

A MULTICENTER TRIAL OF TWO DEXAMETHASONE REGIMENS IN VENTILATOR-DEPENDENT PREMATURE INFANTS

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ABSTRACT

Background Ventilator-dependent premature infants are often treated with dexamethasone. However, the optimal timing of therapy is unknown.

Methods We compared the benefits and hazards of initiating dexamethasone therapy at two weeks of age and at four weeks of age in 371 ventilator-dependent very-low-birth-weight infants (501 to 1500 g) who had respiratory-index scores (mean airway pressure \times the fraction of inspired oxygen) of ≥ 2.4 at two weeks of age. One hundred eighty-two infants received dexamethasone for two weeks followed by placebo for two weeks, and 189 infants received placebo for two weeks followed by either dexamethasone (those with a respiratory-index score of ≥ 2.4 on treatment day 14) or additional placebo for two weeks. Dexamethasone was given at a dose of 0.25 mg per kilogram of body weight twice daily intravenously or orally for five days, and the dose was then tapered.

Results The median time to ventilator independence was 36 days in the dexamethasone-placebo group and 37 days in the placebo-dexamethasone group. The incidences of chronic lung disease (defined as the need for oxygen supplementation at 36 weeks' postconceptional age) were 66 percent and 67 percent, respectively. Dexamethasone was associated with an increased incidence of nosocomial bacteremia (relative risk, 1.5; 95 percent confidence interval, 1.1 to 2.1) and hyperglycemia (relative risk, 1.9; 95 percent confidence interval, 1.2 to 3.0) in the dexamethasone-placebo group, elevated blood pressure (relative risk, 2.9; 95 percent confidence interval, 1.2 to 6.9) in the placebo-dexamethasone group, and diminished weight gain and head growth ($P < 0.001$) in both groups.

Conclusions Treatment of ventilator-dependent premature infants with dexamethasone at two weeks of age is more hazardous and no more beneficial than treatment at four weeks of age. (N Engl J Med 1998;338:1112-8.)

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MANY neonatologists treat premature infants who cannot be weaned from ventilator support with dexamethasone to improve pulmonary compliance and facilitate extubation.¹⁻⁴ Overall, however, these apparent short-term benefits of dexamethasone therapy are not reflected in a substantial decrease in the duration of

oxygen therapy, the length of hospital stay, or later pulmonary morbidity.⁴⁻⁸ In addition, some treated infants may have glucose intolerance and hypertension while receiving dexamethasone.^{1,2,4} Treating ventilator-dependent premature infants shortly after birth with dexamethasone may mitigate acute lung injury and reduce the incidence of chronic lung disease.⁹⁻¹³ However, the risks of starting dexamethasone at an earlier age are not well delineated.⁹⁻¹⁴ We conducted this multicenter, randomized, double-blind trial to compare the benefits and hazards of giving dexamethasone to ventilator-dependent very-low-birth-weight infants at risk for chronic lung disease at two postnatal ages — two and four weeks.

METHODS

The trial was conducted at the 12 centers of the National Institute of Child Health and Human Development Neonatal Research Network from September 1992 to July 1995. The study was approved by the institutional review board of each center, and informed consent was obtained from the parents or guardians of all the infants.

Eligibility

All ventilator-dependent very-low-birth-weight infants (501 to 1500 g) admitted to the network's centers were eligible for the study if they were 13 to 15 days old, had a respiratory-index score (the mean airway pressure multiplied by the fraction of inspired oxygen) of ≥ 2.4 that had been increasing or minimally decreasing during the previous 48 hours or a score of ≥ 4.0 even if there had been improvement during the preceding 48 hours, had received no glucocorticoid treatment after birth, had no evidence or suspicious signs of sepsis as judged by the treating physician, and had no major congenital anomaly of the cardiovascular, pulmonary, or central nervous system. The respiratory-index score criteria were derived from analyses of factors predictive of chronic lung disease among very-low-birth-weight infants admitted to the network's centers during 1991 and 1992.¹⁵

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Randomization

After the eligible infants were identified and consent was obtained, an order form was sent to each center's pharmacy, where the infants were randomly assigned to one of two treatment groups by the urn method, a procedure that promotes an equal distribution of subjects among treatment groups,¹⁶ and the study medication was prepared. In order to blind clinical staff to the treatment-group assignments, different volumes of placebo (saline) were prepared to match the various doses of dexamethasone.

Intervention

One group of infants (the dexamethasone–placebo group) received a tapering course of dexamethasone in doses given twice a day (0.25 mg per kilogram of body weight per dose for five days, then 0.15 mg, 0.07 mg, and 0.03 mg per kilogram per dose for three days each), followed by two weeks of saline. The other group (the placebo–dexamethasone group) received saline for two weeks, followed by either the same tapering two-week course of dexamethasone given to the first group, if the respiratory-index score was ≥ 2.4 on treatment day 14, or an additional two weeks of saline. Study medication was administered intravenously when an intravenous catheter was in place; otherwise it was given orally. The treating physician had the option of withholding the study drug for up to 72 hours if an infant was undergoing an evaluation for sepsis or, after consultation with the local center's principal investigator, discontinuing it if the infant's clinical condition worsened. After the study period, glucocorticoids could be given at the discretion of the treating physician.

Study End Points

The primary end point was the number of days from randomization to ventilator independence, defined as extubation not requiring reintubation, or extubation followed by elective reintubation for seven days or less so that the infant could undergo a surgical procedure. The main secondary end points were death before discharge from the hospital; the duration of assisted ventilation, supplemental oxygen therapy, and hospital stay; the incidence of chronic lung disease (defined as the need for supplemental oxygen at 36 weeks' postconceptional age by the best obstetrical estimate); and the rates of morbidity and mortality from respiratory causes during the first year. Additional secondary end points during the four-week treatment period were a blood glucose concentration of ≥ 200 mg per deciliter (11.1 mmol per liter), a mean arterial blood pressure of ≥ 75 mm Hg,¹⁷ the rates of change in weight and head circumference, and any of the following concurrent diagnoses: nosocomial bacteremia (as ascertained by a positive blood culture), necrotizing enterocolitis,¹⁸ and upper gastrointestinal bleeding (as ascertained by a guaiac-positive gastric aspirate).

Statistical Analysis

All the randomized infants stayed in the groups to which they had been assigned, and the results were analyzed according to the intention-to-treat method. Group differences were analyzed with the use of Student's *t*-tests and Wilcoxon rank-sum tests for continuous variables and chi-square tests for discrete variables. All statistical tests were two-sided.

The distributions of the numbers of days until ventilator independence were estimated by the Kaplan–Meier method, censored for deaths.¹⁹ The Wilcoxon log-rank test was used to compare the numbers of days to ventilator independence. For this analysis, infants who died before becoming independent of the ventilator were assigned a time that exceeded by one day the longest observed time to ventilator independence among the surviving infants.

Four interim analyses were performed, the results of which were reviewed by an independent Data Safety and Monitoring Committee. The stopping boundary was based on the method of Lan and DeMets with the use of the O'Brien–Fleming spending function.²⁰

RESULTS

Of the 2213 infants who were screened, 600 were eligible for enrollment, and 371 of these were enrolled in the study (Fig. 1). The eligible but not enrolled infants were similar to the enrolled infants with regard to birth weight (mean, 821 vs. 805 g), gestational age (mean, 25.9 vs. 25.6 weeks), sex (60 percent vs. 56 percent male), race (50 percent vs. 50 percent black), use of antenatal glucocorticoid therapy (34 percent vs. 28 percent), and use of surfactant therapy (91 percent vs. 90 percent).

Of the 371 enrolled infants, 182 were assigned to the dexamethasone–placebo group and 189 to the placebo–dexamethasone group. Three infants, two in the former group and one in the latter, did not receive any of the assigned treatments. The characteristics of the infants in the two groups were similar, as were their ventilator settings at the time of randomization (Table 1). Of the 173 infants in the placebo–dexamethasone group who were alive on treatment day 14, 31 (18 percent) did not meet the criterion for starting dexamethasone treatment.

Study-Drug Administration and Open-Label Glucocorticoid Therapy

The majority of the missed doses of the study drug were doses withheld during evaluations for sepsis. The proportion of infants who received at least 90 percent of the planned doses of study drug was greater in the dexamethasone–placebo group than in the placebo–dexamethasone group throughout the four-week treatment period (Table 2). Within each group, compliance with treatment during the first and second weeks was similar to that during the third and fourth weeks of treatment.

The proportions of infants for whom treatment was discontinued were similar in both groups (Table 2). The most frequent reasons for discontinuation were clinical sepsis, defined as acute clinical deterioration accompanied by five or more days of antibiotic therapy regardless of blood-culture results, and deteriorating respiratory status, manifested by the need for increasing ventilator support. In both groups, the majority of terminations occurred during the first two weeks of treatment.

Glucocorticoids were given openly in both groups during the four-week treatment period (Table 2). Although infants in the placebo–dexamethasone group were more likely to receive open-label glucocorticoid therapy during the four-week treatment period, 40 percent of the infants in each group received open-label glucocorticoid therapy at some time during their hospitalization, and the average numbers of doses given, including the doses given during the study period, were similar (44 doses in the dexamethasone–placebo group and 48 in the placebo–dexamethasone group).

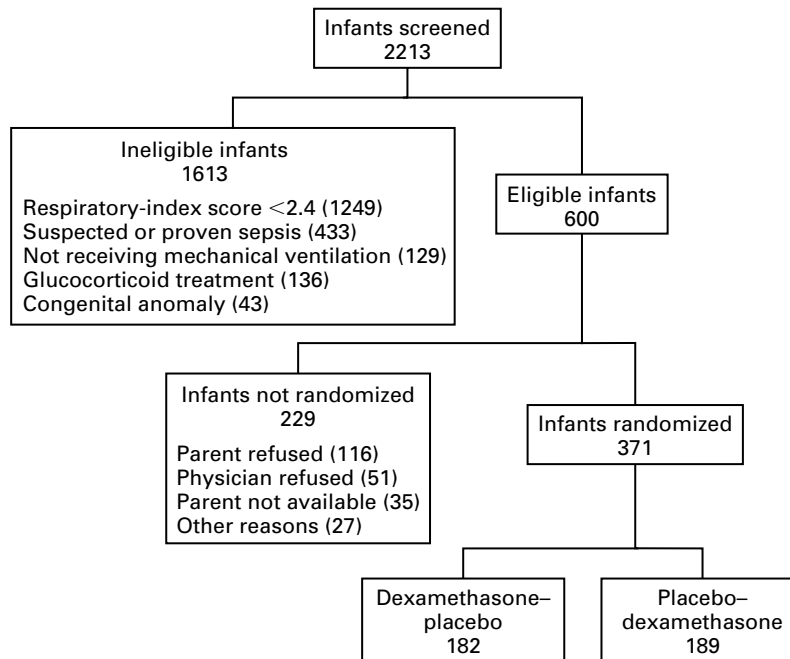


Figure 1. Numbers of Very-Low-Birth-Weight Infants Screened, Eligible, and Randomized in a Multi-center Trial of Two Dexamethasone Regimens in Ventilator-Dependent Premature Infants. Some infants had more than one reason for ineligibility.

Clinical Outcome

Extubation was more likely to be done in both groups during dexamethasone treatment (Fig. 2). During weeks 1 and 2, 22 percent of the infants in the dexamethasone–placebo group and 6 percent of the infants in the placebo–dexamethasone group were extubated, as compared with 17 percent and 36 percent, respectively, during weeks 3 and 4. At the end of the four-week treatment period, the cumulative rates of extubation were similar (39 percent in the dexamethasone–placebo group and 42 percent in the placebo–dexamethasone group). After the four-week treatment period, extubation continued to be performed at similar rates in both groups. The median time to ventilator independence was 36 days in the dexamethasone–placebo group and 37 days in the placebo–dexamethasone group. There were no differences between the groups in mortality, the duration of assisted ventilation, the duration of oxygen therapy, the median length of hospital stay, or the frequency of chronic lung disease (Table 3).

Adverse Events

The complications attributable to dexamethasone are shown in Table 4. During the first two weeks of treatment, more infants in the dexamethasone–placebo group had nosocomial bacteremia (relative risk, 1.5; 95 percent confidence interval, 1.1 to 2.1). The distributions of the organisms cultured were similar;

coagulase-negative staphylococci were the most common, followed by gram-negative organisms and fungi. Blood glucose concentrations of ≥ 200 mg per deciliter were more often detected when dexamethasone was administered during weeks 1 and 2 (relative risk, 1.9; 95 percent confidence interval, 1.2 to 3.0), whereas mean blood pressures of ≥ 75 mm Hg were more common when dexamethasone was given during weeks 3 and 4 (relative risk, 2.9; 95 percent confidence interval, 1.2 to 6.9). The rates of weight gain and head growth were significantly lower in both groups during the periods in which they received dexamethasone ($P < 0.001$). At the end of the four-week treatment period, there were no net differences in growth. During the two weeks after the four-week treatment period, the rates of growth of both groups were similar to that of the placebo–dexamethasone group during weeks 3 and 4. The incidences of necrotizing enterocolitis and upper gastrointestinal bleeding were similar in the two groups.

Mortality and Morbidity at One Year

Of the 328 surviving infants, 309 (94 percent) were followed until they were 12 months of age. The post-discharge mortality rates were 9 percent in the dexamethasone–placebo group and 8 percent in the placebo–dexamethasone group. Oxygen therapy was prescribed for 48 percent of the former group

TABLE 1. BASE-LINE CHARACTERISTICS OF THE VERY-LOW-BIRTH-WEIGHT INFANTS.*

CHARACTERISTIC	DEXAMETHASONE- PLACEBO (N = 182)	PLACEBO- DEXAMETHASONE (N = 189)
Birth weight — g	808±187	801±182
Gestational age — wk	25.7±1.9	25.6±1.6
Male sex — no. (%)	96 (53)	112 (59)
Race or ethnic group — no. (%)		
Black	92 (51)	94 (50)
White	54 (30)	62 (33)
Hispanic	30 (16)	29 (15)
Other	6 (3)	4 (2)
Antenatal glucocorticoid therapy — no. (%)	53 (29)	51 (27)
Apgar score ≤3 — no. (%)		
1 min	93 (51)	96 (51)
5 min	29 (16)	22 (12)
Surfactant therapy — no. (%)	165 (91)	169 (89)
Pulmonary air leak — no. (%)	47 (26)	54 (29)
Patent ductus arteriosus requiring treatment — no. (%)†	128 (70)	113 (60)
Clinical sepsis — no. (%)‡	25 (14)	23 (12)
Fraction of inspired oxygen	0.54±0.18	0.54±0.19
Airway pressure (cm of water)	8±2	8±2
Respiratory-index score	4.6±2.3	4.7±2.6

*Plus-minus values are means ±SD.

†P=0.03 for the comparison between the two groups.

‡Clinical sepsis was defined as acute clinical deterioration accompanied by five or more days of antibiotic therapy, regardless of blood-culture results.

and 52 percent of the latter, for a median of 5.0 and 5.5 months, respectively. The rates of rehospitalization for respiratory problems were similar in the two groups (37 percent and 36 percent).

DISCUSSION

In the Collaborative Dexamethasone Trial, the duration of assisted ventilation was significantly shortened when ventilator-dependent premature infants were treated with dexamethasone at approximately 4 weeks of age (median age, 29 days).⁴ In our study, we found no clear pulmonary benefit from giving dexamethasone therapy at two weeks rather than four weeks of age. Although dexamethasone facilitated extubation in both groups, the times to ventilator independence were similar. In addition, there were no significant differences in the duration of oxygen therapy or the incidence of chronic lung disease.

As in other trials,^{4,13,14} a high proportion of infants received additional glucocorticoid after completion of the treatment protocol. This reflects current clinical practice for infants as ill as those in our study. Except for the timing of dexamethasone treatment, we made no attempt to control other aspects of care that might influence the development of chronic lung disease. This approach is appropriate for a management trial designed to assess treatment effectiveness under usual clinical circumstances.²¹ For this reason, as well as the fact that we studied a hetero-

TABLE 2. ADMINISTRATION OF STUDY MEDICATION AND OPEN-LABEL GLUCOCORTICOID THERAPY DURING THE FOUR-WEEK TREATMENT PERIOD IN VERY-LOW-BIRTH-WEIGHT INFANTS AT RISK FOR CHRONIC LUNG DISEASE.

VARIABLE	STUDY WEEKS 1 AND 2		STUDY WEEKS 3 AND 4	
	DEXAMETHASONE- PLACEBO (N = 182)	PLACEBO- DEXAMETHASONE (N = 189)	DEXAMETHASONE- PLACEBO (N = 175)	PLACEBO- DEXAMETHASONE (N = 173)
	number (percent)			
Infants who received ≥90% of doses	145 (80)	141 (75)	140 (80)	134 (77)
Infants who received ≥50% of doses	166 (91)	164 (87)	145 (83)	137 (79)
Reasons for discontinuing study drug				
Clinical sepsis*	12 (7)	13 (7)	2 (1)	0
Deteriorating respiratory status†	4 (2)	18 (10)	4 (2)	0
Other medical indications	6 (3)	4 (2)	1 (<1)	4 (2)
Parent's or clinician's request	3 (2)	1 (<1)	1 (<1)	1 (<1)
Total	25 (14)	36 (19)	8 (5)	5 (3)
Infants who received open-label glucocorticoid therapy	8 (4)	24 (13)	13 (7)	6 (3)

*Clinical sepsis was defined as acute clinical deterioration accompanied by five or more days of antibiotic therapy, regardless of blood-culture results.

†Deteriorating respiratory status was manifested by the need for increasing ventilator support.

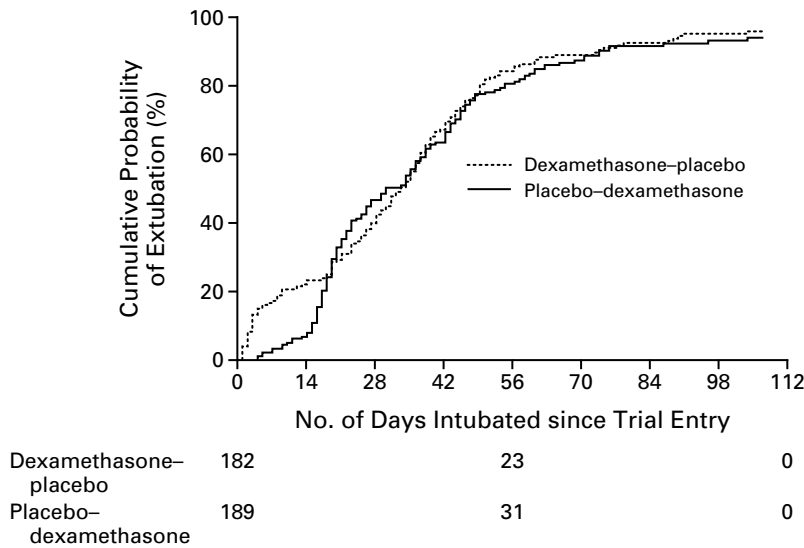


Figure 2. Cumulative Probability of Extubation after Entry into the Trial. The numbers of intubated infants in each group on study days 0, 56, and 112 are shown below the graph. Data on infants who died were censored at death.

geneous group of infants at 12 neonatal centers, our findings may be broadly generalizable to other neonatal centers in the United States.²²

Dexamethasone therapy did not reduce mortality or later pulmonary morbidity among the infants enrolled in the Collaborative Dexamethasone Trial.⁶ In our trial, the infants treated at two weeks of age had outcomes in infancy similar to those of the infants treated at four weeks of age. This may reflect either a lack of long-term benefit of dexamethasone or the development of irreversible lung injury before therapy. Starting dexamethasone therapy in ventilator-dependent very-low-birth-weight infants shortly after birth may mitigate permanent lung injury.¹³

Dexamethasone increases blood glucose concentrations and raises blood pressure in infants.^{1,2,9,10} In our study, the frequency of these complications was related to the time treatment was started. The increase in blood pressure detected during dexamethasone therapy at four weeks of age accords with a previous report that the highest risk of an elevation in blood pressure occurs in infants who are older when therapy is initiated.²³ Unlike previous investigators, we found a substantial increase (50 percent) in nosocomial bacteremia with dexamethasone therapy, but only among infants treated at two weeks of age.^{4,13,24} Nosocomial infections are reported to increase morbidity and prolong the length of hospital stays among very-low-birth-weight infants.²⁵

A short-term negative effect of dexamethasone on weight gain has been reported previously.¹⁰ We also noted slowing of head growth. This finding implies that brain growth in premature infants, like that in

TABLE 3. STUDY OUTCOMES IN THE DEXAMETHASONE-PLACEBO AND PLACEBO-DEXAMETHASONE GROUPS.

OUTCOME	DEXAMETHASONE-PLACEBO (N=182)	PLACEBO-DEXAMETHASONE (N=189)	P VALUE
Died in the hospital — no. (%)	17 (9)	26 (14)	0.18
Survived			
Median duration of assisted ventilation — days*	39 (35–45)	38 (37–42)	0.10
Median duration of oxygen therapy — days*	85 (80–93)	92 (83–97)	0.11
Median length of hospital stay — days*	105 (101–112)	108 (104–118)	0.15
Chronic lung disease — no. (%)†	121 (66)	127 (67)	0.86

*Values in parentheses are 95 percent confidence intervals.

†Chronic lung disease was defined as the need for supplemental oxygen at 36 weeks' postconceptional age.

neonatal animals, is adversely affected by glucocorticoids.^{26,27} Because we treated both groups with dexamethasone, we are unable to assess whether there may also be long-term adverse effects on growth and development. There are few published follow-up studies of very-low-birth-weight infants enrolled in dexamethasone trials.^{6,9} In the Collaborative Dexamethasone Trial, ventilator-dependent infants who were randomly assigned to dexamethasone tended to have an increase in cerebral palsy, and their weight and height were below the third percentile at three years of age.⁶ Preliminary reports from two recent

TABLE 4. COMPLICATIONS ATTRIBUTABLE TO THE STUDY DRUG IN THE DEXAMETHASONE-PLACEBO AND PLACEBO-DEXAMETHASONE GROUPS.*

COMPLICATION	STUDY WEEKS 1 AND 2				STUDY WEEKS 3 AND 4			
	DEXAMETHASONE- PLACEBO (N = 182)	PLACEBO- DEXAMETHASONE (N = 189)	RELATIVE RISK (95% CI)	P VALUE	DEXAMETHASONE- PLACEBO (N = 175)	PLACEBO- DEXAMETHASONE (N = 173)	RELATIVE RISK (95% CI)	P VALUE
Nosocomial bacteremia — no. (%)	65 (36)	45 (24)	1.5 (1.1–2.1)	0.01	38 (22)	27 (16)	1.4 (0.9–2.1)	0.14
Blood glucose ≥200 mg/dl — no. (%)	44 (24)	24 (13)	1.9 (1.2–3.0)	0.004	10 (6)	13 (8)	0.8 (0.3–1.7)	0.49
Mean arterial blood pressure ≥75 mm Hg — no. (%)	11 (6)	6 (3)	1.9 (0.7–5.0)	0.20	6 (3)	17 (10)	0.4 (0.1–0.9)	0.02
Necrotizing enterocolitis — no. (%)	4 (2)	8 (4)	0.5 (0.2–1.8)	0.27	1 (1)	1 (1)	1.0 (0.1–15.8)	1.0
Gastrointestinal bleeding — no. (%)	27 (15)	17 (9)	1.7 (0.9–2.9)	0.08	13 (7)	8 (5)	1.6 (0.7–3.8)	0.27
Weight gain — g	38±101	122±86		<0.001	225±111	140±99		<0.001
Head growth — cm	0.8±0.8	1.2±0.8		<0.001	1.8±0.8	1.4±0.8		<0.001

*Relative risks are for the dexamethasone-placebo group as compared with the placebo-dexamethasone group. Plus-minus values are means ±SD. CI denotes confidence interval.

trials suggest that neuromotor abnormalities and cerebral palsy are more common among ventilator-dependent infants treated with prophylactic dexamethasone for 21 days²⁸ and 42 days.²⁹

Because dexamethasone was commonly used to treat ventilator-dependent infants at risk for chronic lung disease at the participating centers, there was insufficient equipoise to include an untreated group in our trial.³⁰ However, our findings and those of others^{6,28,29} suggest that future studies should include an untreated group to assess whether the short-term pulmonary benefits of dexamethasone outweigh its short-term adverse effects and potential deleterious effects on the developing brain.

In summary, we found no overall benefit and more hazards associated with starting dexamethasone therapy at two weeks instead of four weeks of age in ventilator-dependent very-low-birth-weight infants at risk for chronic lung disease. The dose of dexamethasone and the duration of treatment in this trial are similar to those commonly used to wean premature infants from ventilator support. The curtailment of head growth and weight gain that occurred in both groups during dexamethasone therapy raises the question of whether the current treatment is potentially more harmful than beneficial.

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