Postnatal Steroid (PNS) Administration: Rationale

Background:

Postnatal steroid use has been subjected to intense scrutiny in recent years, the subject of several meta-analyses and most recently been the subject of a Statement by the American Academy of Pediatrics' Committee on Fetus and Newborn (COFN) and the Canadian Paediatric Society's Fetus and Newborn Committee. (The entire COFN statement is reproduced in the Reference Section.)

I. Definition and Physiologic Rationale

PNS use refers to the administration of steroids to VLBW infants to prevent and/or treat Chronic Lung Disease (CLD). The rationale for their use is based on their anti-inflammatory actions (Groneck1993). The terms: steroids and corticosteroids are confusingly used as a shorthand for one agent: dexamethasone or to refer to a variety of differing corticosteroid agents. However, almost all of the data, especially as those related to long term benefits and risks, derive from the study of only one specific agent: dexamethasone. Because of the number and variety of studies completed around this topic, reviewers typically separate usage into three categories: 1) within 96 hours post-natal age, 2) between 7-14 days post-natal age, and 3) beyond 3 weeks post-natal age. Additionally, there are other routes and types of steroids used, and as well as varying uses, e.g. to treat hypotension, aid extubation and others that may yet emerge.

II. Benefits

The original Cochrane Reviews of corticosteroids (33/35 studied dexamethasone) for preventing CLD addressed three different times of administration (HALL2002a, HALL2002b, HALL2002c) and found the following short-term outcomes: decreased PDA (< 96 hr), earlier extubation (all time periods), decreased CLD (<96 hr, 7-14 d), decreased mortality (7-14 d), and decreased mortality or CLD (< 96 hr). Banks found that those treated at less than 48 hrs of age with short courses (1-3 days) showed no significant beneficial effect (either death or CLD at 36 wks), while those treated longer beginning at less than 48 hours showed a decreased risk of death or BPD (Banks2002). Stark et al (Stark2001) reported no effect on either death or CLD at 36 weeks PCA. The COFN concluded that "systemic dexamethasone…does not affect mortality by the time of discharge or length of hospitalization." (COFN2002) In conclusion, there are insufficient data to cite PNS uses for reasons other than to prevent or treat CLD.

III. Risks

The initial Cochrane Reviews note gastrointestinal bleeding, intestinal perforation, hyperglycemia, and hypertension, hypertrophic cardiomyopathy, severe retinopathy of prematurity, and increases in long term neurological sequelae occurring with various modalities and timing of postnatal steroid use. Doyle and Davis (Doyle2000) described significantly higher rates of motor dysfunction in a PNS group with no effect on survival. Barrington's review of PNS trials in which there was adequate neurodevelopment follow-up at one year or more showed higher rates of cerebral palsy in the treated groups. (Barrington2001) Banks (Banks 2002) described increased rates of gastro-intestinal perforation. The Vermont-Oxford Network (Soll1999) reported an increased incidence of periventricular leukocmalacia

among infants receiving early dexamethasone therapy (7%) compared with selective late treatment at 14 days (3%). Stark et al (Stark2001) reported an association with gastrointestinal perforation and decreased growth in weight and head circumference at 36 weeks PCA. The COFN Statement also noted these adverse effects. The more recent Cochrane reviews by Halliday et al, (Hall 2003, HL Halliday, RA Ehrenkranz, LW Doyle. Early postnatal (<96 hours) corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database of Systematic Reviews* 2003, Issue 1. Art. No.: CD001146. DOI: 10.1002/14651858.CD001146.,) for the early use of popstnatal steroids reported that while the benefits of PNS previously reported were found, they described the results for the available follow-up of infants enrolled in these trials. For the nine trials which reported such late outcomes, several adverse neurological effects including developmental delay (not defined), cerebral palsy and abnormal neurological exam where notedthere was no significant increase in major neurosensory disabilityeither overall in the 4 studies where this outcome could be determined, or in the 2 individual studies where the rate of cerebral palsy and abnormal neurological exam were significantly increased. There was also no significant increase in the combined outcome of death or major neurosensory disability. The more recent review by Halliday et al (Hall 2009)
which grouped the late use of postnatal steroid as after 7 days of age (Halliday HL, Ehrenkranz RA, Doyle LW. Late (>7 days) postnatal corticosteroids for chronic lung disease in preterm infants. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD001145. DOI: 10.1002/14651858.CD001145.pub2.) noted a trend towards an increase in risk of infection and GI bleeding but not NEC. and an increase in severe ROP (overall and a trend in survivors) but no significant increase in blindness. While there was a trend towards a reduction in severe IVH but only 247 infants were enrolled in five studies reporting this outcome. The findings of a trend of an increase in cerebral palsy or abnormal neurological examination was partially offset by a trend of a decrease. Thus the combined rate of death or cerebral palsy was not significantly different between steroid and control groups. In addition the findings of major neurosensory disability, and the combined rate of death or major neurosensory disability, were not significantly different between steroid and control groups. There were no substantial differences between groups for other outcomes in later childhood, including respiratory health or function, blood pressure, or growth.These authors have concluded that with evidence of both benefits and harms and the limitations of the evidence at present, that the use of late corticosteroids should be limited to infants who cannot be weaned from mechanical ventilation utilizing a minimal dose and duration of such therapy.

Doyle et al (Doyle 2005, 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. 2005 Mar; 115, (3): 655-661.) performed a meta regression analyses on 21 studies with data on 1721 randomized infants. They examined the relationship between the combined outcome, death or CP, and the risk for CLD in control groups for infants who were treated with PNS. They reported that when the risk for CLD was below 35%, corticosteroid treatment significantly increased the chance of death or CP, whereas when the risk for CLD exceeding 65%, it reduced the occurrence of death or CP. This observation has been widely quoted and has been used to justify the continuing use of PNS for infants a high risk of developing BPD.

More recent trials have demonstrated that 10 days of dexamethasone for ELBW infants who were ventilator dependent after the first week of life may facilitate extubation of ELBW infants without short term harm, but also without affecting death or survival with BPD. (Doyle 2006, Doyle, L. W.; Davis, P. G.; Morley, C. J.; McPhee, A., and Carlin, J. B. Low-dose dexamethasone facilitates extubation among

chronically ventilator-dependent infants: a multicenter, international, randomized, controlled trial. Pediatrics. 2006 Jan; 117(1):75-83.

Since these analyses there have been subsequent observations of the effects of PNS on the neurodevelopmental outcomes of ELBW infants. the NICHD Neonatal Research Network documented the outcomes of 2358 ELBW infants from the Benchmarking prospective study (WilsonCostello 2009). Of these , 1667 survived to 18 to 22 months and had a neurodevelopmental assessment. There were 366 infants who survived and were exposed to post natal steroids after 7 days of life, and 72% were judged to ba at high risk for BPD. They reported that PNS exposure was associated with an increased risk of neurodevelopmental impairment or death, and that impairment increased with higher dose; with 71% of infants in the highest dose tertile being dead or impaired.. They noted that each 1 mg/kg dose was associated with a 2.0-point reduction on the Mental Developmental Index and a 40% risk increase for disabling cerebral palsy. Infants treated after 33 weeks' postmenstrual age had the greatest harm while not receiving the highest dose. Increasing BPD risk tended to reduce harm. (WilsonCostello, D.; Walsh, M. C.; Langer, J. C.; Guillet, R.; Laptook, A. R.; Stoll, B. J.; Shankaran, S.; Finer, N. N.; VanMeurs, K. P.; Engle, W. A., and Das, A. Impact of Postnatal Corticosteroid Use on Neurodevelopment at 18 to 22 Months' Adjusted Age: Effects of Dose, Timing, and Risk of Bronchopulmonary Dysplasia in Extremely Low Birth Weight Infants. Pediatrics. 2009; 123(3):e430-e437

With the recognition that there were potential problems with the use of dexamethasone used for the prevention of BPD a number of centers have begun to use less potent corticosteroids. Peltoniemi, et al (Peltoniemi,2009, Peltoniemi O. M.; Lano, A.; Puosi, R.; Yliherva, A.; Bonsante, F.; Kari, M. A., and Hallman, M. Trial of Early Neonatal Hydrocortisone: Two-Year Follow-Up. Neonatology. 2009; 95(3):240-247) reported that their use of hydrocortisone in a randomized trial given for 10 days to ELBW infants did not increase the rate of CP or survival with cognitive impairment. They also analyzed a total of 3 trials and 411 infants and reported the same overall results indicating that hydrocortisone may ne associated with less neurodevelopmental impairment.

Postnatal Corticosteroids for Hypotension

Hypotension occurs in approximately 20% of VLBW infants and may be associated with subsequent brain injury, and its treatment is problematic. Hypotension requiring vasoactive drug treatment occurred in the first 24 hours of life in approximately 40% of the infants enrolled in the PROPHET trial, and up to 33% of the infants of less than 750 gm birth weight in the NEOPAIN study.36 It has been postulated that such hypotension may be a reflection of adrenal insufficiency. As a result, corticosteroids have been used to treat hypotension in such infants and found to be equivalent to dopamine in one prospective randomized trial. These observations have led to an increased use of early post natal steroids to treat such hypotension.

CPQCC prospectively reviewed the use and indications for PNS during 2003 in a cohort of VLBW infants born in hospitals in California participating in the California Perinatal Quality Care Collaborative. (Finer, N. N.; Powers, R. J.; Ou, C. H. S.; Durand, D.; Wirtschafter, D., and Gould, J. B. Prospective evaluation of postnatal steroid administration: A 1-year experience from the california perinatal quality care collaborative. Pediatrics. 2006; 117(3):704-713. We found that PNS for CLD were

administered for CLD to 8.2 % of all VLBW infants in 2003. Of the 1401 VLBW infants in the surveyed hospitals 19.3 % received PNS; 3.6 % received PNS for only CLD, 11.8% for only non-CLD indications, and 4.0 % for both indications. At all birth weight categories, non-CLD use was significantly greater than CLD use. The highest use of PNS was among infants between 500 to 749 gm birth weight, with 8.2% receiving PNS for only CLD, 22.5 % for only non-CLD indications, and 11.1% for both indications. The most common non-CLD indication was hypotension (180 infants 81.4%) followed by extubation stridor for which 36 infants were treated (16.3%). For hypotension medications used were hydrocortisone followed by dexamethasone, (86.4% and 13.1%). Infants treated with PNS exclusively for hypotension had a significantly higher incidence of intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) and death, when compared with infants treated only for CLD, or those who did not receive PNS (IVH, 23.4% vs 8.3% vs 6.9%, PVL, 7% vs 4.2%* vs 2.5%, death, 25.6% vs 6.% vs 13.7% , significant for all but *, P <.025).
While dopamine is the agent most frequently used for the treatment of low blood pressure in the VLBW infant, recent studies by Osborn et al have demonstrated that dopamine may not increase cardiac output. This group has demonstrated that low BP is not equivalent to low cardiac output or low organ blood flow, including brain blood flow. Kluckow and Evans developed a technique to measure of superior vena cava flow using ultrasound Doppler studies and reported that low SVC flow, not BP, was the only independent risk factor for late P/IVH in both cohorts (1995-1996 adjusted OR: 20.39; 1998-1999 adjusted OR: 5.16). In a retrospective review of infants with hypotension unresponsive to volume and dopamine alone or in combination with other agents including dobutamine or epinephrine, Seri et al reported rapid normalization of the cardiovascular status and sustained decreases in volume and pressor requirement with hydrocortisone treatment. Another group reported similar results using a single dose of dexamethasone in hypotensive infants unresponsive to dopamine and epinephrine. It is postulated that steroids exert their effects on dopaminergic receptors as well as through direct cardiac effects. There is reason to believe that dopamine may lead to increased splanchnic vasoconstriction, and thus its use may aggravate any bowel ischemia and possibly increase the occurrence of necrotizing enterocolitis, Volume alone is seldom effective in treating low blood pressure in VLBW infants and a low blood pressure is not predictive of a low blood volume in the preterm infant.22 In addition volume administration may increase left to right ductal shunting and is less effective than dopamine in increasing blood pressure. There is also a recent suggestion that volume administration to preterm hypoxic animals may impair cerebral oxygen delivery.

There is some evidence that circulatory collapse in preterm infants may be a coinsequence of the failure of adequate cortisol synthesis in the face of stress. (Masumoto, K.; Kusuda, S.; Aoyagi, H.; Tamura, Y.; Obonai, T.; Yamasaki, C.; Sakuma, I.; Uchiyama, A.; Nishida, H.; Oda, S.; Fukumura, K.; Tagawa, N., and Kobayashi, Y. Comparison of serum cortisol concentrations in preterm infants with or without late-onset circulatory collapse due to adrenal insufficiency of prematurity. Pediatric Research. 2008; 63(6):686-690)
Bonsante et al (Bonsante, F.; Latorre, G.; Iacobelli, S.; Forziati, V.; Laforgia, N.; Esposito, L., and Mautone, A. Early low-dose hydrocortisone in very preterm infants: A randomized, placebo-controlled trial. Neonatology. 2007; 91(4):217-221) performed a propspecxtive randomized trial on 50 mechanically ventilated preterm infants from 500 to 1249 gm birthweight using either hydrocortisone 0.5 mg/kg/12 h for 9 days, then HC 0.5 mg/kg/24 h for 3 days or placebo. They reported a significant reduction in CLD and mortality in the hydrocortisone group (64 vs. 32%, 16% vs 40%) and noted that hypotension after recruitment was reduced by HC (0 vs. 30%) in the hydrocortisone group.

Efird et al (Efird, M. M.; Heerens, A. T.; Gordon, P. V.; Bose, C. L., and Young, D. A. A randomized-controlled trial of prophylactic hydrocortisone supplementation for the prevention of hypotension in extremely low birth weight infants. J Perinatol. 2005 Feb; 25(2):119-24) studied the early use (3 hours of age continuing for 5 days) use of prophylactic hydrocortisone on 34 ELBW infants. They reported that the only 25% of the hydrocortisone group required vasopressor support compared with 44% of the placebo group at 24 hours of age, and on day 2 only 7% of the hydrocortisone infants were given vasopressors compared to 39% of the placebo group ($p<0.05$).

There is now a current Cochrane Review of the use of corticosteroids for hypotension in preterm infants (Subhedar NV, Duffy K, Ibrahim H. Corticosteroids for treating hypotension in preterm infants. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD003662. DOI: 10.1002/14651858.CD003662.pub3) This analysis including only 2 small trials, with a total of 57 preterm infants, reported in the late 1990s. The authors concluded that there is insufficient evidence to support the routine use of steroids in the treatment of primary or refractory neonatal hypotension. In addition they noted that Hydrocortisone may be as effective as dopamine in treating primary hypotension, but there are no data regarding the long-term safety of steroids used for this indication. They also stated that a single dose of dexamethasone may be effective in treating preterm infants with refractory hypotension receiving epinephrine, but that the lack of data on long-term safety for dexamethasone did not support its routine use in preterm hypotension.

Included Studies in Cochrane Review:

Bourchier D, Weston PJ. Randomised trial of dopamine compared with hydrocortisone for the treatment of hypotensive very low birth weight infants. Archives of Disease in Childhood: Fetal and Neonatal Edition 1997;76:F174-8.

	Gaissmaier RE, Pohlandt F. Single dose dexamethasone treatment of hypotension in preterm infants. Journal of Pediatrics 1999;134:701-5.

IV. PQIP Comment

PNS use both nationally and in California is decreasing: the median and interquartile range in California in 2000 was 14.3% (4.7%-40.8%) and in 2001 was 11.8% (2.1%- 28.1%). Our view, and that of the AAP Committee on the Fetus and Newborn, is that there is inadequate evidence to support the widespread PNS use in very low birth weight neonates. (COFN2002) We recognize the concern that there may be clinical situations in which modifying the infant's inflammatory response might be critical to its pulmonary function and therefore the infant's survival. When PNS use is contemplated, the risks and benefits of PNS use should be discussed with the parents.

We commend the view that infants who have received postnatal steroids should be carefully followed for neurodevelopmental sequellae, in addition to being monitored for the short-term events such as glucose intolerance, hypertension, infection, gastrointestinal bleeding, gastrointestinal perforation and hypertrophic cardiomyopathy.

We caution both practitioners and parents that most of the available PNS use data were developed from studies of dexamethasone that primarily addressed therapeutic thresholds; further studies designed to address long-term outcomes are needed. Risks and benefits have been extrapolated to other steroids, which may or may not be found by further study to be applicable. Better studies are anticipated to aid us in revising this tentative assessment.

V. What to tell parents?

Perinatal Quality Improvement Panel Comments:

We endorse the view that physicians and families should discuss the risks and benefits of postnatal steroid use, especially in view of the lack of trials focused on long-term outcomes in which the placebo arms were not significantly "contaminated" by "off-label" or "rescue" postnatal steroid use. While preliminary calculations of relative risks and benefits have been made, we believe that additional data will be necessary to assign numbers with greater confidence. (See Table below for compilation of currently reported odds.) Ultimately, the way to remove the stimulus for postnatal steroid use depends on reassessing and improving the indications and methods for intubation, ventilation and extubation

a. Banks2002. Banks BA. Postnatal dexamethasone for bronchopulmonary dysplasia: A systematic review and meta-analysis of 20 years of clinical trials. NeoReviews 2002; 3:c24-c34 (Reproduced in full in the Reference Section.)

   Barrington, K.J. Hazards of systemic steroids for ventilator-dependent preterm infants: what would a parent want? CMAJ2001 Jul10: 165(1): 33-4. (Reproduced in full in the Reference Section.)

c. Information for Counseling on the Beneficial and Harmful Effects of Postnatal Steroids: Review of Published Meta-Analyses (see Table #1)

Introduction

We have chosen to highlight available data using the format: number needed to treat and number needed to harm. The number needed to treat (NNT) represents the number of patients treated to avoid one adverse outcome. (It is calculated as follows: NNT = (1- absolute risk reduction)). Similarly, the number needed to harm (NNH) represents the number of patients treated who then develop one adverse outcome. (It is calculated as follows: NNH = (1-absolute risk increase)). *

The various meta-analyses differ in their conclusions (and thus the suggested NNT and NNH numbers) by reason of several factors: 1) differing outcomes studied; 2) differing types of studies included in their analyses; and 3) differing criteria for viewing heterogeneous trials.

Table 1: Information for Counseling on the Beneficial and Harmful Effects of Postnatal Steroids: Review of Published Meta-Analyses

	Banks BA NeoReviews 2002, 3(2) c24	Barrington KJ BMC Pediatrics 2001, 1:1 www.biomedcentral.com/1471-2431/1/1
Sample Selection Notes:	Postnatal dexamethasone studies; 1981-2001; RCTs-double-blinded with sample size N > 40	RCTs of postnatal steroids with neurologic follow-up for >1 yr; studies with later treatment of controls were divided by those with < or > 30% contamination"; only those with <30% reported here
Beneficial Outcomes:		
Mortality	NS**	NS
Death of BPD at 36 wks Postmenstrual Age	Short course (1-3d) started @ < 48 hr PNA- NS	
	Longer course (4 or more d) started @ < 48 hr PNA- **NNT=8.8**	
	Cites three uncombinable studies where PNS started @ > 6 d PNA---------- Brozanski (JPeds 126:769) (3 d pulse q 10 d) **NNT = 3.9** ---------- Kovacs (ActaPaed 87:792) (3 d pulse followed by inhaled steroids)- NS ---------- Kothadia (Pediatric104:22) (42 d course) **NNT = 4.5**	
Patent Ductus Arteriosus	Short course (1-3d) started @ < 48 hr PNA-**NNT= 8.7**	
Adverse Outcomes:		
Gastro-intestinal perforation	Short course (1-3d) started @ < 48 hr PNA-**NNH= 23**	
Cerebral palsy and/or abnormal neuromotor outcome	4 trials combined from early short-course to late, long-course- **NNH=5.5**	Neurodevelopmental impairment- **NNH = 11** Cerebral palsy**- NNH = 7**