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Prospective Evaluation of Postnatal Steroid Administration: A 1-Year Experience From the California Perinatal Quality Care Collaborative

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ABSTRACT

OBJECTIVE. Postnatal steroids (PNSs) are used frequently to prevent or treat chronic lung disease (CLD) in the very low birth weight (VLBW) infant, and their use continues despite concerns regarding an increased incidence of longer-term neurodevelopmental abnormalities in such infants. More recently, there has been a suggestion that corticosteroids may be a useful alternative therapy for hypotension in VLBW infants, but there have been no prospective reports of such use for a current cohort of VLBW infants.

METHODS. The California Perinatal Quality Care Collaborative (CPQCC) requested members to supplement their routine Vermont Oxford Network data collection with additional information on any VLBW infant treated during their hospital course with PNS, for any indication. The indication, actual agent used, total initial daily dose, age at treatment, type of respiratory support, mean airway pressure, fraction of inspired oxygen, and duration of first dosing were recorded.

RESULTS. From April 2002 to March 2003 in California, 22 of the 62 CPQCC hospitals reported supplemental data, if applicable, from a cohort of 1401 VLBW infants (expanded data group [EDG]), representing 33.2% of the VLBW infants registered with the CPQCC during the 12-month period. PNSs for CLD were administered to 8.2% of all VLBW infants in 2003, 8.6% of infants in the 42 hospitals that did not submit supplemental data (routine data-set group, compared with 7.6% in EDG hospitals). Of the 1401 VLBW infants in the EDG, 19.3% received PNSs; 3.6% received PNSs 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 most common non-CLD indication was hypotension, followed by extubation stridor, for which 36 (16.3%) infants were treated. For hypotension, medications used were hydrocortisone followed by dexamethasone. Infants treated with PNSs exclusively for hypotension had a significantly higher incidence of intraventricular hemorrhage, periventricular leukomalacia, and death when compared with infants treated only for CLD or those who did not receive PNSs.

CONCLUSIONS. The common early use of hydrocortisone for hypotension and the high morbidity and mortality in children receiving such treatment has not been recognized previously and prospective trials evaluating the short- and long-term risk/benefit of such treatment are urgently required.

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Key Words

chronic lung disease, hydrocortisone, hypotension, preterm infant

Abbreviations

PNS—postnatal steroid
RDS—respiratory distress syndrome
IVH—intraventricular hemorrhage
CLD—chronic lung disease
ELBW—extremely low birth weight
CPQCC—California Perinatal Quality Care Collaborative
VON—Vermont Oxford Network
VLBW—very low birth weight
IQR—interquartile range
BPD—bronchopulmonary dysplasia
Fio₂—fraction of inspired oxygen
EDG—expanded data group
RDG—routine data group
PVL—periventricular leukomalacia

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THE FIRST STUDIES of postnatal steroid (PNS) use for the preterm infant with respiratory distress were published ~16 years before the initial reports of prenatal steroids. The first study evaluated corticosteroids in 32 infants of diabetic mothers and reported that there was no significant reduction in the incidence and severity of respiratory distress syndrome (RDS).¹ Altman² suggested a benefit for such treatment in infants with moderate to severe distress in 1965, but the first controlled evaluation was performed by Baden et al³ in 1972. This study was a blinded comparison of 12.5 mg/kg of hydrocortisone versus placebo given at admission and 12 hours later in 44 premature infants with RDS and reported no significant benefit to steroid administration. In the same year, Ewerbech and Helwig⁴ reported on the outcome of 10 infants with severe RDS who were treated with prednisolone, of whom 5 died, 3 of whom had autopsies with evidence of massive intraventricular hemorrhage (IVH).

There have been a plethora of studies evaluating the effects of PNSs for the prevention or treatment of chronic lung disease (CLD).^{5,6} Metaanalyses of early (<96 hours of age)⁷ and later use of PNSs to reduce CLD^{8,9} demonstrated significant benefits with regard to earlier extubation and decreased risks of CLD at both 28 days and 36 weeks, death, or CLD at 28 days and 36 weeks, but there was a disturbing tendency toward an increase in neurodevelopmental impairment consistent with previous animal experiments, which had shown that glucocorticoids administered during critical periods of brain development may impair myelination, brain cell division, and longer-term behavioral effects.¹⁰⁻¹⁶ The American Academy of Pediatrics Committee on the Fetus and Newborn cautioned that PNS use outside of randomized trials should be reserved for "exceptional clinical circumstances."¹⁷

The use of PNSs for the prevention or treatment of CLD remains common, especially for the extremely low birth weight infant (ELBW) whose birth weight is <1000 g, and information from the Vermont Oxford Network (VON), of which the California Perinatal Quality Care Collaborative (CPQCC) is a contributing member, indicates that for the year 2001, 38% of ELBW infants (22-65%) received PNSs.¹⁸ In California, the use of PNSs for the very low birth weight (VLBW) infant was 14.3%, with an interquartile range (IQR) of 4.7 to 40.8 in 2000 and 11.8% (2.1% to 28.1%) in 2001.

There is now substantial emerging evidence that PNSs are associated with both increased short-term neonatal complications and long-term adverse effects. At least 2 large prospective trials of PNSs have been terminated because of short-term toxicity, including gastrointestinal hemorrhage and intestinal perforation requiring surgery.^{19,20} Other prospective trials have also reported a high incidence of other adverse effects, including an increase in nosocomial sepsis, meningitis, and hypergly-

cemia^{21,22}; hypertriglyceridemia; increased free fatty acid levels²³; increased protein catabolism and poorer somatic growth²⁴⁻²⁶; and pituitary-adrenal suppression,²⁷ which can last for 1 month after therapy.^{28,29}

None of the published trials evaluating PNSs were powered to evaluate long-term follow-up. A number of reports, many describing follow-up studies of infants enrolled in randomized, controlled trials of PNSs to prevent or ameliorate bronchopulmonary dysplasia (BPD), noted that such use was associated with a significantly increased occurrence of neurodevelopmental impairment, especially if the risk of the development of CLD was <35% in the control infants.³⁰⁻³²

Low blood pressure is frequently seen in the ELBW infant, and it has been postulated that this may be a reflection of adrenal insufficiency. As a result, corticosteroids have been used to treat hypotension in such infants and have been found to be equivalent to dopamine in 1 prospective randomized trial.^{33,34} These observations have led to an increased use of early PNSs to treat such hypotension. To date, there has not been any prospective study evaluating the overall use of corticosteroids, including the treatment of low blood pressure in a population of VLBW infants and the resultant neonatal outcomes. In an effort to further delineate the current indications and use of PNSs in VLBW infants, including the use of early PNSs for the treatment of low blood pressure, we developed a prospective expanded data set for use within the CPQCC for a full calendar year.

METHODS

The CPQCC data set is identical to the VON data set for infants ≤ 1500 g at birth. The CPQCC requested that all of its members submit, for calendar year 2003, a single additional supplemental data form for all infants who received any PNS during their hospital stay (see Appendix). These additional data provided information about the age of the infant in days at the first dose of PNS, its indication, the mean airway pressure and fraction of inspired oxygen (F_{iO_2}), and the type of ventilation for infants treated for CLD, the initial daily dose, and the total duration of steroids given. The cohort of infants from those hospitals voluntarily contributing supplemental data on PNS use constitute the expanded data group (EDG). The cohort of infants from those hospitals choosing not to contribute data constitute the routine data group (RDG). After completion of data collection for 2003, the incidence of the use of PNSs for CLD as reported in the CPQCC data were calculated for the overall population and the infants <1000 g and 750 g at birth. We calculated the number and percentage of infants for whom the supplemental data were submitted. The means, medians, SDs, and IQRs were calculated. Comparisons between cohorts were done with χ^2 or

Student's *t* test as appropriate. A *P* value of $<.05$ was considered significant.

RESULTS

For 2003, 22 of the 62 CPQCC member hospitals submitted supplemental forms for all of their infants treated with PNSs. These hospitals cared for 33.2% of the total 4219 VLBW CPQCC cohort. In the 62 member hospitals, PNSs were administered for CLD to 8.2% of VLBW. The use of PNSs for CLD was 8.6% in the RDG and 7.6% in the EDG ($P = .26$). Other demographic comparisons are shown in Table 1. The only significant differences were a higher percentage of inborn infants and a slightly lower birth weight in the EDG group ($P < .001$ and $P < .05$, respectively). In addition to CLD, the EDG reported that 15.8% of their infants also received PNSs for other indications. Of the 1401 VLBW infants that were cared for in the EDG hospitals, 50 (3.6%) received PNSs for only CLD, 165 (11.8%) for only other indications, and 56 (4.0%) for both CLD and other indications. The birth weight-specific use rates for the administration of PNSs for CLD are shown in Fig 1. In the EDG cohort, PNSs were used most frequently for infants of 500 to 749 g birth weight; 117 (41.8%) of the 280 infants in this weight group were treated with PNSs. Of these 117 infants, 94 (80.3%) received PNSs for non-CLD indications compared with 54 (46.2%) who received PNSs for CLD. Total PNS exposure by indication in the EDG cohort is shown in Fig 2. At every birth weight, the use of PNSs for non-CLD indications exceeded its use for CLD.

In the 221 EDG infants who were treated with PNSs for other indications, the most common non-CLD indication was hypotension ($n = 180$ [81.5%]) followed by "to prevent or treat extubation edema," for which 36 infants (16.3%) were treated. Overall, 12.9% of all infants cared for in the EDG received PNSs for hypotension. Of these 180 infants, 140 (77.8%) received PNSs only for hypotension and 40 (22.2%) for both hypoten-

sion and CLD. Hydrocortisone was the most frequently used preparation (86.4%) followed by dexamethasone (13.1%) for this indication. The first course of PNSs for hypotension was begun at a median age of 2 days (IQR: 1–10 days). Infants received an average of 1.6 courses and were treated for an average of 7.8 days (median: 3; IQR: 2–60).

Dexamethasone was used for 41.5% of EDG infants treated for CLD, followed by inhaled steroids, which were used for 38.7% of such infants. Before their first dose of PNSs for CLD, administered at a median of 34 days (IQR: 23.5–45.5 days), 59 (55.7%) of 106 infants were receiving conventional ventilation, and 41 (38.7%) were receiving high-frequency ventilation, with a median F_{iO_2} of 0.53 and a median mean airway pressure of 10 cm H_2O . There were 2 infants receiving continuous positive airway pressure and 2 on nasal cannula. Twelve (11.3%) of the infants treated with PNSs for CLD had pulmonary interstitial emphysema, 77 (72.6%) were receiving diuretics, and 7 (6.6%) were receiving bronchodilators. The median number of courses was 1 (IQR: 1–2) both for infants treated only for CLD (50) and those treated for both CLD and another indication (56). However, the total days of treatment was longer in infants treated for both CLD and another indication (median: 27 days; IQR: 8–56) than in infants who received PNSs only for CLD (median: 14.5 days; IQR: 5–35). For both groups, the 25% who constituted the upper quartiles were exposed to PNS treatment for >35 days in the CLD-only infants and for >56 days in the dual indication group.

Table 2 shows the treatment profiles by indication and steroid preparation. The longest average exposure to PNSs was 51.8 days, seen in infants treated with inhaled steroids for CLD. The shortest average exposure was 4.1 days, seen in infants treated with hydrocortisone for weaning from the respirator. Infants treated for hypotension with hydrocortisone averaged 9 days, and those treated with dexamethasone averaged 8.4 days of administration (Table 2).

TABLE 1 Demographic Data Comparing Infants in Nonsupplemental Units and the EDG Infants

Variable	EDG	RDG
NICUs	22	40
Inborn, %	83.4 ^a	72.4 ^a
No. of VLBW infants	1401	2818
Mean birth weight	1020 ^b	1040 ^b
Birth weight <1000 g, %	47.2	44.3
Birth weight <750 g, %	23.7	21.9
PNSs, %	7.6	8.6
Oxygen at 36 wk, %	22.6	20.6
With head ultrasound exams, %	88.8	88.8
Grade 3–4 IVH, %	9.6	10.7
PVL, %	3.2	2.2
Mortality per 1000	148.5	147.3

Comparisons are not significant unless noted otherwise.

^a $P < .001$.

^b $P = .04$.

Comparison of Outcomes by Treatment Indication

Table 3 lists outcomes by treatment indications in the RDG and EDG infants. RDG infants who did not receive PNSs had a lower incidence of CLD and lesser rates of severe IVH ($P = .04$). There were only 4 deaths at <14 days among the 242 RDG infants who received PNSs for CLD and no such deaths in the 106 EDG infants treated for CLD. The overall mortality for all of the VLBW infants in the CPQCC for the year was 14.8%. Mortality was 8.7% for the 242 RDG infants who received PNSs for CLD compared with 4.7% among the 106 EDG infants who received PNSs for CLD ($P = .195$). EDG infants treated for only CLD ($n = 50$) had a mortality of 6.0% compared with 29.1% for the 165 EDG infants receiving PNSs only for other indications ($P < .001$). EDG infants

FIGURE 1
PNS use for CLD according to birth weight comparing the CPQCC, EDG, and RDG. □, CPQCC; ■, RDG group; ▨, EDG group.

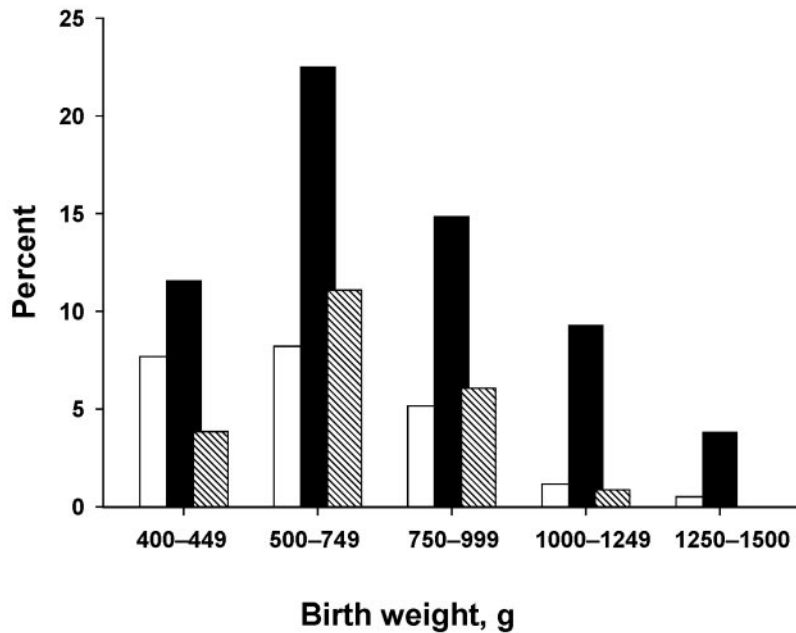
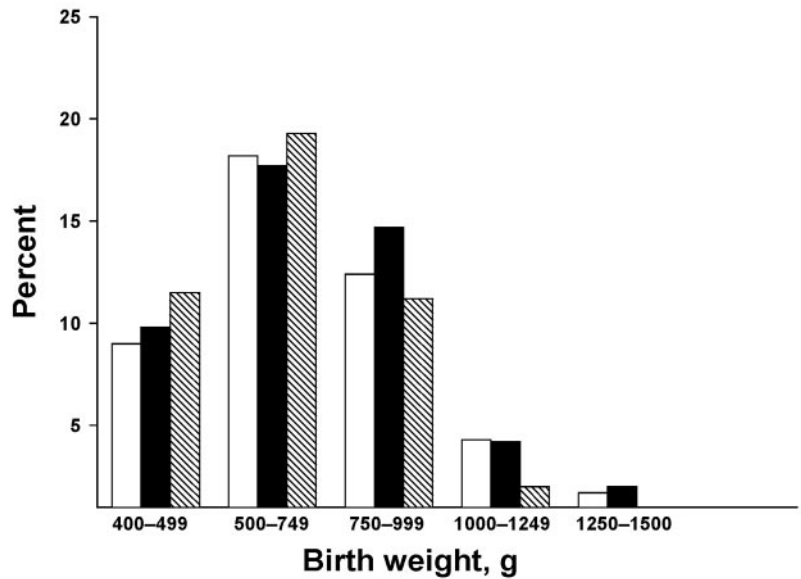


FIGURE 2
PNS use according to birth weight and indication for the EDG infants. □, CLD; ■, non-CLD; ▨, both indications.

TABLE 2 Days and Courses of Steroid Preparation According to Type and Indication

Steroid Preparation	n (%)	Mean No. of Courses (Median)	Mean Total Days (Median, IQR)
Dex for CLD	45 (3.2)	2 (1)	18.6 (8, 4-20)
Inhaled steroid for CLD	42 (3.0)	1.4 (1)	51.8 (48.5, 30-67)
Hydro for hypotension	174 (12.4)	1.7 (1)	9 (3, 2-8)
Hydro for weaning	13 (0.9)	1.3 (1)	4.1 (3, 2-5)
Dex for hypotension	5 (0.4)	1.8 (2)	8.4 (8, 8-9)
Dex for weaning	23 (1.6)	1.5 (1)	4.9 (2, 2-5)

Dex indicates dexamethasone; Hydro, hydrocortisone.

treated with PNSs only for CLD compared with EDG infants who did not receive PNSs had a higher rate of CLD at 36 weeks (74.0% vs 16.4%, $P = .001$; severe

IVH: 8.3% vs 6.9%, $P = .20$; periventricular leukomalacia [PVL]: 4.2 vs 2.5%, not significant, $P = .20$) and a lower mortality (6% vs 13.7% [not significant, $P =$

TABLE 3 Outcomes Related to PNS Use Comparing the EDG and RDG Groups

Variable	No. of Infants	CLD at 36 wk, %	Grade 3–4 IVH, %	PVL, %	Death, %
RDG					
No PNS	2273	16.6	10.3	2.2	16.4
PNS for CLD	242	64	14.5	2.9	8.7
EDG					
No PNS	1130	16.4	6.9	2.5	13.7
PNS for only CLD	50	74	8.3	4.2	6
PNS for only other	165	29.7	23.4	3.8	29.1
PNS for hypotension	180	35.6	23.4	7	25.6
PNS for extubation	36	75	17.1	2.9	5.6
PNS for CLD and other	56	82.1	18.2	12.7	3.6

.20]). EDG infants who received PNSs for only non-CLD (other) indications had a higher rate of CLD at 36 weeks (29.7% vs 16.4%, $P = .001$; severe IVH: 23.4% vs 6.9%, $P = .001$; PVL: 3.8 vs 2.5%, not significant, $P = .20$) and mortality (29.1% vs 13.7%, $P = .001$) when compared with EDG infants who did not receive PNSs. These adverse outcomes were increased in infants for whom the PNS indication was hypotension only compared with infants who did not receive PNSs. When compared with the EDG group with no PNSs, the EDG infants treated with PNSs for hypotension had 35.6% vs 16.4% incidence of CLD at 36 weeks ($P = .001$), 23.4% vs 6.9% incidence of severe IVH ($P = .001$), 7% vs 2.5% incidence of PVL ($P = .01$), and mortality of 25.6% vs 13.7% ($P = .001$; Table 3). Infants treated for hypotension had a lower rate of CLD (35.6% vs 75%; $P = .004$), a higher rate of severe IVH (23.4% vs 17.1%; not significant), PVL (7% vs 2.9%, not significant), and death (25.6% vs 5.6%; $P = .01$) when compared with EDG infants treated for extubation (Table 3). When compared with EDG infants without PNS treatment, EDG infants who were treated with PNSs for both CLD and another indication had a higher rate of CLD at 36 weeks (82.1% vs 16.4%; $P = .001$), severe IVH (18.2% vs 6.9%; $P = .001$), and PVL (12.7 vs 2.5%; $P = .01$) and a lower mortality (3.6% vs 13.7%; $P = .05$).

DISCUSSION

This report describes contemporary use of PNSs in the VLBW infant by California neonatologists. Neonatologists were early adopters of PNSs because of tangible short-term benefits such as decreasing the burden of CLD³⁵ and managing volume-resistant, pressor-resistant hypotension.³³ There has been widespread use of PNSs for the treatment or prevention of CLD in the VLBW infant not only in North America but in Europe as well. Overall, 67% of 14 European centers surveyed in 1999–2000 used PNSs: 48% initiated treatment in nonintubated infants and 53% at 7 to 14 days. Treatment duration was 4 to 15 days in 62% and >15 days in 21%.³⁶ Twenty-one percent of British consultant pediatricians reported administering PNSs after the first week of life to

ventilated neonates.³⁷ There have been many commentaries regarding the most appropriate use or nonuse of PNSs.¹⁰ Barrington³¹ reviewed 8 reports describing longer-term outcomes of infants enrolled in prospective trials of PNSs to prevent or treat BPD/CLD. These analyses demonstrated that PNSs were associated with an increased risk of neurodevelopmental impairment and cerebral palsy, with relative risks of 1.36 (95% CI: 1.09–1.58) and 2.01 (95% CI: 1.51–2.71), respectively, among surviving infants. These results were consistent with previous animal experiments, which had shown that glucocorticoids administered during critical periods of brain development may impair myelination, brain cell division, and longer-term behavioral effects.^{11–14,16} As a result of these observations, neonatologists began to abandon PNSs for CLD when they learned of the long-term toxicities associated with PNS use for CLD.

The American Academy of Pediatrics Committee on the Fetus and Newborn cautioned neonatologists in March 2002 that PNS use, outside of clinical trials, should be reserved only for “exceptional clinical circumstances (eg, an infant on maximal ventilatory and oxygen support).”¹⁷ We describe the actual use of PNSs for the observed calendar year of 2003, 8 to 20 months after the Committee of the Fetus and Newborn statement and the CPQCC’s efforts to bring this recommendation to the attention of California’s neonatology community through the development of a toolkit designed to inform about the evidence for PNS use in preterm infants.³⁸ The use of PNSs for CLD has fallen in California from 11.8% in 2001 to 7.9% in 2003. This recent trend has also been described for the VON, the National Institute of Child Health and Human Development Neonatal Research Network, and the Canadian Neonatal Network, with an indication that, currently, ~7% of VLBW infants continue to receive PNSs to prevent or treat CLD.³⁹ Our study indicates that there is a significant and unreported use of PNSs for managing hypotension, and because we do not have any antecedent information on the use of PNSs for hypotension, we cannot comment on whether this use is increasing.

There is evidence that the very premature infant has

an incomplete adrenal hormone response after birth, which may result in an exaggerated inflammatory response and an increased incidence of BPD at 36 weeks, an observation that has been recently refuted.^{40,41} Watterberg et al evaluated the use of hydrocortisone given for the first 12 days of life in such infants and noted a reduction in BPD without associated morbidity.⁴² A subsequent multicenter study by the same investigators was stopped because of evidence of bowel perforation, and, to date, there has not been any report of the long-term outcome of infants treated in these 2 trials.⁴³ Antenatal maternal steroid has been shown to improve blood pressure in the VLBW infant.⁴⁴ Animal models have confirmed this effect.⁴⁵ More recently, Ng et al⁴⁶ demonstrated that basal, peak, and incremental rise in serum cortisol on day 7 were associated significantly with the lowest systolic, mean, and diastolic blood pressures recorded during the first 2 weeks of life ($r > 0.25$; $P < .005$). They also reported that the serum cortisol at the 50th centile in hypotensive infants had high specificity and positive predictive value (0.80–0.93 and 0.81–0.89, respectively) for predicting early neonatal hypotension.

Hypotension occurs in ~20% of VLBW infants and may be associated with subsequent brain injury, and its treatment is problematic.⁴⁷ Hypotension requiring vasoactive drug treatment occurred in the first 24 hours of life in ~40% of the infants enrolled in the Watterberg et al trial and up to 33% of the infants of <750 g birth weight in the Hall et al study.^{44,48} Dopamine is the agent most frequently used for the treatment of low blood pressure in the VLBW infant. However, recent studies by Osborn et al⁴⁹ have demonstrated that dopamine may not increase cardiac output. Others have developed a technique to measure superior vena cava flow using ultrasound Doppler studies^{50,51} and reported that low superior vena cava flow, not blood pressure, was the only independent risk factor for late IVH in both cohorts (1995–1996 adjusted odds ratio: 20.39; 1998–1999 adjusted odds ratio: 5.16).⁵²

In a retrospective review of 21 preterm infants with hypotension unresponsive to volume and dopamine alone or in combination with other agents including dobutamine or epinephrine, Seri et al⁵³ 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.⁵⁴ 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.⁵⁵ 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.^{56,57} In addition, volume administration may increase left to right ductal shunting and is less effective than dopamine in increasing blood pressure.^{58,59} There was also a recent suggestion that volume administration to preterm hypoxic animals may impair cerebral oxygen delivery.⁶⁰

These observations may be encouraging the use of alternate pharmacological approaches for the hypotensive VLBW infant. For the EDG units surveyed in this study, >15% of VLBW infants received hydrocortisone for hypotension confirming the high incidence of hypotension in this population. Before the present study, there has not been any report describing the extent of the use of hydrocortisone, dexamethasone, or any other steroid preparation for the treatment of early hypotension in the VLBW infant. All of the previous reports described small numbers of infants, and none have reported any clinical short- or longer-term outcomes in infants treated with any steroid preparation for low blood pressure. We believed that there was a substantial use of PNSs for hypotension involving the use of single or repeated doses of hydrocortisone for VLBW infants. The current study represents the largest series of infants reported for whom early PNSs were prescribed for the treatment of low blood pressure.

Our prospective survey has confirmed that the use of hydrocortisone for hypotension has become a common practice, being used almost twice as often as PNSs for CLD and that although it would appear that the use of PNSs for CLD has fallen, the overall use of PNSs may have actually increased in California. The infants who received PNSs for CLD in the EDG were typically 35 days old, ventilated on a mean airway pressure of ~10 cm H₂O and a F_{IO₂} of .53. All of the previous information on the use of PNSs in the VLBW infant comes from prospective randomized trials in which the use of the PNSs followed a protocol for the prevention or treatment of CLD. Current PNS use differs from previous randomized trials, even in those where therapy began at >21 days of age, in that treatment was begun later and was not uniformly initiated for study indications. In many of the previous studies of PNSs for CLD, the infants were treated early with criteria that were felt to predict CLD. The delay observed in our survey for treating infants with PNSs for CLD may reflect the concern that earlier use may be associated with greater longer-term neuro-morbidity and the use of other respiratory approaches, including early continuous positive airway pressure,⁶¹ early intubation for surfactant followed by extubation,⁶² and noninvasive ventilation support.⁶³

A major shortcoming of our study is that only 22 of 62 units voluntarily submitted supplemental data, with these units contributing information for ~33% of all infants for whom data were collected through the

CPQCC in 2003. The groups differed only in the higher percentage of inborn infants and slightly lower birth weight seen in the EDG units. It is difficult to be certain if the results obtained are reflective of all of the CPQCC units, and, indeed, one may speculate that the units that completed the supplemental forms for their infants believed that they were not frequent users of PNSs. The overall results suggested that for PNS use for CLD, this was true but not significantly different from the RDG units, and we do not have a contemporary comparison group for the non-CLD use of PNSs.

At the present time, our observations suggest that there is significant use of PNSs for the treatment of low blood pressure in the VLBW infant and that, overall, 19% of VLBW infants in California receive PNSs, the majority for indications other than CLD, specifically, hypotension. Such infants experience high mortality and significantly greater morbidities, most likely secondary to the hypotension; however, this is not a proven relationship, and caution is required regarding the possible contributing role of early PNSs. We would suggest that there is an urgent need for large, well-designed trials to evaluate the safety and efficacy of PNSs to treat hypotension in the VLBW infant and to evaluate both short- and longer-term neurodevelopmental outcomes in such infants before this practice gains increased use.

REFERENCES

- Haddad H, Hsia D, Gellis S. Studies on respiratory rate in the newborn: its use in the evaluation of RDS in IDM. *Pediatrics*. 1956;17:204–213
- Altman H. The respiratory distress syndrome of the newborn: a report of 135 cases treated conservatively. *S Afr Med J*. 1965; 39:746–748
- Baden M, Bauer CR, Colle E, et al. A controlled trial of hydrocortisone therapy in infants with RDS. *Pediatrics*. 1972;50:526–534
- Ewerbech H, Helwig H. Treatment of idiopathic respiratory distress with large doses of corticoids. *Pediatrics*. 1972;49: 467–468
- Bhuta T, Ohlsson A. Systematic review and meta-analysis of early postnatal dexamethasone for prevention of chronic lung disease. *Arch Dis Child Fetal Neonatal Ed*. 1998;79:F26–F33
- Halliday HL. Clinical trials of postnatal corticosteroids: inhaled and systemic. *Biol Neonate*. 1999;76:29–40
- Halliday HL, Ehrenkranz RA, Doyle LW. Early postnatal (<96 hours) corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database Syst Rev*. 2003;(1):CD001146
- Halliday HL, Ehrenkranz RA, Doyle LW. Moderately early (7–14 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database Syst Rev*. 2003;(1):CD001144
- Halliday HL, Ehrenkranz RA, Doyle LW. Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants. *Cochrane Database Syst Rev*. 2003;(1):CD001145
- Finer NN, Craft A, Vaucher YE, et al. Postnatal steroids: short-term gain, long-term pain? *J Pediatr*. 2000;137:9–13
- Weichsel ME. The therapeutic use of glucocorticoid hormones in the perinatal period: potential neurological hazards. *Ann Neurol*. 1977;46:364–366
- Benesova O, Pavlik A. Perinatal treatment with glucocorticoids and the risk of maldevelopment of the brain. *Neuropharmacology*. 1989;28:89–97
- Vicedomini JP, Nonneman AJ, DeKosky ST, et al. Perinatal glucocorticoids disrupt learning: a sexually dimorphic response. *Physiol Behav*. 1986;36:145–149
- Huang WL, Beazley LD, Quinlivan JA, et al. Effect of corticosteroids on brain growth in fetal sheep. *Obstet Gynecol*. 1999;94: 213–218
- Quinlivan JA, Dunlop SA, Newnham JP, et al. Repeated, but not single, maternal administration of corticosteroids delays myelination in the brain of fetal sheep. *Prenat Neonatal Med*. 1999;4:47–55
- Uno H, Lohmiller L, Thieme C, et al. Brain damage induced by prenatal exposure to dexamethasone in fetal rhesus macaques. 1. Hippocampus. *Dev Brain Res*. 1990;53:157–167
- Blackmon LR, Bell EF, Engle WA, et al. Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. *Pediatrics*. 2002;109:330–338
- Vermont Oxford Network. *2001 Database Summary*. Burlington, VT: Vermont Oxford Network; 2003
- Stark AR, Carlo W, Bauer C, et al. Complications of early steroid therapy in a randomized controlled trial [abstract]. *Pediatrics*. 1999;104:739A
- Soll RF; Vermont Oxford Network Steroid Study Group. Early postnatal dexamethasone therapy for the prevention of chronic lung disease [abstract]. *Pediatr Res*. 1999;42:123A
- Papile LA, Tyson JE, Stoll BJ, et al. A multicenter trial of two dexamethasone regimens in ventilator-dependent premature infants. *N Engl J Med*. 1998;338:1112–1118
- Stoll BJ, Temprosa M, Tyson JE, et al. Dexamethasone therapy increases infection in very low birth weight infants. *Pediatrics*. 1999;104(5). Available at: www.pediatrics.org/cgi/content/full/104/5/e63
- Amin SB, Sinkin RA, McDermott MP, et al. Lipid intolerance in neonates receiving dexamethasone for bronchopulmonary dysplasia. *Arch Pediatr Adolesc Med*. 1999;153:795–800
- Van Goudoever JB, Wattimena JD, Carnielli VP, Sulkers EJ, Degenhart HJ, Sauer PJ. Effect of dexamethasone on protein metabolism in infants with bronchopulmonary dysplasia. *J Pediatr*. 1994;124:112–118.
- Leitch CA, Ahlrichs J, Karn C, Denne SC. Energy expenditure and energy intake during dexamethasone therapy for chronic lung disease. *Pediatr Res*. 1999;46:109–113
- Berry MA, Abrahamowicz M, Usher RH. Factors associated with growth of extremely premature infants during initial hospitalization. *Pediatrics*. 1997;100:640–646
- Rizvi ZB, Aniol HS, Myers TF, et al. Effects of dexamethasone on the hypothalamic-pituitary-adrenal axis in preterm infants. *J Pediatr*. 1992;120:961–965
- Ng PC, Blackburn ME, Brownlee KG, et al. Adrenal response in very low birthweight babies after dexamethasone treatment for bronchopulmonary dysplasia. *Arch Dis Child*. 1989;64:1721–1726
- Kari MA, Heinonen K, Ikonen RS, Koivisto M, Raivio KO. Dexamethasone treatment in preterm infants at risk for bronchopulmonary dysplasia. *Arch Dis Child*. 1993;68:566–569
- Shinwell ES, Karplus M, Reich D, et al. Early postnatal dexamethasone treatment and increased incidence of cerebral palsy. *Arch Dis Child Fetal Neonatal Ed*. 2000;83:F177–F181
- Barrington KJ. The adverse neuro-developmental effects of postnatal steroids in the preterm infant: a systematic review of RCTs. *BMC Pediatr*. 2001;1:1
- Doyle LW, Halliday HL, Ehrenkranz RA, et al. 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
- Helbock HJ, Insoft RM, Conte FA. Glucocorticoid-responsive

- hypotension in extremely low birth weight neonates. *Pediatrics*. 1993;92:715–717
34. Bourchier D, Weston PJ. Randomised trial of dopamine compared with hydrocortisone for the treatment of hypotensive very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed*. 1997;76:F174–F178
 35. Mammel MC, Green TP, Johnson DE, Thompson TR. Controlled trial of dexamethasone therapy in infants with bronchopulmonary dysplasia. *Lancet*. 1983;1(8338):1356–1358
 36. Truffert P, Empana JP, Breart G, et al. Treatment strategies for bronchopulmonary dysplasia with postnatal corticosteroids in Europe: the EURAIL survey. *Acta Paediatr*. 2003;92:948–951
 37. Williams O, Greenough A. Post-natal corticosteroid use. *Eur J Pediatr*. 2003;162:613–615
 38. Wirtschafter DD, Murphy B, Nisbet CC, for the California Perinatal Quality Care Collaborative. *Postnatal Steroid Administration Quality Improvement Toolkit*. 2003. Available at: www.cpqcc.org/PNS.html. Accessed February 25, 2005
 39. Walsh MC, Yao O, Horbar JD, et al. Changes in postnatal steroid (PNS) use in VLBW neonates in 3 large neonatal networks. *Pediatr Acad Soc*. 2005;57:2078
 40. Romagnoli C, Latella C, Zecca E, Papacci P, Tortorolo G. Adrenocortical function and chronic lung disease of pre-maturity: an unresolved problem? *J Endocrinol Invest*. 2002;25:759–764
 41. Watterberg KL, Scott SM, Backstrom C, et al. Links between early adrenal function and respiratory outcome in preterm infants: airway inflammation and patent ductus arteriosus. *Pediatrics*. 2000;105:320–324
 42. Watterberg KL, Gerdes JS, Gifford KL, Lin HM. Prophylaxis against early adrenal insufficiency to prevent chronic lung disease in premature infants. *Pediatrics*. 1999;104:1258–1263
 43. Watterberg KL, Gerdes JS, Cole C, et al. Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. *Pediatrics*. 2004;114:1649–1657
 44. Demarini S, Dollberg S, Hoath SB, et al. Effects of antenatal corticosteroids on blood pressure in very low birth weight infants during the first 24 hours of life. *J Pathol*. 1999;19:419–425
 45. Smith LM, Ervin MG, Wada N, et al. Antenatal glucocorticoids alter postnatal preterm lamb renal and cardiovascular responses to intravascular volume expansion. *Pediatr Res*. 2000;47:622–627
 46. Ng PC, Lee CH, Lam CW, et al. Transient adrenocortical insufficiency of prematurity and systemic hypotension in very low birthweight infants. *Arch Dis Child*. 2004;89:119–126
 47. Dasgupta SJ, Gill AB. Hypotension in the very low birthweight infant: the old, the new, and the uncertain. *Arch Dis Child Fetal Neonatal Ed*. 2003;88:F450–F454
 48. Hall RW, Kronsberg SS, Barton BA, Kaiser JR, Anand KJ; NEOPAIN Trial Investigators Group. Morphine, hypotension, and adverse outcomes among preterm neonates: who's to blame? Secondary results from the NEOPAIN trial. *Pediatrics*. 2005;115:1351–1359
 49. Osborn D, Evans N, Kluckow M. Randomized trial of dobutamine versus dopamine in preterm infants with low systemic blood flow. *J Pediatr*. 2002;140:183–191
 50. Kluckow M, Evans N. Superior vena cava flow in newborn infants: a novel marker of systemic blood flow. *Arch Dis Child Fetal Neonatal Ed*. 2000;82:F182–F187
 51. Osborn DA, Evans N, Kluckow M. Hemodynamic and antecedent risk factors of early and late periventricular/intraventricular hemorrhage in premature infants. *Pediatrics*. 2003;112:33–39
 52. Evans N, Kluckow M, Simmons M, et al. Which to measure, systemic or organ blood flow? Middle cerebral artery and superior vena cava flow in very preterm infants. *Arch Dis Child*. 2002;87:181–184
 53. Seri I, Tan R, Evans J. Cardiovascular effects of hydrocortisone in preterm infants with pressor-resistant hypotension. *Pediatrics*. 2001;107:1070–1074
 54. Gaissmaier RE, Pohlandt F. Single-dose dexamethasone treatment of hypotension preterm infants. *J Pediatr*. 1999;134:701–705
 55. Zhang J, Penny DJ, Kim NS, Yu VY, Smolich JJ. Mechanisms of blood pressure increase induced by dopamine in hypotensive preterm neonates. *Arch Dis Child Fetal Neonatal Ed*. 1999;81:F99–F104
 56. Bauer K, Linderkamp O, Versmold HT. Systolic blood pressure and blood volume in preterm infants. *Arch Dis Child*. 1993;69:521–522
 57. Aladangady N, Aitchison TC, Beckett C, Holland BM, Kyle BM, Wardrop CA. Is it possible to predict the blood volume of a sick preterm infant? *Arch Dis Child Fetal Neonatal Ed*. 2004;89:F344–F347
 58. Gill AB, Weindling AM. Randomised controlled trial of plasma protein fraction versus dopamine in hypotensive very low birthweight infants. *Arch Dis Child*. 1993;69:284–287
 59. Pladys P, Wodey E, Betremieux P, et al. Effects of volume expansion on cardiac output in the preterm infant. *Acta Paediatr*. 1997;86:1241–1245
 60. Mayock DE, Gleason CA. Cerebrovascular effects of rapid volume expansion in preterm fetal sheep. *Pediatr Res*. 2004;55:395–399
 61. Lindner W, Vossbeck S, Hummler H, et al. Delivery room management of extremely low birthweight infants: spontaneous breathing or intubation? *Pediatrics*. 1999;103:961–967
 62. Verder H, Albertsen P, Ebbesen F, et al. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. *Pediatrics*. 1999;103(2). Available at: www.pediatrics.org/cgi/content/full/103/2/e24
 63. Barrington KJ, Bull D, Finer NN. Randomized trial of nasal synchronized intermittent mandatory ventilation compared with continuous positive airway pressure after extubation of very low birth weight infants. *Pediatrics*. 2001;107:638–641

**California Perinatal Quality Care Collaborative VLBW
Postnatal Steroid Administration Data Supplement Complete items**

1-5 for *all* infants who meet the following criteria:

- Birthweight **401 - 1500 grams**
- Birthdate **January 1, 2003 - December 31, 2003**

Infant received **any** postnatal steroids (excluding ocular drops) **Complete Items 6-11** for infants who received any post-natal steroids *for indications other than the prevention or treatment of CLD.*

Complete Items 12-19 for infants who received steroids *for prevention or treatment of CLD* **A List of Definitions is provided on the back of this page.**

How to Fill Out this Form: *Fill in dates and numbers in the spaces provided. For checkboxes, fill in as follows:*



1. **1.** 3-digit VON Center Number _____
2. **2.** 5-digit Network ID number _____
3. **3.** Date of Birth (mm/dd/yy) _____ / _____ / _____
- 4.** Did the infant receive postnatal steroid treatment during this hospitalization *for an indication other than prevention or treatment of CLD?*
 - a. No
 - b. Yes (complete items 6-11)
5. Did the infant receive postnatal steroid treatment during this hospitalization *for prevention or treatment of CLD?*
 - a. No
 - b. Yes (complete items 12-19)

-----Steroids For Indications Other Than CLD -----

6. Date postnatal steroids started *for indications other than prevention or treatment of CLD* (mm/dd/yy) _____ / _____ / _____
7. Type of medication started on above date
 - a. hydrocortisone (Cortef, Solu-cortef, A-Hydrocort)
 - b. dexamethasone (Decadron, Hexadrol)
 - c. inhaled steroid (Flovent, Beclovent)
 - d. other (specify _____)
1. **8.** For IV or PO steroids, record total dose given in the first 24 hours after initiating steroids: _____ . _____ mg/kg
- 9.** Indication for starting steroids on above date
 - a. hypotension
 - b. prevent or treat post-extubation upper airway edema and/or stridor
 - c. other (specify _____)

1. **10.** Total number of courses of *steroids for indications other than prevention or treatment of CLD* _____

2. **11.** Total number of days infant received steroids *for indications other than prevention or treatment of CLD*, including first and subsequent courses: _____ days

1. **12.** Date postnatal steroids started *for prevention or treatment of CLD* (mm/dd/yy) ____ / ____ / ____

...**13.** Type of medication started on date in item 12:

- a. hydrocortisone (Cortef, Solu-cortef, A-Hydrocort)
- b. dexamethasone (Decadron, Hexadrol)
- c. inhaled steroid (Flovent, Bedivent)
- d. other (specify _____)

1. **14.** For IV or PO steroids, record total dose given in the first 24 hours after initiating steroids:

____ . ____ mg/kg

...**15.** Type of respiratory support when steroids were initiated on date in item 12 (*select only one*)

- a. Conventional ventilation via ETT
- b. High Frequency Ventilation
- c. Nasal CPAP (not including high-flow nasal cannula)
- d. Nasal Positive Pressure Ventilation
- e. Nasal cannula (including FiO₂ 0.21)
- f. Hood O₂
- g. Room air (no support)

16. If answer to item 15 was ventilator or CPAP, settings recorded when steroids were initiated:

16a. Mean airway pressure ____ . ____ cmH₂O

16b. FiO₂ ____ . ____

17. In the 24-hour period prior to the first dose of steroids given on date in item 12, were any of these conditions present? (*select all that apply*)

- a. PIE (pulmonary interstitial emphysema)
- b. Pneumothorax
- c. Diuretics given (Spironolactone, Furosemide, Chlorothiazide)
- d. Bronchodilators given (Albuterol, Ibutropium, Atropine, Atrovent)

1. **18.** Number of courses of steroids for *treatment or prevention of CLD* _____

2. **19.** Total number of days infant received steroids *for treatment or prevention of CLD*, including first and subsequent courses: _____ days

Prospective Evaluation of Postnatal Steroid Administration: A 1-Year Experience From the California Perinatal Quality Care Collaborative

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