

# Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants



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**Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants.** *Paediatr Child Health* 2002;7(1):20-28.

This statement is intended for health care professionals caring for neonates and young infants. The objectives of this statement are to review the short and long term effects of systemic and inhaled postnatal corticosteroids for the prevention or treatment of evolving or established chronic lung disease, and to make recommendations for the use of corticosteroids in infants with very low birth weight. The routine use of systemic dexamethasone for the prevention or treatment of chronic lung disease in infants with very low birth weight is not recommended.

**Key Words:** *Chronic lung disease; Corticosteroids; Infant; Newborn; Preterm; Very low birth weight*

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## BACKGROUND

Chronic lung disease (CLD), also known as bronchopulmonary dysplasia, is an important cause of mortality and morbidity in preterm infants (1,2). The incidence of CLD among surviving infants with very low birth weight ([VLBW]; birth weight less than 1500 g) in two large databases was 26% in Canada (1996/97) (1) and 23% in the United States (1995/96) (2). CLD is usually defined as oxygen dependency at 36 weeks' postmenstrual age (PMA) or 28 days' postnatal age (PNA), in conjunction with persistent clinical respiratory symptoms and compatible abnormalities on chest radiographs (3-6).

Because inflammation plays an important role in the pathogenesis of CLD, corticosteroids, in particular dexamethasone, have been widely used to prevent or treat CLD (1,2,7). Postnatal corticosteroids were given to 25% of infants with VLBW in Canada (1996/97) (1) and to 19% in the United States (1995/96) (2). Corticosteroid use is higher in infants with a birth weight less than 1000 g (1,2). Numerous studies suggest that the use of systemic corticosteroids decreases the duration of ventilator dependence (8-

16). However, early beneficial effects on the pulmonary system may be outweighed by an increased risk of serious short and long term adverse effects (8-24).

## OBJECTIVES

The objectives of this statement are to review the short and long term effects of systemic and inhaled postnatal corticosteroids for the prevention or treatment of evolving or established CLD, and to make recommendations for the use of corticosteroids in infants with VLBW. The focus of this statement is limited to the use of corticosteroids in neonates with VLBW for the prevention or treatment of CLD.

## LITERATURE REVIEW

An attempt was made to identify all published systematic reviews and meta-analyses on the use of corticosteroids (systemic or inhaled) for the prevention or treatment of CLD in preterm infants, using the MEDLINE, EMBASE, CINAHL and Cochrane Library electronic databases, and personal files from 1983 to April 2001. Data were also included from two trials published after the identified systematic reviews (19,25). Twelve systematic reviews published between 1992 and 2001 were identified (8-16,26-28). Nine addressed the use of systemic steroids (8-11,13-16,28), two described the use of inhaled steroids (26,27) and one addressed both (12). Numerous outcomes were evaluated. The results are presented in five sections: the first three sections report on the effects of systemic corticosteroids on the basis of age at which the infants were treated; the fourth section reports on the effects of inhaled steroids; and the fifth section describes the effects of systemic corticosteroids on neurodevelopmental outcomes.

### Systemic early postnatal corticosteroid therapy (less than 96 h of age)

The most complete systematic reviews were published in 2001 (13,16). In addition, the meta-analysis for systemic

early postnatal corticosteroid therapy by Shah and Ohlsson (16) was updated by incorporating data from two subsequently published studies (19,25). Infants studied were preterm, demonstrated respiratory distress syndrome on chest radiographs and required mechanical ventilation with oxygen at the time of enrollment (8-11,13,16,19,25). Systemic corticosteroids were given intravenously within 96 h of birth; dexamethasone was used in all but two studies (29,30). The most commonly used dosages were 0.5 mg/kg body weight per day for three days, followed by a tapering course of 0.25, 0.125 and 0.05 mg/kg/day each for three days (13,16). One study (19) used a considerably lower dosage (0.15 mg/kg/day for three days, 0.10 mg/kg/day for three days, 0.05 mg/kg/day for two days and 0.02 mg/kg/day for two days). The combined outcome of death or CLD at 28 days' PNA or at 36 weeks' PMA (13,16) was significantly decreased by early corticosteroid treatment. There was no effect on mortality at 28 days' PNA, at 36 weeks' PMA, or at discharge (13,16). Corticosteroid treatment decreased CLD incidence at 28 days' PNA and at 36 weeks' PMA (8-11,13,16). On the basis of an analysis including data from the most recently published trials (19,25), 10 infants would need to be treated with corti-

costeroids to prevent one from developing CLD at 28 days' PNA or at 36 weeks' PMA.

Weaning from mechanical ventilation was more successful in infants treated with dexamethasone (13,16). The use of additional systemic dexamethasone by clinicians outside of the study protocols (open-label use) was decreased (13,16).

The incidences of hypertension (16), hyperglycemia (13), insulin therapy for hyperglycemia (16), gastrointestinal bleeding (16) or perforation (13), and hypertrophic obstructive cardiomyopathy (13) were increased by early corticosteroid treatment. The rates of pulmonary air leaks (13) and patent ductus arteriosus were decreased (13,16). There was no difference in the incidence of infection (13,16), necrotizing enterocolitis (NEC) (16), intraventricular hemorrhage (13,16) or severe retinopathy of prematurity (13,16). Weight gain was decreased during dexamethasone therapy (13,16). A borderline increased risk of periventricular leukomalacia (PVL) in the infants who received dexamethasone was noted in one (13) but not in the other recent systemic review (16). In an update of the review by Shah and Ohlsson (16), including the two recently published studies (n=1096) (19,25), the relative risk of PVL was 1.41 (95% CI 0.93 to 2.13). Long term outcomes are shown in Table 1.

**TABLE 1**  
**Neurodevelopmental outcome data for early (less than 96 h of age) postnatal corticosteroid use for prevention of chronic lung disease in infants**

Author	Drug, dosage and duration of therapy	Number of patients enrolled	Outcome data
Fitzhardinge et al, 1974 (39); original study by Baden et al, 1972 (29)	Hydrocortisone (12.5 mg/kg of body weight) was administered 12 h apart in the first 24 h, or two placebo injections of a lactose solution were administered	44	28 of 44 survived the neonatal period. 24 of 28 were evaluated for a minimum of one year. Follow-up data were not available on two subjects. One control infant died at 10 months with microcephaly and extensive brain damage. One study infant had limited data that was obtained by letter  Three of 13 infants in the steroid group had evidence of neuromotor dysfunction (one had moderate degree of spastic quadriplegia, one had hypotonia and slow motor development, and one had increased extensor tone and slow motor development)  Two of 13 infants in the placebo group had evidence of neuromotor dysfunction (one had mild spastic diplegia, one had microcephaly and spastic diplegia [RR 1.50, 95% CI 0.30–7.55])  Four of 13 infants in the steroid group had EEG abnormalities (mild paroxysmal changes with no epileptiform patterns). No EEG abnormalities were noted in the placebo group  Mean developmental quotient (using Griffith Developmental Scale): no statistically significant differences were noted between groups (steroid group, 95.4 compared with placebo group, 97.9)  Locomotor scale: there was a significant difference in the results for gross motor development (steroid group, 93 compared with placebo group, 104 [P<0.05])
Stark et al, 2001 (41); original study by	Dexamethasone was administered within 24 h after	220	Of the 166 survivors, 123 (74%) were evaluated at 18 to 22 months of age using the BSID II, a standardized neurological examination and hearing and vision assessment. Neurodevelopmental impairment was

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**TABLE 1 (continued)****Neurodevelopmental outcome data for early (less than 96 h of age) postnatal corticosteroid use for prevention of chronic lung disease in infants**

Author	Drug, dosage and duration of therapy	Number of patients enrolled	Outcome data
Stark et al, 2001 (19)	birth (0.15 mg/kg/day for three days, then tapered over seven days) or placebo was administered		<p>defined as a Bayley score less than 70, abnormal neurological examination, or deafness or blindness</p> <p>34 of 67 infants in the steroid group had MDI of less than 70, compared with 24 of 56 in the placebo group (RR 1.18, 95% CI 0.81–1.74)</p> <p>20 of 67 in the steroid group had a PDI of less than 70 compared with 20 of 56 in the placebo group (RR 0.84, 95% CI 0.50–1.39)</p> <p>Abnormal neurological examination was noted in 17 of 67 infants in the steroid group compared with 14 of 56 infants in the placebo group (RR 1.02, 95% CI 0.55–1.87)</p>
Shinwell et al, 2000 (38)	Dexamethasone was administered (0.5 mg/kg/day) in two divided doses for three days (administered before 12 h of age) or saline placebo was administered	248	<p>Of the 195 infants who survived to discharge, five died in the postneonatal period. Follow-up data were obtained on 159 of 190 (84%) survivors at a mean (<math>\pm</math> SD) age of 53<math>\pm</math>18 months. 31 were lost to follow-up (10 in the placebo group and 21 in the steroid group)</p> <p>As detailed, Bayley, Griffith or other developmental assessments were not available in all cases, developmental status was defined as normal, mildly abnormal or severely abnormal</p> <p>Severe abnormality was defined as any of the following: motor disability in children who were not independently ambulatory, global retardation, deafness requiring hearing aids and blindness</p> <p>39 of 80 infants in the steroid group developed cerebral palsy compared with 12 of 79 infants in the placebo group (RR 3.21, 95% CI 1.82–5.66). Spastic diplegia was the most common form of cerebral palsy noted</p> <p>44 of 80 infants in the steroid group were noted to have developmental delay compared with 23 of 79 in the placebo group (RR 1.89; 95% CI 1.27–2.81)</p> <p>No differences were found in visual or hearing problems between groups</p>
Subhedar et al, 2000 (40)	Dexamethasone was administered at 96 h of age (1 mg/kg/day for three days, then 0.5 mg/kg/day for three days). For three infants, the starting dosage was decreased to 0.5 mg/kg/day because of an observed increase in gastrointestinal adverse effects. No placebo was administered	42	<p>Of the 42 infants in the trial, 20 died (17 before discharge and three in the postneonatal period)</p> <p>Detailed assessment was performed in 21 of the 22 survivors at 30 months of age (one was lost to follow-up) using the BSID II</p> <p>Cerebral palsy was defined as the presence of any abnormal motor signs. Developmental delay was defined as an MDI or PDI less than 70. Severe neurodisability was defined as cerebral palsy with or without significant developmental delay and with or without significant visual or hearing impairment</p> <p>Cerebral palsy was noted in 0 of 10 infants in the steroid group compared with two of 11 in the control group (RR 0.22, 95% CI 0.01–4.06). Significant developmental delay was noted in 0 of 10 in the steroid group compared with four of 11 in the control group (RR 0.12, 95% CI 0.01–2.00). Severe neurodisability was noted in one of 10 infants in the treated group compared with four of 11 in the control group (RR 0.28, 95% CI 0.04–2.07).</p>
Yeh et al, 1998 (31)	Dexamethasone administration commenced at less than 12 h of age (0.5 mg/kg/day	270	<p>Of the 270 infants included in the initial study, eight were excluded from data analysis (six died from culture-proven sepsis within 12 h of birth, two had severe asphyxia), and 83 infants died in the neonatal period. Of the 179 survivors, nine infants in the control group and 13 in the steroid group were lost to follow-up</p>

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TABLE 1 (continued)

## Neurodevelopmental outcome data for early (less than 96 h of age) postnatal corticosteroid use for prevention of chronic lung disease in infants

Author	Drug, dosage and duration of therapy	Number of patients enrolled	Outcome data
	for seven days, then 0.24 mg/kg/day for seven days, then 0.1 mg/kg/day for seven days, and then 0.04 mg/kg/day for seven days), or saline placebo was administered		Follow-up data at two years of age is available for 133 of 157 patients (in nine infants, follow-up study could not be completed because of the lack of parental consent or cooperation from the child). In addition, 15 infants died in the postneonatal period. Neuromotor dysfunction was classified as mild, moderate or severe on the basis of mobility of the child. EEG was also performed, including visual and auditory stimulation. Psychometric evaluations were performed using BSID II 25 of 63 infants in the steroid group had neuromotor dysfunction compared with 12 of 70 in the control group (RR 2.32, 95% CI 1.27–4.21) Significant handicap, defined as severe neurological defect and/or intellectual defects (MDI and/or PDI less than 70), was seen in 26 of 63 in the steroid group compared with 22 of 70 in the control group (RR 1.31, 95% CI 0.83-2.07)

RR and 95% CI were calculated using SAS Version 8 for Windows (SAS Institute Inc, USA). When there was no outcome event in one group, 0.5 was added to each cell to calculate the RR. BSID II Bayley Scales of Infant Development II; EEG Electroencephalography; MDI Mental developmental index; PDI Psychomotor developmental index

### Systemic moderately early postnatal corticosteroid therapy (seven to 14 days' PNA)

The most current reviews were published in 2001 (14,16). Infants in the studies included in the meta-analyses were preterm and dependent on mechanical ventilation with oxygen at enrollment (9-11,14,16). All trials used dexamethasone. The drug was administered intravenously for two to 42 days, starting between seven and 14 days of age or given as a pulse dose for three days at 10-day intervals until the infant no longer required supplemental oxygen or ventilation, or had reached 36 weeks' PMA. The initial dosage was 0.5 mg/kg/day, which was maintained for the duration of the study period, decreased over seven to 42 days or followed by inhaled budesonide (9,14,16).

The combined outcome of death or CLD was decreased at 28 days' PNA and at 36 weeks' PMA (14,16). Mortality was not decreased in the treatment group at the time of discharge (14,16). In one review, mortality was not decreased at 28 days' PNA or 36 weeks' PMA (16); the other showed decreased mortality at 28 days' PNA (14). The incidence of CLD at 28 days' PNA and 36 weeks' PMA (14,16) was decreased. The number of infants who needed to be treated with dexamethasone was seven and four to prevent CLD at 28 days' PNA and 36 weeks' PMA, respectively (16). Infants were more likely to be extubated by seven and 28 days after initiation of treatment with dexamethasone (14,16). However, the duration of hospitalization or need for supplemental oxygen was not decreased (16). The subsequent use of additional systemic steroids in the infants

who had received dexamethasone during the study period was decreased (14,16).

The incidences of pneumothorax, severe retinopathy of prematurity, intraventricular hemorrhage and NEC were not increased (14,16). Infants in the dexamethasone group had an increased risk of developing hypertension (14,16). The two reviews differed in reporting statistically significant differences between treatment and control groups for hyperglycemia, gastrointestinal bleeding, hypertrophic obstructive cardiomyopathy and infection (14,16). Long term outcomes are shown in Table 2.

### Systemic delayed postnatal corticosteroid therapy (older than three weeks of age)

There are two overlapping systematic reviews on systemic corticosteroid use started after three weeks of age (12,15). All infants enrolled in the primary studies were preterm and were dependent on oxygen or mechanical ventilation at approximately three weeks of age and older, with or without abnormalities of CLD evident on chest radiographs. Dexamethasone was administered intravenously or enterally at 0.5 to 1 mg/kg/day for a duration of three days to three weeks. The dosage was then tapered every three days in different ways; in some studies, the infants subsequently received hydrocortisone.

The combined outcome of death or CLD at 36 weeks' PMA was decreased by dexamethasone treatment. Dexamethasone did not affect survival at discharge or duration of hospitalization, but fewer infants were discharged home from the hospital on oxygen therapy.

**TABLE 2**  
**Neurodevelopmental outcome data for moderately early (seven to 14 days) postnatal corticosteroid use for the prevention of chronic lung disease**

Author	Drug, dosage and duration of therapy	Number of patients enrolled	Outcome data
Cummings et al, 1989 (32)	Dexamethasone was administered to infants at 14 days of age (0.5 mg/kg/day for three days, then 0.3 mg/kg/day for three days, and then decreased by 10% every three days until 0.1 mg/kg/day was administered for three days, and then 0.1 mg/kg/day on alternate days for one week [total duration of therapy, 42 days]; or in a dose of 0.5 mg/kg/day for three days and then decreased by 50% every three days to 0.06 mg/kg/day for three days and then 0.06 mg/kg/day on alternate days for one week [total duration of therapy, 18 days]), or placebo was administered	36	Neurodevelopmental outcomes were assessed at six and 15 months of age. Developmental evaluations were made using BSID II A good neurological outcome was defined as normal neurological findings and Bayley mental and psychomotor indices of 84 or higher Twenty-three of 36 (64%) infants survived to discharge A good outcome was noted in seven of nine infants in the 42-day course. Two of nine infants in the 18-day course, and two of five in the placebo group ( $P < 0.05$ ). The results for adverse outcomes in the two groups that were given steroids were combined and compared with those of the placebo group (RR 0.83, 95% CI 0.36–1.95)
Hofkosh et al, 1995 (42); original study by Brozanski et al, 1995 (43)	Infants with VLBW who were ventilator dependent at seven days PNA were randomly assigned to receive pulse doses of dexamethasone (0.5 mg/kg/day, divided twice daily [ $n=39$ ]) or saline placebo ( $n=39$ ), for three days at 10-day intervals until they no longer required supplemental oxygen or ventilation, or reached 36 weeks' PMA	78	65 infants survived to term. 44 were available for follow-up at 12 months' adjusted age (25 in the dexamethasone group and 19 in the control group). Outcome measures included MDI and PDI indices of the BSID II. Mean ( $\pm$ SD) MDI was $89.5 \pm 23.7$ in the dexamethasone group and $80.8 \pm 26.0$ in the control group ( $P=0.18$ ). PDI scores were $87.0 \pm 26.1$ in the dexamethasone group and $75.2 \pm 24.8$ in the control group ( $P=0.14$ ). Measurements of length, weight and head circumference did not differ between groups
O'Shea et al, 1999 (37); original study by Kothadia et al, 1999 (36)	Dexamethasone administration commenced between 15 and 25 days of age (0.5 mg/kg/day for three days, then 0.3 mg/kg/day for three days, and then decreased by 10% every three days until 0.1 mg/kg/day was administered for three days, and then 0.1 mg/kg/day on alternate days for one week [total duration of therapy, 42 days]), or saline placebo was administered	118	A neurodevelopmental assessment was performed at one-year adjusted age using the BSID II, Vineland Adaptive Behavioral scales, a physical and neurological examination by a developmental paediatrician, and auditory testing. Cerebral palsy was diagnosed only if a paediatrician and a physical therapist agreed on the presence of abnormal control of movement and posture with impaired motor function Of the 118 infants enrolled in the study, 95 survived to discharge. Follow-up data are available from 93 infants and two parents refused evaluation of their infant Cerebral palsy was diagnosed in 12 of 48 infants in the steroid group compared with three of 45 in the placebo group (RR 3.75, 95% CI 1.13–12.43) No differences were noted between groups for MDI or PDI scores

BSID II Bayley Scales of Infant Development II; MDI Mental developmental index; PDI Psychomotor developmental index; PMA Postmenstrual age; PNA Postnatal age; VLBW Very low birth weight

Extubation was facilitated by seven and 28 days after initiation of the treatment. Dexamethasone also improved respiratory compliance and decreased the need for oxygen supplementation, resulting in a borderline significant decrease in the incidence of CLD at 36 weeks' PMA. Late rescue treatment with dexamethasone was decreased in the treated infants. The risk of

hypertension was increased by dexamethasone, but there was no difference in incidence of infection, NEC or gastrointestinal bleeding compared with controls. More infants in the dexamethasone group than in the control group experienced poor weight gain or even weight loss (12,15). Long term outcomes are shown in Table 3.

**TABLE 3**  
**Neurodevelopmental outcome data for late (older than three weeks of age) postnatal corticosteroid use for the treatment of chronic lung disease**

Author	Drug, dosage and duration of therapy	Number of patients enrolled	Outcome data
Vincer et al, 1998 (35)	Dexamethasone was administered after 28 days of age in infants who were ventilator-dependent (0.5 mg/kg/day for three days and 0.3 mg/kg/day for the final three days), or saline placebo was administered	20	Of the 20 infants enrolled in the study, 11 received dexamethasone and nine received placebo. Three infants died before discharge from the hospital (two from the steroid-treated group and one from the placebo group) Cerebral palsy was reported in four of nine infants in the steroid-treated group compared with two of eight in the placebo group (RR 1.78, 95% CI 0.44–7.25)
Ohlsson et al, 1992 (20); original study by Ohlsson, 1990 (44)	Dexamethasone was administered to infants between 21 and 35 days of age (1 mg/kg/day for three days, then 0.5 mg/kg/day for the next three days, then 0.25 mg/kg/day for the next three days, and then 0.125 mg/kg/day for the last three days), or sham injections were given	25	Outcome data are available for 24 of 25 infants enrolled in the study (one infant died at 238 days) The mean corrected age ( $\pm$ SD) was 26.5 $\pm$ 7.8 months in the steroid-treated group compared with 28.8 $\pm$ 7.5 months in the control group Cerebral palsy was noted in one of 11 infants in the steroid-treated group compared with three of 13 in the control group (RR 0.39, 95% CI 0.05–3.27) Delayed motor development was noted in three of 11 subjects in the treatment group compared with two of 13 subjects in the control group (RR 1.77, 95% CI 0.36–8.77) Bayley scores were 90 $\pm$ 15 in the treatment group, compared with 100 $\pm$ 20 in the control group (P=0.287)
Jones et al, 1995 (34); original study by the Collaborative Dexamethasone Trial Group, 1991 (33)	Dexamethasone was administered between two and 12 weeks of age (0.5 mg/kg/day for a week), or normal saline placebo was administered. There was an option to administer a second tapering nine-day course of steroids if relapse occurred after the initial improvement	287	Information regarding cerebral palsy, global retardation, and visual or hearing loss was obtained from health visitors and general practitioners. Information from parents was obtained using a questionnaire regarding the use of health services such as physiotherapy, speech therapy, and occupational therapy. Also, information on development from parents was obtained using a Minnesota Child Development Inventory Follow-up data were obtained on 209 of the 223 survivors at three years of age Cerebral palsy was noted in 20 of 100 infants in the steroid-treated group compared with 18 of 109 in the placebo group (RR 1.21, 95% CI 0.68–2.16) Global retardation was noted in 15 of 100 in the steroid group compared with 13 of 109 in the placebo group (RR 1.26, 95% CI 0.63–2.51).

### Inhaled steroids

Two systematic reviews (12,26) address the effectiveness of inhaled corticosteroids to prevent CLD in ventilated infants with VLBW enrolled within two weeks after birth. No benefit of inhaled corticosteroids was shown, except the borderline significant decrease of subsequent administration of systemic dexamethasone. It is uncertain whether inhaled corticosteroids simply do not work for this condition or whether the type, dosage or delivery methods were inadequate. Other meta-analyses studied infants with VLBW enrolled after two weeks of age, with administration of inhaled corticosteroids for one to four weeks (12,27). Inhaled corticosteroids appeared to improve the extubation

rate; however, there was heterogeneity among studies for this finding. No other differences were found, possibly because of lack of statistical power. Additional studies may help to determine whether inhaled corticosteroids decrease the need for systemic treatment or facilitate extubation.

### Neurodevelopmental outcome

Two systematic reviews are available that focus on mortality and long term neurodevelopment of infants enrolled in randomized controlled trials of corticosteroids (11,28). In one review of five trials (31-37), 475 (91%) of 522 survivors were followed. Mortality was not significantly different in the steroid and control groups (11). Motor dysfunction was

significantly greater with postnatal corticosteroid treatment, with an event rate difference of 11.9% favouring the controls (95% CI 4.6 to 19.2). The rate of survival free of motor dysfunction was lower in the postnatal corticosteroid-treated group (event rate difference of 7.8% favouring controls [95% CI 0.5 to 15.1]).

Barrington (28) identified three additional trials (29,38-40) that reported on long term outcome after postnatal exposure to corticosteroids. These eight studies represent 1052 infants; 292 of them died and 679 (89%) of the 760 survivors were followed for one year or longer. One important difficulty in evaluating long term effects of corticosteroids is that many control subjects were treated with open-label dexamethasone after the initial study period. Barrington (28) tried to take this into account by arbitrarily dividing the studies into two groups on the basis of whether they had less than 30% contamination (corticosteroids given to infants in the control group) (group 1), or more than 30% contamination or did not report on contamination (group 2). The outcomes evaluated were the incidences of cerebral palsy and neurodevelopmental impairment; the latter was defined as a developmental score more than two SD below the mean, or cerebral palsy or blindness.

The studies demonstrated a relative risk of neurodevelopmental impairment among surviving children exposed to corticosteroids of 1.34 (95% CI 1.09 to 1.64), compared with controls (28). In the four studies with less than 30% contamination, the relative risk was 1.66 (95% CI 1.26 to 2.19) (28). Including all studies, the relative risk of developing cerebral palsy in the surviving infants exposed to corticosteroids was 2.02 (95% CI 1.51 to 2.71) (28). For infants from studies with less than 30% contamination, the relative risk of developing cerebral palsy among exposed infants was 2.89 (95% CI 1.96 to 4.27) (28). Thus, there appears to be a trend in the size of the apparent effect, which decreases as the degree of contamination increases (28).

Three additional trials (19,20,41-44) that reported long term outcomes after exposure to corticosteroids for the prevention or treatment of CLD were identified, increasing the sample size to a total of 870 children evaluated at one year of age or later (Tables 1-3). The identified trials are heterogeneous in the study populations, timing and dosage of postnatal corticosteroid treatment, crossover rates, event rates in the control groups, follow-up rates, time of assessment of neurodevelopment, and instruments used to assess neurodevelopment. Furthermore, not all are peer-reviewed publications. Discrepancies between results reported in abstracts and full publications of the same randomized controlled trial are common (45). Therefore, the data were not combined using meta-analytic techniques; instead, available details are presented in Tables 1 to 3.

## DISCUSSION

Systemic dexamethasone administration with the intent to prevent or treat CLD in the preterm infant does not affect mortality by the time of discharge or length of hospitaliza-

tion. Early and moderately early systemic administration of dexamethasone decreases the incidence of CLD at 28 days' PNA and 36 weeks' PMA and allows for earlier extubation and fewer ventilator days. However, for these short term benefits, there are many short term adverse effects, including hyperglycemia often requiring insulin therapy, hypertension, gastrointestinal bleeding and intestinal perforation, hypertrophic obstructive cardiomyopathy, poor weight gain and poor growth of the head circumference, and a trend toward higher incidence of PVL.

The short term pulmonary benefits of systemic dexamethasone do not appear to confer long term benefits. Survival does not improve after dexamethasone administration. Furthermore, data indicating an increased incidence of neurodevelopmental delay and cerebral palsy raise serious concerns about adverse long term outcomes.

Dexamethasone is a potent anti-inflammatory corticosteroid. The pharmacological doses commonly used in trials and in practice are more than 10 to 15 times the estimated physiological secretion rate of cortisol in neonates. Furthermore, the limited pharmacokinetic data available in infants with extremely low birth weight indicate a prolonged half-life of dexamethasone compared with that in children and adults (46,47). High levels of dexamethasone may increase the rate of adverse effects. Possible alternatives to dexamethasone that may have fewer adverse effects include methylprednisolone, low hydrocortisone doses administered before chronic lung changes have developed or inhaled corticosteroids (48). These interventions require further investigation. However, it is uncertain whether neurodevelopmental abnormalities are linked to the systemic use of corticosteroids in general or just to dexamethasone (28).

The additional three trials noted in the tables (19,20,41-44) increased the sample size by 191 children followed compared with the review by Barrington (28), and by 395 compared with the review by Doyle and Davis (11); this increase in sample size would affect the results of these two previously published meta-analyses (11,28). The results of the three additional trials support the concept that corticosteroids should not be used routinely to prevent or treat infants at high risk of developing CLD or those with established CLD.

In view of the concerns regarding short and long term adverse effects, dexamethasone should not be routinely used to prevent or treat CLD. Enough uncertainty remains with regard to short and long term benefits and harms of corticosteroids to justify further well-designed and executed trials that would use a combination of survival and long term developmental impairments as the primary outcome.

## SUMMARY

- Systemic administration of dexamethasone to preterm infants who are mechanically ventilated decreases the incidences of CLD and extubation failure but does not decrease overall mortality.
- Treatment of infants with VLBW with dexamethasone

is associated with an increased risk of short and long term complications, including impaired growth and neurodevelopmental delay.

- No substantial short or long term benefits have been demonstrated from the use of inhaled corticosteroids in the prevention or treatment of CLD.

### RECOMMENDATIONS

- On the basis of limited short term benefits, the absence of long term benefits, and the number of serious short and long term complications, the routine use of systemic dexamethasone for the prevention or treatment of CLD in infants with VLBW is not recommended.
- Postnatal use of systemic dexamethasone for the prevention or treatment of CLD should be limited to carefully designed randomized double-masked controlled trials. The primary outcome of these trials

should be survival without long term developmental impairments, and the potential confounding factors of contamination and crossover should be avoided.

- Long term neurodevelopmental assessment of infants who are or have been subjects in trials of dexamethasone to prevent or treat CLD is strongly encouraged.
- Clinical trials investigating the use of alternative anti-inflammatory corticosteroids, systemic and inhaled, are required before further recommendations can be made.
- Outside the context of a randomized controlled trial, the use of corticosteroids should be limited to exceptional clinical circumstances (eg, an infant on maximal ventilatory and oxygen support). In those circumstances, parents should be fully informed about the known short and long terms risks and agree to treatment.

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The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.

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