

eNeonatal Review

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

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DECEMBER 2005 VOLUME 3, NUMBER 4

In this issue...

Anemia of prematurity (AOP) occurs commonly in preterm neonates less than 32 weeks gestation and/or birth weight <1500 grams. AOP is a hyporegenerative anemia, due to inadequate endogenous erythropoietin (Epo) production. Other contributing factors may include a shortened life span of fetal red blood cells, and cumulative phlebotomy losses. Symptomatic anemia of prematurity is treated with packed red blood cell (RBC) transfusions. Recombinant erythropoietin (rEpo), approved for use in humans in 1989, offers an alternative to treat or at least attenuate this anemia of prematurity.

In this issue, we review neurodevelopmental outcomes of very low birth weight (VLBW) infants, the effectiveness of a short-course of rEpo during convalescent care, the potential of long-acting erythropoietin therapy in newborns, and the possible neuroprotective relationship of erythropoietin to the neonatal central nervous system.

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This Issue

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- **ASK THE AUTHOR**

Guest Editors of the Month



Commentary & Reviews:
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Director of Neonatology, JHBMC,
Assistant Professor of Pediatrics,

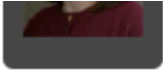
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Reviews:
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Faculty Disclosure

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Guest Faculty Disclosure:

Maureen M. Gilmore, MD

Faculty Disclosure: No relationship with commercial supporters.

Daniel J. Kwak, MD

Faculty Disclosure: No relationship with commercial supporters.

Unlabelled/Unapproved Uses:

The following faculty member have disclosed that their presentation will reference unlabeled/unapproved use of drugs or products.

Maureen M. Gilmore, MD

Has indicated that the presentation includes information on Darbepoetin used for anemia of prematurity.

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 recent findings that recombinant erythropoietin (rEpo) stimulates erythropoiesis in neonates, and recognize that the clinical goal of reduced RBC transfusions for neonates is effected in part by timing, dosage, and route of Epo administration.
- Discuss the important systemic effects of the wide distribution of erythropoietin and erythropoietin receptors in non-hematologic tissues.
- Analyze whether new, long-acting formulations of erythropoietin may have a role in the the neonatal population for treatment of anemia of prematurity.

Commentary

Preterm, very low-birth weight (<1,500g) neonates are at high risk of developing early anemia during the acute phase of their illness, often followed weeks later by an anemia of prematurity (AOP) due to insufficient endogenous erythropoietin production. More than 80% of infants <1,000 gms require treatment with red blood cell (RBC) transfusions. As an alternative to RBC transfusion, recombinant erythropoietin (rEpo) has been studied extensively since it became available for human use in 1989. Multiple randomized, controlled trials of rEpo and iron have confirmed a significant increase in erythropoiesis in Epo-treated infants compared to controls, but with a marked variability in reduction of RBC transfusion requirements. Selected large trial results are represented below:

Author (year)	N	Gest age (wks) (Epo / control)	Epo dose (U/kg /wk)	Timing of Epo Tx	Outcomes (Epo v. controls)
Meyer ¹ (1994)	80	30.4 / 30.1	600	Wk 3 - 8	Higher Hct, retic ^a ; Decr transfusions, 7 v. 21 (p=0.002)
Maier ² (1994)	241	29 / 29	750	Day 3-42	Higher Hct, retic; Decr transfusions, mean 0.87 v. 1.25 (p=0.004); Success rate = no RBCs, Hct>32%, 27.5% v. 4.1% (p=0.008)
Shannon ³ (1995)	157	26.8 / 27.1	500	~Wk 3, for 6 wks	Higher Hct, retic; Decr transfusions, 1.1 v. 1.6 (p=0.046); Decr volume RBC transfused (p=0.023)
Ohls ⁴ (2001)	172	26 / 26	1200	Day 4 - 35 wk PCA	Higher Hct, retic; No difference in transfusions, 84% v. 87% (p=0.56), in # transfusions per infant (p=0.09), or in total volume per infant (p=0.16)
Maier ⁵ (2002)	219	26 (E), 27 (L)/ 27 ^b	750	Early grp: Wk 1, x 9 wks Late grp: Wk 4, x 6 wks	Higher Hct, retic; Success rate = no RBCs, Hct>30%, was 13% (E) v. 11% (L) v. 4%, with p=0.03 for E-Epo v. control; Decr median RBC volume 0.4(E) v. 0.5(L) v. 0.7 (p=0.02)

- a. Significantly higher Hct and retic for Epo-treated group compared to control group in all studies.
- b. Two treatment groups, (E) Early rEpo and (L) Late rEpo, compared to control group.

The articles summarized in this issue confirm and extend the observations from these large trials. Reiter et al. observed that a course of rEpo successfully stimulated erythropoiesis, but did not alter the need for RBC transfusions during convalescence. However, one third of control infants received rEpo after the study period, diminishing the difference between groups, and it is unclear if this regimen would reduce risk of multiple donor RBC exposure. Despite several large Epo trials, there remains no clear consensus for the efficacy of Epo in neonates, and currently its use remains inconsistent between centers. Ohls et al. provide important long-term outcome data for ELBW infants enrolled in the early Epo and iron trial from 2001. In that study, they found no clinically significant differences in growth parameters or in neurodevelopmental impairments between groups. The use of darbepoetin, a long-acting Epo, in preterm neonates was explored in a pilot study by Warwood and Ohls, who observed an erythropoietic response to a single dose of darbepoetin in anemic but otherwise older, healthy preterm infants. Larger studies are needed to evaluate and better define dosage, frequency, age at dosing, and safety considerations before darbepoetin can be recommended for routine clinical use in preterm infants.

Erythropoietin receptors (EpoR) are present on numerous cell types within brain, and Epo activation has resulted in cell-specific effects. Epo has provided neuroprotection in several adult models of brain injury. Demers et al, using a rat model for neonatal hypoxic-ischemic brain injury, offer both anatomical and neurobehavioral evidence that Epo can protect the basal ganglia and dopaminergic neurons, at least to some degree. Some speculate that for ELBW infants, a single dose of darbepoetin with its long half-life, given at

birth, could act as a neuroprotective agent. The potential for neuroprotection in newborns with rEpo therapy is very exciting, yet there are clearly unanswered questions about safety and efficacy to be studied before it becomes widely applied. For example, what impact might rEpo have on apoptosis⁶ within the extremely premature, developing brain?

A different issue to consider with rEpo therapy is the potential for an autoimmune reaction. In 2002, Casadevall⁷ reported 13 cases of red cell aplasia in adults receiving Epo due to development of anti-erythropoietin antibodies. Severe, transfusion-dependent anemia resistant to Epo developed at 3 to 67 months of ongoing treatment. Gershon⁸ at the FDA noted in 2002 that 82 adult cases of red-cell aplasia were reported to Med-Watch over 4.5 years. The FDA noted that 78 of 82 cases involved a rEpo product distributed in Europe, which is a different formulation than rEpo used within the US. The finding that no infants required transfusions after discharge in the Ohls follow-up study, suggests a lack of anti-Epo antibody development up to 22 months corrected age. Also, none of the 1706 adult renal patients treated with at least one dose of darbepoetin developed anti-Epo antibodies. While red-cell aplasia has not been reported to date in any preterm infants treated with Epo, Zipursky⁹ warns that rEpo therapy must be carefully considered and used only when there is strong evidence of its need and effectiveness.

Variability in the success of rEpo-therapy in numerous studies of neonates is related to multiple factors including the wide range of dosage regimens (75 to 1500 Units/kg/week), differences in timing of rEpo with early (age <3 wks) vs. late (>3 wks) administration, inadequate iron supplementation in some studies, and severity of illness of the study population. It seems clear that the major clinical goal for neonates with anemia is to reduce RBC transfusions, so as to minimize multiple donor exposures, infection, and immune risks. Epo alone cannot achieve this goal reliably. Rather, a combination of strategies is best, including reduction of phlebotomy losses, strict adherence to a conservative transfusion protocol, selected use of rEpo with sufficient dosing, and optimizing nutrition to promote growth and hematopoiesis. We need to be prepared to accept lower Hgb/Hct levels in asymptomatic neonates, recognizing that overall growth and stability are more important than any specific Hgb number for an individual infant.

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9. Zipursky A. [The Risk of Hematopoietic Growth Factor Therapy in Newborn Infants.](#) Pediatr Res. 2002;51(5):549.

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NEURODEVELOPMENTAL OUTCOME AFTER EARLY EPO AND IRON

Ohls RK, Ehrenkranz RA, Das A, Dusick AM, Yolton K, Romano E, Delaney-Black V, Papile L, Simon NP, Steichen JJ, Lee KG, for the NICHD Neonatal Research Network.

Neurodevelopmental Outcome and Growth at 18 to 22 Months' Corrected Age in Extremely Low Birth Weight Infants Treated with Early Erythropoietin and Iron. *Pediatrics*. 2004;114(5):1287-1291.

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The NICHD Neonatal Research Network conducted this follow-up to their 2001 trial to test the hypothesis that there would be no difference in neurodevelopmental outcome at 18 to 22 months corrected age between Epo-treated and placebo/control infants. In that initial trial, 172 ELBW infants were enrolled, with the Epo-treated group given 1200 units/kg/wk of Epo plus IV iron, while the placebo/control group received only supplemental iron. Treatment was begun by 96 hours of age and continued through 35 weeks postmenstrual age. Follow-up data were collected for 51 of 72 (71%) surviving Epo-treated infants and 51 of 70 (73%) surviving placebo/control babies.

Among infants evaluated at the 18 to 22 month follow-up, the anthropometric measures and neurodevelopmental outcomes were similar with 2 exceptions. First, the Epo-treated group had a higher rate of Bayley Psychomotor DI (PDI) <70 than did the placebo/control group (31% Epo vs. 13%, $p < 0.05$). Despite this, the mean PDI scores were not different between treatment groups, nor was the incidence of cerebral palsy (19% Epo vs. 18%). Second, more of the placebo/control group had a head circumference (HC) <10th percentile (15% Epo vs. 34%), though there were no significant differences in mean HC, nor in Bayley Mental DI (MDI) <70 (31% Epo vs. 36%). Also, this smaller HC subgroup did not have a higher proportion of infants with PDI <70. The authors state that they believe these differences are likely not clinically significant. Overall, there were no significant differences between groups for the incidences of Bayley MDI score <70 (34% Epo vs. 36%), blindness (0 vs. 2%), deafness (2% each), or presence of any neurodevelopmental impairment (42% vs. 44%). Likewise, the rates of rehospitalization (53% Epo vs. 43%) were similar. All infants had been discharged with "adequate" hematocrits, and there were no differences between groups in number of subsequent transfusions.

Prior to this follow-up, studies of long-term developmental outcomes after Epo therapy had been limited. In this study, the authors evaluated the largest population to date of Epo-treated infants followed for neurodevelopmental and anthropometric outcomes. Overall, the findings confirm that early Epo and iron did not affect neurodevelopment or anthropometric measures at hospital discharge or at 18 to 22 months corrected age. There was already a 30% loss to follow-up for this study, limiting the likelihood of any further follow-up studies from the initial early Epo and iron study cohort.

ERYTHROPOIETIN DURING CONVALESCENT CARE FOR PRETERM INFANTS

Reiter PD, Rosenberg AA, Valuck R, and Novak K.

Effect of Short-Term Erythropoietin Therapy in Anemic Premature Infants. *Jnl of Perinatology*. 2005;25:125-129.

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Reiter et al. conducted a prospective randomized trial in a single center to determine the effectiveness of a 10-day course of rEpo during the convalescent phase of care. They hypothesized that a short course would increase hematocrit (Hct) and reticulocyte count (retic) at the end of 10 days, and would reduce the need for late RBC transfusions in preterm infants. Conservative transfusion guidelines were in place, which for convalescent infants included: Hct <28% with symptomatic anemia (tachycardia, poor growth, or metabolic acidosis), or Hct <20%. There were no significant differences between the 2 groups at baseline, and postconceptional age at study entry was 33.5wks Epo vs. 33.8 wks control. Group A received rEpo at 300 Units/kg/dose s.c. daily for 10 days plus oral iron, while the control group received only supplemental oral iron (no placebo was given). Twelve infants had previously received rEpo for anemia, 7 in group A and 5 in Group B, but none were being treated at enrollment.

Data was analyzed for 57 enrolled infants. As expected, Group A neonates had a significantly higher post-treatment Hct ($p < 0.001$) and retic ($p < 0.05$) than Group B. However, by 40 weeks post-conceptual age and at 6 months of age, these differences had disappeared. Subsequent to the 10-day study period, anemia was treated at the discretion of the clinical team, and 32% of Group B babies did eventually receive rEpo, compared to only 7% of Group A ($p = 0.01$). There were no significant differences in growth, nutritional intake, or bradycardia episodes between groups. This Epo-regimen did not significantly reduce RBC transfusions. After study enrollment, 2 RBC transfusions were required in Group A, while 8 were required in Group B infants, and the volume of blood required did not significantly differ ($p = 0.47$). The additional rEpo given after the study period did produce a 28% risk reduction in need for RBC transfusion for those babies so treated ($p = 0.30$).

With this short 10-day regimen of rEpo, the authors confirm that preterm neonates in the convalescent phase do have a significant erythropoietic response to rEpo. It is disappointing that there was only a trend toward decreased late RBC transfusions, because the clinically relevant issue is prevention of additional donor exposure. The authors speculate that the additional rEpo given to control infants after the 10-day study period pushed the 2 groups toward equality after study treatment. This makes further interpretation of the effectiveness of this Epo regimen on RBC usage difficult. Future trials of similar regimens should consider an extended study period and the possibility of tighter control of rEpo usage.

LONG-ACTING ERYTHROPOIETIN: AN ALTERNATIVE TO STANDARD rEPO?

Ohls RK and Dai A.

Long-Acting Erythropoietin: Clinical Studies and Potential Uses in Neonates. *Clin Perinatol.* 2004;31:77-89.

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Warwood TL, Ohls RK, Wiedmeier SE, Lambert DK, Jones C, Scofield SH, Neeraj G, Veng-Pedersen P, Christensen RD.

Single-Dose Darbepoetin Administration to Anemic Preterm Neonates. *J Perinatol.* 2005;25:725-730.

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Darbepoetin was created from recombinant erythropoietin (rEpo) by modifying five amino acid sites, thereby adding 2 carbohydrate binding sites which confer a longer half-life and greater potency than the original rEpo. In a review article, Ohls and Dai describe an *in vitro* study in which darbepoetin stimulated growth of erythroid colonies derived from progenitor cells from human fetal liver, bone marrow, and cord blood. Currently, there are no guidelines for darbepoetin use in neonates, and no published studies of its safety, efficacy or pharmacokinetics in this population. To address this need, Warwood et al. conducted a prospective pilot study to help guide selection of a dose and dosing interval for darbepoetin.

The immature reticulocyte fraction (IRF) and absolute reticulocyte count (ARC) were measured to assess the erythropoietic effect of 1 vs. 4 mcg/kg of darbepoetin. Serial plasma Epo concentrations were also measured after dosing to assess the half-life ($t_{1/2}$). Twelve neonates were enrolled who had an average BW of 1129 g, gestation of 29.2 weeks, were 43 +/- 12 days old, and had a Hgb of 9.6 +/- 1g/dl at time of study drug dosing. Two groups prospectively received a single dose of darbepoetin subcutaneously (s.c.) at either 1 mcg/kg or 4 mcg/kg, and no adverse events were reported.

Following a single s.c. dose of darbepoetin, both the IRF and ARC increased ($p < 0.05$), indicating release of younger reticulocytes from bone marrow (consistent with stimulation of red cell production). The Epo drug concentration in the 1 mcg/kg group was significantly lower than in the 4 mcg/kg group ($p < 0.002$), and peaked at 6-12 hrs. There was no significant dose dependency for either drug clearance or terminal $t_{1/2}$. A shorter drug half-life (26 hrs) after s.c. dosing in neonates compared to adults (49 hrs) suggests that darbepoetin is released faster from a s.c. injection site in neonates. Increasing the darbepoetin dose from 1 to 4 mcg/kg results in only a small gain in erythropoietic activity.

The requirement of fewer doses of darbepoetin and at a potential lower cost compared to rEpo make the use of this drug attractive for the neonatal population. The Warwood study begins to hone in on the question of

how much drug, and how often, for anemic neonates. Their data suggest that neonates may require higher dosing per kg and a shorter dosing interval as compared to adults. Randomized trials comparing darbepoetin, rEpo and controls are clearly needed to better define these parameters for darbepoetin in neonates, as well as to address concerns of safety and efficacy.

ERYTHROPOIETIN AND THE CENTRAL NERVOUS SYSTEM

Demers EJ, McPherson RJ, and Juul SE.

Erythropoietin Protects Dopaminergic Neurons and Improves Neurobehavioral Outcomes in Juvenile Rats after Neonatal Hypoxia-Ischemia. *Pediatr Res.* 2005;58(2):297-301.

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Demers et al. tested the hypothesis that rEpo would improve neurobehavioral outcomes after neonatal hypoxic-ischemic brain injury. Rat pups at age 7-days, with brain maturity comparable to near-term humans, underwent unilateral common carotid artery ligation and then 90 minutes of hypoxemia. This produced brain injury in multiple areas, and specifically the basal ganglia impacting dopamine (DA) neurotransmission. An additional group of sham animals had a simple surgical incision but no induced brain injury. Rats were then treated with rEpo (2500 units/kg/day s.c.) or placebo. This high-dose of Epo was chosen based upon a prior study indicating therapeutic levels of Epo in CSF of immature non-human primates with intact blood-brain barriers. There were no differences in CBC indices between groups, an indication of safety for this dose in these neonatal animals.

At 4 weeks of age, the rats underwent neurodevelopmental behavioral assessment by 2 tests: a) sensory neglect, a reliable test for unilateral brain injury; and b) DA-agonist induced rotations, i.e. movements. Epo-treated rats had less sensory neglect than placebo-treated rats ($p < 0.0001$), but Epo did not completely prevent this functional deficit. In addition, the placebo-treated animals demonstrated asymmetric rotational movements (indicating a functional DA receptor imbalance), but both the Epo-treated and sham animals were protected. Further, the investigators found no differences between Epo-treated and placebo-treated animals for observed gross brain injury. However, upon immunohistochemical staining of brains, high-dose Epo protected DA neurons in 2 basal ganglia regions compared to placebo-treated animals ($p < 0.01$).

Demers et al provide further evidence to the growing body of literature that supports a neuroprotective role for rEpo in neonatal brains, as studied in animal models thus far. However, as seen in some human adult brain injury studies, these findings offer exciting possibilities for human neonatal brain injury. Yet we must proceed with caution, as the immature brain is markedly different from mature adult brains, and there are numerous effects of Epo on brain development that have yet to be explored.

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LAST MONTH'S Q & A November 2005 - Volume 3 - Issue 3

Last issue we reviewed the use of PNCS (systemic postnatal corticosteroids), their effects on brain development and neurological outcomes in children born prematurely, and the clinical dilemma of prescribing PNCS when a premature infant requires prolonged respiratory support.

**Cynthia H. Cole, MD, MPH**

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We received the following question from one of our subscribers.

Q 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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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 recent findings that recombinant erythropoietin (rEpo) stimulates erythropoiesis in neonates, and recognize that the clinical goal of reduced RBC transfusions for neonates is effected in part by timing, dosage, and route of Epo administration.
- Discuss the important systemic effects of the wide distribution of erythropoietin and erythropoietin receptors in non-hematologic tissues.
- Analyze whether new, long-acting formulations of erythropoietin may have a role in the the neonatal population for treatment of anemia of prematurity.

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- Dr. Nogee 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.

Unlabelled/Unapproved Uses · [back to top](#)

The following faculty members have disclosed that their presentation will reference unlabeled/unapproved use of drugs or products.

Maureen M. Gilmore, MD

Has indicated that the presentation includes information on Darbepoetin used for anemia of prematurity.

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