Month



Commentary & Reviews:  
**Cynthia H. Cole, MD, MPH**

Director of Research  
Department of Neonatology  
Beth Israel Deaconess

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#### Learning Objectives

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CE activity.

#### At the conclusion of this activity, participants should be able to:

- Summarize findings that suggest postnatal corticosteroid (PNCS) effect on neurological and developmental outcomes may be influenced by the type of corticosteroid, timing (onset) of therapy, and underlying risk for bronchopulmonary dysplasia (BPD).
- Consider whether the new information presented herein should be incorporated into clinical practice prior to availability of reliable evidence. And, if so, how may it be incorporated.
- Understand the consequences of uncritical acceptance of PNCS therapy and the importance of scientific uncertainty.
- Understand the key lessons taught by constraints of past PNCS trials regarding trial requirements to obtain reliable evidence.

#### Length of Activity

1.0 hours

#### Expiration Date

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#### Next Issue

December 15, 2005

## Commentary

Follow-up studies and meta-analyses of systemic postnatal corticosteroid (PNCS) therapy for bronchopulmonary dysplasia (BPD) indicate that PNCS therapy is associated with neurological impairment.<sup>1-4</sup> These reports jolted prescriptive enthusiasm for PNCS and prompted recommendations to not routinely use PNCS to treat BPD.<sup>5</sup> However, if PNCS offers a net benefit to a subset of infants with progressive pulmonary disease, it is rational to identify criteria that maximize outcome and minimize harm.

Doyle's weighted meta-regression of PNCS trials (primarily dexamethasone) revealed a higher rate of cerebral palsy (CP) after PNCS exposure. Also, PNCS effect on death or CP was inversely modified by risk for BPD. Improved prediction of BPD may target PNCS therapy in infants more likely to benefit.

Jones and Gross report outcomes of preterm-born teenagers randomly assigned to dexamethasone or placebo when  $\geq 2$  weeks of age. Similar to the trials reported by Doyle, neither the Jones or Gross studies were designed to assess long-term outcome. Thus, there was inadequate power to detect differences between groups. Jones' Collaborative Trial suggested a trend toward increased CP in the dexamethasone group, and, appropriately, discusses consequences of inadequately powered, placebo-contaminated, randomized trials with insufficient follow-up. Gross' trial, despite its small size and the limitations noted above, avoided open-labeled steroid contamination and provided 100% follow-up of survivors. The "42-day dexamethasone" teenagers had a consistent trend toward better neurodevelopmental outcome than 18-day dexamethasone or placebo groups. Gross cautiously speculates on explanations for the favorable trend in the 42-day dexamethasone group.

Lodygensky et al's longitudinal study of 8-year-old, preterm-born children treated and not treated with hydrocortisone therapy for BPD revealed no detectable adverse effects of hydrocortisone therapy on neurostructure and neurofunction. This and other studies<sup>6-12</sup> suggest that hydrocortisone may be less

neurotoxic relative to dexamethasone. Lodygensky, Gross, Jones, and Doyle also speculate, based on their studies, whether later initiation of PNCS is associated with fewer neurosequelae. If Lodygensky's findings prove true, then one may question whether this lack of detectable neuroimpairment is related to hydrocortisone therapy, later onset, or both.

In addition to their scientific contributions, the investigators of each report reinforce three lessons learned from William A. Silverman and others:

1. **Uncritical, enthusiastic acceptance of a therapy** before we have reliable evidence of safety and efficacy often leads to dire consequences. It may destroy the opportunity to obtain reliable evidence of an intervention's risks, benefits, and tradeoffs.
2. **Scientific uncertainty is important.** Acknowledging uncertainty facilitates learning a therapy's full effect on multiple, often competing, outcomes.
3. **Education** of colleagues, staff, parents, research committees, governments, general public, and institutions sponsoring neonatal research is key to progress.

The reports reviewed herein are part of the humbling progress of unraveling "whether, when, and in whom" to use "which corticosteroid, at what dosage for how long". Notwithstanding their limitations, these studies provide further evidence that corticosteroid type (e.g. dexamethasone, hydrocortisone), timing (onset) of therapy, and underlying BPD risk may influence PNCS' effect on the brain.

Further research is obviously needed to increase our knowledge-base and our ability to provide better patient care. Key areas of exploration should include:

1. Prioritizing strategies to reduce neonatal lung injury throughout the neonatal course, and thus, reduce the need for PNCS therapy.
2. Developing and validating models that can predict BPD risk based on factors during first the 14 days of age, prior to initiating a randomized, double-masked, placebo-controlled, clinical trial of hydrocortisone therapy for reduction of BPD. Such a trial may include later onset ( $\geq 10$  days of age) of hydrocortisone therapy in preterm infants who, at 10 -14 days of age, have a high predicted risk ( $>60\%$ ) of subsequent BPD.
3. Developing dose-response studies and randomized clinical trials of hydrofluoroalkane (HFA) formulations of inhaled glucocorticoid therapy (e.g. HFA-beclomethasone [QVAR, 3M] or new designer inhaled glucocorticoids.)

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## PNCS & CEREBRAL PALSY - A RETROSPECTIVE ANALYSIS

**Doyle LW, Halliday HL, Ehrenkranz RA, Davis PG, Sinclair JC.**

Impact of Postnatal Systemic Corticosteroids on Mortality and Cerebral Palsy in Preterm Infants: Effect Modification by Risk for Chronic Lung Disease. Pediatrics 2005; 115: 655-661.

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Doyle et al tested the hypothesis that the treatment effect of PNCS on "survival free of CP" preterm infants was less favorable in trials conducted in populations at low risk for BPD and more favorable in trials conducted in populations at high risk for BPD. Specific objectives included determining the effect of PNCS on cerebral palsy (CP) and death, the effect of study design characteristics on CP and death, and whether PNCS effect on death &/or CP was modified by the infant's risk for BPD. To this end, the literature was systematically searched for randomized, controlled, clinical trials of PNCS therapy that reported rates of both mortality and CP. Doyle et al reviewed and synthesized data from 20 eligible trials (n=1721 subjects). The relationships between PNCS effect on combined outcome "death and CP" and the risk for BPD were analyzed by weighted meta-regression.

The investigators found that PNCS had no detectable effect on death or "death and CP" through analysis of all trials and of trials with early (< 7 days) and later (≥ 7 days) treatment onset. PNCS was associated with higher rate of CP (expressed as Typical Risk Difference; 95% Confidence Interval) when analyzed by all trials (5%; 2% - 8%) and by early-onset PNCS trials: (6%; 2%-10%), but not by later-onset trials (2%; -2% to +7%). Detection of PNCS effect on death and/or CP was increasingly compromised by the rate of contamination of steroid use in the control groups. There was a negative relationship between PNCS effect on death or CP and the risk for BPD in the control groups. The lower the risk for BPD, the greater the PNCS effect on death or CP. If BPD risk was <35%, PNCS therapy was associated with increased risk of death or CP. If risk of BPD was >65%, PNCS treatment was associated with reduced the risk of death or CP.

In summary, the three main points of this study are that PNCS is associated with higher rate of CP, that this higher rate was primarily related to trials with early PNCS onset (<7 days age), and that the risk level of BPD inversely modifies the effect of PNCS on CP.

## LONG-TERM OUTCOMES OF MODERATELY EARLY DEXAMETHASONE

**Gross SJ, Anbar RD, Mettelman BB.**

Follow-up at 15 Years of Preterm Infants from a Controlled Trial of Moderately Early Dexamethasone for the Prevention of Chronic Lung Disease. Pediatrics 2005;115:681-687

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Gross et al sought to investigate growth, neurodevelopment, and pulmonary outcomes of adolescents at 15 years of age who had been enrolled in a randomized, double-masked, placebo-controlled trial of dexamethasone (0.5 mg/kg/day initial dose) beginning at 2 weeks of age for prevention of BPD. In the initial trial, thirty-six infants (birth weight  $\leq 1250$  g and gestational age  $\leq 30$  weeks), who were dependent upon assisted ventilation at 2 weeks of age and at high-risk for poor pulmonary outcome, death, and neurodevelopmental morbidity, were randomized to one of three groups: 42-day course of dexamethasone (n=13), 18-day course of dexamethasone (n=12), or saline placebo (n=11). At time of randomization, ventilator rates averaged 36-41, and FiO<sub>2</sub> averaged 50-60%. Twenty-two of 36 participants survived to 15 years (69% of the 42 day course, 67% of the 18 day course, 45% of the control group). Primary outcome was "intact survival" — defined as normal neurological examination, IQ>70, and education in a regular classroom.

The study found that there were no significant differences between groups for growth or neurological abnormalities. Mean (SD) IQ for the 42-day, 18-day, and placebo groups were 85±10, 60±20, and 73±23, respectively. Education in a regular classroom for 42-day, 18-day, and placebo groups were 100%, 50%, and 40%, respectively. Intact survival for the 42-day, 18-day, and placebo groups were 69%, 25%, 18%, respectively. Pulmonary function, as measured by forced expiratory volume in 1 second (FEV<sub>1</sub>) for 42-day versus 18-day groups were 90±16 vs 72±15% respectively.

The findings of this small randomized trial reinforce a consistent story told over 15 years. Despite the fact that the original trial was not powered to detect long-term outcomes, Gross' findings suggest improvement in intact survival and trends toward improved neurodevelopmental outcome in survivors who received the "42-day course of dexamethasone" compared to the 18-day course and control groups. The trial's strengths include no use of open-labeled corticosteroid in the placebo group and 100% follow-up of all survivors at 15 years of age. However, a very large randomized clinical trial would be required to determine if infants at high risk for BPD, death, and adverse neurodevelopmental outcome might obtain "net benefit" with PNCS therapy; such findings await the collective will of the neonatal community to resolve this specific issue.

## LONG-TERM OUTCOMES: AN INTERNATIONAL PERSPECTIVE

### RAK Jones on behalf of the Collaborative Dexamethasone Trial Follow-up Group.

Randomized, Controlled Trial of Dexamethasone in Neonatal Chronic Lung Disease: 13- to 17-Year Follow-up Study: I. Neurologic, Psychological, and Educational Outcomes. *Pediatrics* 2005;116:370-378.

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Jones reported on a follow-up study to determine neurological, educational, and psychological outcomes in adolescents who were randomized in a placebo-controlled trial of postnatal dexamethasone treatment for BPD. In the initial 1984-1989 trial, 287 premature infants who required respiratory support between 2-12 weeks of age were randomly assigned (at median age ~4 to 5 weeks) to a 1-week course of dexamethasone or placebo, with an option for a second course. 195 children from 25 British and Irish study centers were eligible for follow-up. Outcome was assessed in 150 children (gestational age at randomization ~27 weeks), primarily in home visits, between 13 to 17 years of age. Primary outcome was defined as the proportion of children >2SD below the mean for nonverbal reasoning or British Picture Vocabulary Scale Scores. Secondary outcomes included cerebral palsy (CP), sensory and neurosensory impairments, and educational difficulties.

Thirty-five percent of assessed children had moderate to severe disabilities, with no significant differences detectable in primary or secondary outcomes between study groups. There was a trend toward increased CP in the dexamethasone group (RR 1.58, 95% CI 0.81-3.07). Subgroup analysis by centers' use of open-labeled dexamethasone and placebo-group contamination revealed a consistent trend of greater disability (CP and nonverbal reasoning score) in the dexamethasone group in centers with no open-labeled dexamethasone use.

This trial, the largest teenage follow-up of former premature infants, was an international collaborative accomplishment. Investigators were persistent and their approach pragmatic, with information obtained on

77% (150/195) of eligible children between 13 to 17 years of age. Yet in the end, this study failed to provide reliable information about dexamethasone's effect on neuropsychological and educational outcomes, because the sample size enrolled ( $n=287$ ) and followed ( $n=150$ ) had insufficient power to detect meaningful small-to-moderate effects of dexamethasone on clinically important outcomes. In addition, the use of open-labeled steroid further compromised the study's ability to detect any dexamethasone effect on short- and long-term outcomes. Over the past decade, clinical researchers have increasingly learned the importance of both adequate power to detect clinically meaningful differences in major outcomes and the necessity to maximize protocol compliance with no contamination of open-labeled study intervention (e.g. dexamethasone).

## EFFECT ON BRAIN DEVELOPMENT

**Lodygensky GA, Rademaker K, Zimine S, Gex-Fabry M, Liefink AR, Lazeyras F, Groenendaal F, De Fries LS, Huppi PS.**

Structural and functional brain development after hydrocortisone treatment for neonatal chronic lung disease. *Pediatrics* 2005;116:1-7.

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Lodygensky et al report on a trial to determine whether neonatal systemic hydrocortisone therapy for prevention of BPD was associated with different structural and functional brain development compared to brain development in preterm-born infants not treated with hydrocortisone and in healthy term-born infants. Children born at gestational age  $<32$  weeks and /or birth weight  $\leq 1500$  g between March 1991 and March 1993 were enrolled in a long-term follow-up study at Wilhelmina Children's Hospital (Utrecht, Netherlands). During the last 6 months of the study, quantitative, three-dimensional, volumetric MRI analysis was added to the protocol. This report focuses on a subset of subjects ( $n=60$ ) who had MRI scans.

Preterm infants who were ventilator dependent with increasing oxygen requirements were treated with hydrocortisone therapy (5 mg/kg/day tapered over 3 weeks), beginning at a median age of 18 days (range 4-43), with a median duration of therapy was 26 days (range 22-171). The healthy term-born children were included as a comparison group. All study children were evaluated at 8 years of age with MRI and neuropsychological assessments (Wechsler Intelligence scales for children Revised, WISC-R). Measurements of tissue volumes of cerebral grey matter, white matter, cerebrospinal fluid, and hippocampus were compared.

"Hydrocortisone-treated, preterm" children ( $n=23$ , gestational age  $28\pm 1.6$  weeks), "no hydrocortisone therapy, preterm" children ( $n=35$ , gestational age  $30.4\pm 1.5$  weeks), and "healthy term" children ( $n=21$ ) were evaluated at mean age of 8 years, 7 months (SD 8.6 months). MRI measures and neurodevelopment assessment of all "preterm" and "term" children revealed the following:

	PRETERM	TERM	
CEREBRAL GRAY MATTER VOLUME	649 $\pm$ 4.4 mL	666 $\pm$ 7.3 mL	P=0.046
TOTAL HIPPOCAMPAL VOLUME	6.1 $\pm$ 0.1mL	6.56 $\pm$ 0.2 mL	P=0.94
WISC-R SCORE	99.4 $\pm$ 12.4 mL	109.6 mL $\pm$ 8.8 mL	P=0.001

In addition, cerebral white matter volume was similar between "preterm" ( $512\pm 3.8$ ) and "term" ( $513\pm 6.2$  mL) children. MRI structural measures of cerebral gray matter volume, total hippocampal volume, white matter, and neurocognitive assessment (WISC-R scores) were similar between both groups of "preterm-born" infants.

Lodygensky's finding that children born preterm have decreased structural (cortical gray matter and hippocampal volume) and functional brain development is supported by other studies<sup>1-5</sup>. The unique contributions of this report lie in the long-term quantitative, volumetric, three-dimensional MRI assessment of

postnatal hydrocortisone treatment on neurostructure (especially hippocampal volume) combined with neurofunctional assessment. The study did not detect adverse effects of hydrocortisone therapy (as used in this preterm-born subgroup) on brain structure or function. The lack of adverse neurostructural and neurofunctional findings in the "hydrocortisone-treated" preterm children (compared to "no hydrocortisone" preterm children) stands in contrast to the impaired neurostructural and neurofunctional findings in other studies<sup>6-7</sup> of preterm-born children treated with dexamethasone for BPD.

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### Ask the Author

Ask a Question about this Newsletter 

We received the following question from one of our subscribers.

 My question involves the potential long-term harmful effects of short period use of oral dexamethasone in preterms with BPD. In our protocol, dosage has been 0.1 to 0.3mg/kg/day, for 3 to 5 days, in children older than 5 weeks with a weight close to discharge (1800-2000g) who are dependent on small amounts of oxygen through hood or nasal cannula, and who did not respond to diuretics.

The short term benefits of this oral dexamethasone approach include sooner home discharge without the need for supplemental oxygen, but we are concerned about long term effects. Your opinion?

**A** Regarding adverse neurological effects of this approach, there is no reliable evidence to answer your question. My opinion: I would not recommend using low-dose, short-course DXM in the clinical setting you describe because I have concerns about the potential risks outweighing the potential benefits.

I avoid the use of dexamethasone (DXM) based on evidence of neurotoxicity reported even with short courses of DXM. Two studies by Baud reflect brain injury after 2-3 days of DXM exposure, although, admittedly, the dose and timing of DXM in these two studies differ from the regimen described above. Baud's retrospective assessment ([Baud et al. Antenatal glucocorticoid treatment and cystic periventricular leukomalacia in very premature infants N Engl J Med 1999;341:1190-6](#)) of

the effect of antenatal steroid exposure on neonatal cystic PVL found increased cystic PVL in infants whose mothers received DXM (6 mg x 4 doses): 11% compared to betamethasone (4.4%) or control (8.4%). After controlling for GA, mode of delivery, chorioamnionitis, and >24 hours ruptured membranes before delivery, the odds of cystic PVL was lowest in infants exposed to betamethasone compared to DXM or control. Comparison of infants exposed to DXM vs. control revealed a trend toward increased cystic PVL in the DXM exposed infants (OR 1.5, 95%CI 0.8 to 2.9).

Further, Baud's evaluation of the impact of DXM therapy on neuronal differentiation in mouse pups aged 3 and 4 postnatal days ([Baud et al. Injectable dexamethasone administration enhances cortical GABAergic neuronal differentiation in a novel model of postnatal steroid therapy in mice. Pediatr Res. 2005 Jan;57\(1\):149-56](#)) revealed DXM (1 mg/kg x 5 doses) was associated with a 20-30% reduction in body and brain weight and in cortical thickness on postnatal days 5 and 10. The data suggest that apoptotic neuronal loss in the cortical plate occurred after injectable DXM treatment and involved nonGABAergic neurons.

In deciding who to treat, when, with which glucocorticoid, at what dose, and for how long, I consider the severity of the infant's pulmonary status and level of respiratory support required, the infant's respiratory course, nutritional intake, feeding ability, and growth. For infants who require nasal cannula oxygen or oxyhood, I do not recommend systemic steroid therapy. Some clinicians use inhaled steroid therapy, the discussion of which is beyond the scope of this response. Clinicians may also consider the use of methylprednisolone or hydrocortisone, but again, there are no data regarding net benefit and tradeoffs in outcomes.

Obviously, the paramount need is to maximize the infant's overall clinical status; in the scenario you describe, bronchodilators and diuretics are likely better choices than dexamethasone. I suggest reviewing the choice of diuretic agent, dose, and duration in those babies who did not respond to diuretic therapy to develop a more efficacious diuretic regimen.

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- Summarize findings that suggest postnatal corticosteroid (PNCS) effect on neurological and developmental outcomes may be influenced by the type of corticosteroid, timing (onset) of therapy, and underlying risk for bronchopulmonary dysplasia (BPD).
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- Understand the consequences of uncritical acceptance of PNCS therapy and the importance of scientific uncertainty.
- Understand the key lessons taught by constraints of past PNCS trials regarding trial requirements to obtain reliable evidence.

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- Dr. Noguee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories.
- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.
- Dr. Lehmann has indicated a financial relationship with Eclipsys Corporation.

All other faculty have indicated that they have not received financial support for consultation, research, or evaluation, nor have financial interests relevant to this e-Newsletter.

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