Dexamethasone Therapy Increases Infection in Very Low Birth Weight Infants

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ABSTRACT. *Background.* **Infection is a major complication of preterm infants, resulting in increased morbidity and mortality. We recently reported the results of a multicenter trial of dexamethasone initiated at 14 or 28 days in very low birth weight (VLBW) infants who were at risk for chronic lung disease; the results showed an increase in nosocomial bacteremia in the group receiving dexamethasone. This study is an in-depth analysis of bacteremia/sepsis and meningitis among infants enrolled in the trial.**

Methods. **Data on cultures performed and antibiotic therapy were collected prospectively. Infections were classified as definite or possible/clinical.**

Results. **A total of 371 infants were enrolled in the trial. There were no baseline differences in risk factors for infection. For the first 14 days of study, infants received either dexamethasone (group I, 182) or placebo (group II, 189). During this period, infants in group I were significantly more likely than those in group II to have a positive blood culture result (48% vs 30%) and definite bacteremia/sepsis/meningitis (22% vs 14%). Over the 6-week study period, 47% of those cultured had at least one positive blood culture result (53% in group I vs 41% in group II) and 25% of the infants had at least one episode of definite bacteremia/sepsis/meningitis (29% in group I vs 21% in group II). Among infants with definite infections, 46.8% were attributable to Gram-positive organisms, 26.6% to Gram-negative organisms and 26.6% to fungi. The factors present at randomization were evaluated for their association with infection. Group I assignment and H_2 blocker therapy (before study entry) were associated with increased risk of definite infection, whereas cesarean section delivery and increasing birth weight were associated with decreased risk.**

Conclusions. **Infants who received a 14-day course of dexamethasone initiated at 2 weeks of age were more likely to develop a bloodstream or cerebrospinal fluid infection while on dexamethasone therapy than were those who received placebo. Physicians must consider this increased risk of infection when deciding whether to treat VLBW infants with dexamethasone.** *Pediatrics* **1999; 104(5). URL: http://www.pediatrics.org/cgi/content/full/104/5/e63;** ***very low birth weight, dexamethasone, nosocomial infection.***

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ABBREVIATIONS. VLBW, very low birth weight; NICHD, National Institute of Child Health and Human Development; CLD, chronic lung disease; CONS, coagulase-negative staphylococcus; CSF, cerebrospinal fluid; RR, relative risk; CI, confidence interval; OR, odds ratio; RIS, respiratory index score; LP, lumbar punctures; C/S, cesarean section.

Dexamethasone is used widely in very low birth weight (VLBW) infants to shorten the duration of mechanical ventilation,[1–8] but no long-term benefits of corticosteroid therapy have been established.[9–11] A major question for physicians regarding the use of postnatal dexamethasone is whether the benefits outweigh the potential complications.[12–15] Nosocomial infection is a major complication of preterm infants. Among nearly 8000 VLBW infants (401–1500 g at birth) in the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network, 25% of those who survived beyond 3 days had one or more episodes of blood culture-proven sepsis, with rates as high as 50% for the cohort of infant weighing 401 to 750 g at birth.[16] Nosocomial infections contributed to prolonged length of mechanical ventilation, prolonged duration of hospitalization, and increased risk of death. This study is an in-depth analysis of infectious complications among VLBW infants enrolled in a multicenter, randomized trial of dexamethasone.[17]

METHODS

A multicenter, randomized, double-blind trial was conducted by the NICHD Neonatal Research Network to compare the effects of dexamethasone therapy started at two different ages in VLBW infants at high risk for chronic lung disease (CLD).[17] Ventilator-dependent VLBW (501–1500 g) infants were randomized at 13 to 15 days of age to a 14-day tapering course of dexamethasone (beginning at 0.25 mg/kg/dose every 12 hours) followed by 14 days of placebo (group I); or a 14-day course of placebo followed by 14 days of either dexamethasone, if needed (ie, still at risk for CLD by predefined respiratory criteria), or placebo (group II;

Fig 1). The primary outcome for this trial was time to extubation. This paper reports secondary analyses from the primary trial. The design of this trial allowed us to assess whether 1) dexamethasone affects the incidence of infection while infants are receiving corticosteroids (analyses during the 2 weeks after randomization when group I received dexamethasone and group II received placebo); and 2) the timing of dexamethasone administration affects the overall incidence of infection (analyses over the entire study period).

For 42 days after randomization, information was collected prospectively on various factors, including respiratory support, blood pressure, blood glucose, central venous and arterial catheters, medications, and clinical suspicion of infection. All cultures performed (date, source, and results) and antibiotics given were recorded. The suspected infections were classified as definite or possible/clinical, based on the following definitions. Definite infection (bacteremia/sepsis/meningitis) was defined as the clinical suspicion of infection plus one or more positive blood culture results for an organism known to be associated with sepsis (ie, group B streptococcus or *Escherichia coli*) or two or more positive blood culture results for an organism that could be either a true cause of sepsis or a contaminant (ie, coagulase-negative staphylococcus [CONS]), drawn on the same day or the following 2 days or any organism in cerebrospinal fluid (CSF), except CONS, which required two positive CSF culture results drawn within 4 days. In addition, definite infection required treatment with antibiotics for ≥5 days unless an infant died. Possible/clinical infection was defined as the clinical suspicion of infection with negative blood culture results or one positive blood culture result for CONS and antibiotic therapy for ≥5 days.

Statistical Methods

Data were analyzed using the intent-to-treat paradigm. SAS and S-Plus software packages were used,[18,19] and the characteristics of the groups were compared using χ^2 analyses. We calculated the relative risk (RR) and 95% confidence interval (CI) for each difference between the groups. Logistic regression models were used to estimate the association of baseline risk factors with subsequent definite infection using odds ratio (OR). The Kaplan Meier method[20] was used to estimate the distribution of times to first definite infection, and the differences between groups were evaluated by the log rank test. The effect of the treatment groups

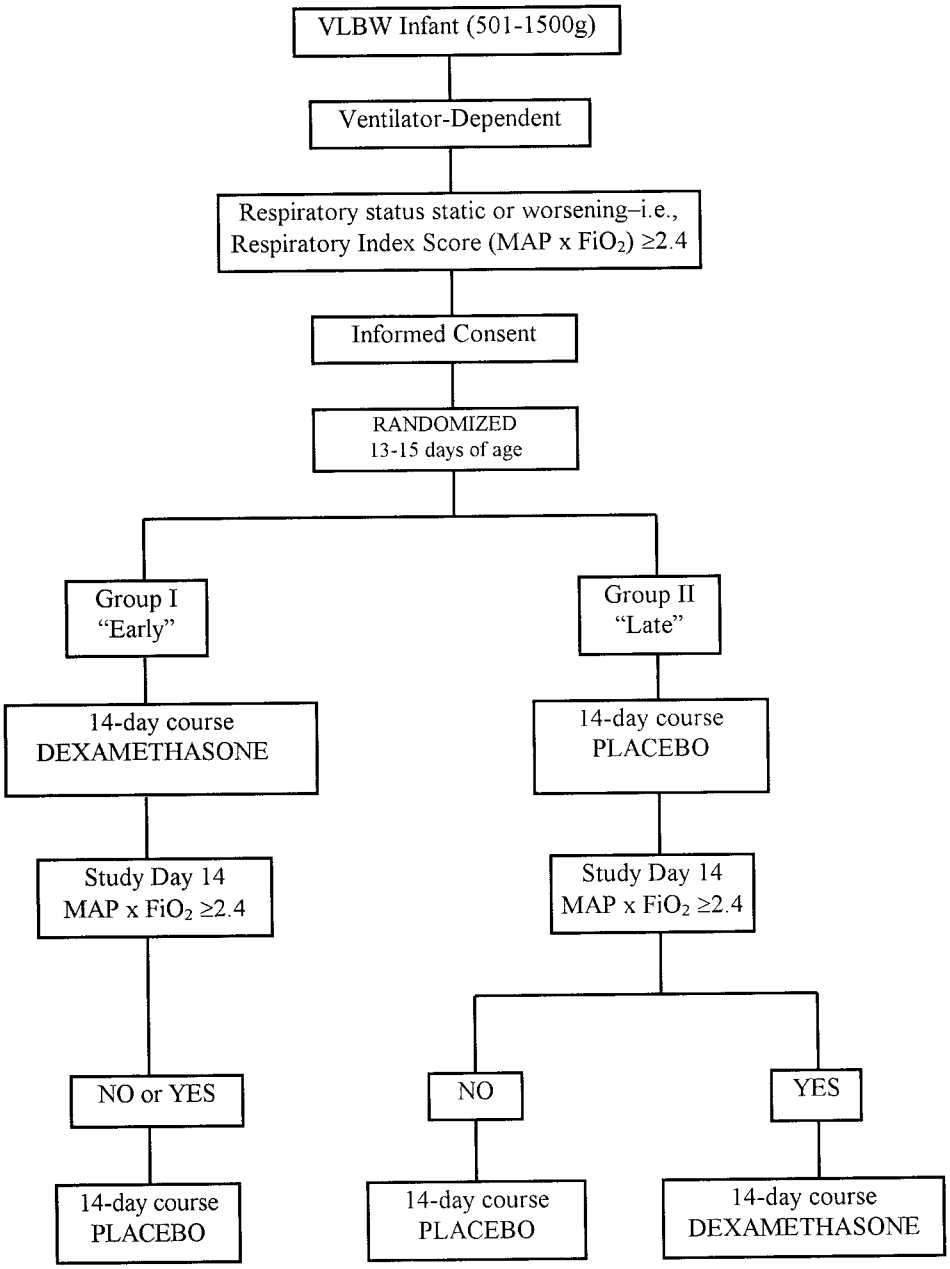

Fig 1. Trial design.

across centers was assessed using the Breslow-Day test for homogeneity of OR.[21]

RESULTS

Between September 1992 and July 1995, 371 infants were enrolled in the trial (group I = 182; group II = 189). At the time of enrollment, there were no differences between groups in birth weight (mean ± standard deviation: 808 ± 187 g vs 801 ± 182 g), gestational age (mean ± standard deviation: 25.7 ± 1.9 weeks vs 25.6 ± 1.6 weeks), sex (53% vs 59% male), race (51% vs 50% black), antenatal steroids (29% vs 27%), postnatal surfactant (91% vs 89%), or severity of lung disease (mean respiratory index score [RIS] = mean airway pressure × F_{IO_2}; 4.6 ± 2.3 vs 4.7 ± 2.6).[17] In addition, there were no significant differences in antibiotic treatment (48% vs 46%), and either early onset sepsis (≤72 hours; 1.6% both groups) or late onset sepsis before randomization (12% vs 11%).

Corticosteroid Use and Infection

Infections During the Period of Corticosteroid Administration

This analysis was confined to the first 2 weeks of the trial when infants were randomized to receive either dexamethasone (group I) or placebo (group II). Compliance with the protocol was high during this period: 85% of infants received ≥80% of all scheduled study doses, and 92% received ≥10 consecutive doses. Of the group II infants, 12% (22/189) received corticosteroids rather than placebo at some time during the first 2 weeks of the trial at the insistence of the attending neonatologist. We excluded observations from the second 2 weeks of the study from our analyses to assess whether dexamethasone administration increases the likelihood of infection. Although the two groups were comparable at randomization and received either dexamethasone or placebo, during the next 2 weeks, only the subset of group II infants who still met predefined respiratory criteria received dexamethasone (Fig 1).

Over the first 2 weeks of the study, infants in group I (dexamethasone exposed) were significantly more likely to have at least one positive blood culture result, if cultured, than were infants in group II (48% vs 30%; RR: 1.62; 95% CI: 1.20, 2.18). Infants in group I also were significantly more likely to develop one or more definite infections (bloodstream and/or CSF) than were those in group II (22% vs 14%; RR: 1.60; CI: 1.02, 2.51). Possible/clinical infection was more frequent in group II (29% vs 38%; RR: 0.75; CI: 0.56, 1.01; Table 1). Although the above analyses were performed using an intent-to-treat paradigm, there was a similar increase in both nosocomial bacteremia and definite infections when patients who received dexamethasone (drug-exposed group) were compared with those who did not receive dexamethasone (not exposed) over the first 2 weeks of the study (group I vs group II, positive blood culture results: 35% vs 23%; RR: 1.52; CI: 1.08, 2.15; definite infections: 22% vs 13%; RR: 1.68; CI: 1.04, 2.71).

Lumbar punctures (LPs) were performed on 33% of infants during the first 2 weeks of the trial. The criteria for performing LPs, differed across centers.

TABLE 1. Infection Analyses: Dexamethasone Trial

	Group I (n = 182)	Group II (n = 189)	RR (95% CI)
Study days 1–14			
Blood cultures	135 (74%)	151 (80%)	0.93 (0.83, 1.04)
+ Blood cultures*	65 (48%)†	45 (30%)†	1.62 (1.20, 2.18)
Definite infections*	40 (22%)	26 (14%)	1.60 (1.02, 2.51)
Clinical infections	52 (29%)	72 (38%)	0.75 (0.56, 1.01)
Study days 1–42			
Blood cultures	156 (86%)	174 (92%)	0.93 (0.87, 1.0)
+ Blood cultures*	83 (53%)†	71 (41%)†	1.30 (1.03, 1.64)
Definite infections	53 (29%)	40 (21%)	1.38 (0.96, 1.97)
Clinical infections	97 (53%)	110 (58%)	0.92 (0.76, 1.10)

* $P < .05$

† Of those with blood cultures performed.

LPs were performed more frequently on infants in group I than group II (41% vs 26%; RR: 1.59; CI: 1.18, 2.14), perhaps reflecting the higher frequency of positive blood culture results in this group. There were no differences, however, in the percentages of infants with LPs performed who had positive CSF culture results (16% vs 14%; RR: 1.12; CI: 0.47, 2.65). (Overall, 7% of infants in group I vs 4% of infants in group II had positive CSF culture results.)

Infections Over the 6-Week Study Period

Infants received coded study medication for 28 days and had clinical follow-up for 42 days after randomization. Observations over the entire 6-week study period were used to address the question of whether the timing of dexamethasone administration had an overall effect on infection. Over the 4-week dosing period, 81% of group I infants and 77% of group II infants received ≥80% of scheduled study doses, 6% (11/182) of infants in group I received open-labeled corticosteroids at a time when placebo was assigned by protocol, and 12% (22/189) of infants in Group II received corticosteroids when they should have received placebo. These protocol deviations were physician mandated, not dosing errors.

The infants who were enrolled in this trial were very small and sick, requiring mechanical ventilation at 2 weeks of age with ventilatory criteria that predicted development of CLD among VLBW infants admitted to Network centers in 1991 through 1992.[22] The majority of infants (89%) were suspected of being infected and had blood cultures performed at some time during the 42-day study period. Between 1 and 20 cultures were drawn from the 330 infants who were cultured, resulting in a total of 1481 cultures. Of the infants, 34% had 5 or more cultures with no difference between groups in the number of cultures performed. Over the 42-day study period, 154 of 371 (42%) infants had at least one positive blood culture result, and 417 of 1481 (28%) blood culture results were positive.

One quarter of the infants (93/371) were judged to have one or more definite infections; and 56% (207/371) developed at least one episode of possible/clinical infection. Among the 330 infants with blood cultures performed, infants in group I were significantly more likely to have a positive blood culture

result (Table 1; 53% vs 41%; RR: 1.30; CI: 1.03, 1.64). Although definite bloodstream and/or CSF infections were more common among infants in group I, the differences did not reach statistical significance (29% vs 21%; RR: 1.38; CI: 0.96, 1.97). The percentage of infants with possible/clinical infection did not differ between groups (53% vs 58%; RR: 0.92; CI: 0.76, 1.10). LPs were performed on 54% (199/371) of infants. The infants in group I had a significantly higher proportion of positive CSF culture results than did those in group II (10% vs 4%; RR: 2.47; CI: 1.11, 5.49). The cumulative probability of a definite infection (by group) is shown in Fig 2. A separation in the time to first infection is seen after day 7 of the study.

The distribution of organisms isolated from patients with definite infections is presented in Table 2. There were no significant differences between groups I and II in the type of organisms associated with definite infection for either the first 2 weeks of the study or the entire 6-week study period. Among infants with definite infections (for both days 1–14 and days 1–42), 46.8% of the definite infections were attributable to Gram-positive organisms 26.6% to Gram-negative organisms, and 26.6% to fungi. *Staphylococcus aureus* was the only organism isolated significantly more frequently from patients receiving dexamethasone (days 1–14 group I vs group II: 23% vs 10%; $P < .05$; days 1–42 group I vs group II: 17% vs 8%; $P < .05$). There were no differences in the results related to infection among the study centers. Table 3 summarizes the likelihood of specific conditions occurring in group I versus group II when the differences in treatment effect at the 12 clinical centers are considered. Overall, there were no specific centers where the influence of dexamethasone on infection was significantly different than for the entire cohort at the 12 sites. There were no significant differences in the estimated ORs across centers in the number of blood or CSF cultures performed, the percentage of positive culture results, the distribution of organisms (fungi, Gram-negatives, CONS, and Gram-positives without CONS), or the number of infants with definite or possible/clinical infection.

A total of 43 infants died before hospital discharge (17 from group I and 26 from group II). It is acknowledged that it is often difficult to determine the specific cause of death. Nonetheless, per Network protocol, cause of death was assigned by each principal investigator, who was blinded to the study group. Predefined causes of death related to infection included proven or suspected sepsis/infection and infection associated with respiratory distress, bronchopulmonary dysplasia, or necrotizing enterocolitis. Of the 43 deaths, 29 (67%) were attributed to infection (10 from group I and 19 from group II). Eleven patients had autopsies performed. These data were taken into consideration in assigning a cause of death; all autopsied patients were believed to have had infection-related deaths. Although infants in group I had fewer infection-associated deaths, there were no significant differences between groups in the number of infection-associated deaths overall (10/182 vs 19/189; RR: 0.55; CI: 0.16, 1.40) or in the number of infection-associated deaths among infants with definite infections for study days 1 through 14 (3/40 vs 6/26; RR: 0.33; CI: 0.01, 2.39).

Baseline Risk Factors and Subsequent Infection

Various factors present before randomization were evaluated for their possible association with subsequent infection, including birth weight, gestational age, race, sex, prenatal care, antenatal steroid, C/S delivery, RIS, high frequency ventilation, early and late onset sepsis, urinary tract infection, necrotizing enterocolitis, central venous (surgical and percutaneous) and/or arterial catheter use, assigned treatment group, and therapy with antibiotics, indomethacin, xanthines, and/or H_2 blockers (Table 4). Variables entered into the logistic regression analyses were chosen because they are considered to be possible risk factors for nosocomial infection. Increasing birth weight and gestational age and C/S delivery were associated with a decreased risk of definite infection for the first 2 weeks of the trial, whereas randomization to group I, late onset sepsis, and H_2 blocker therapy before randomization were associated with an increased risk of definite infection (unadjusted).

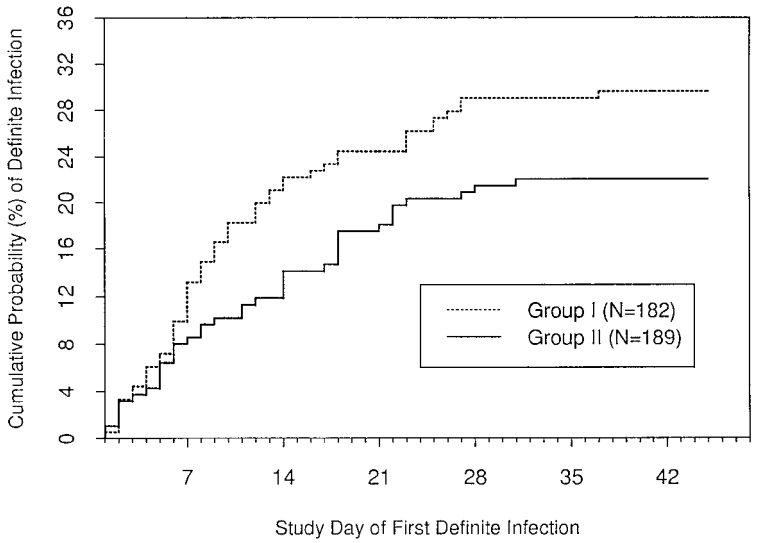

Fig 2. Cumulative probability of the first definite infection in infants enrolled in the NICHD Neonatal Research Network Dexamethasone Trial (deaths censored).

TABLE 2. Organisms Associated With Definite Infection*

Organisms	Study Days 1 to 14		Study Days 1 to 42	
	Group I**	Group II**	Group I**	Group II**
Gram-positives				
*Staphylococcus aureus****	11	3	12	4
Coagulase-negative staphylococci	7	10	13	15
Other	3	3	8	6
All	21	16	33	25
Gram-negatives				
Escherichia coli	3	2	5	2
Klebsiella	3	2	3	4
Enterobacter	5	3	7	5
Other	2	1	4	3
All	13	8	19	14
Fungi				
Candida albicans	7	3	11	6
Candida parapsilosis	6	2	6	4
Other	1	2	2	4
All	14	7	19	14

* Definite infection was defined as one or more positive blood culture results for an organism known to be associated with sepsis (eg, group B streptococcus or *Escherichia coli*) or two or more positive blood culture results for an organism that could be either a true cause of sepsis or a contaminant (eg, CONS) drawn on the same day or the following 2 days or any organism in CSF except CONS, which required two positive CSF culture results drawn within 4 days.
** Days 1 to 14: 48 infections among 40 infants with definite infection in group I versus 31 infections among 26 infants with definite infection in group II.
Days 1 to 42: 71 infections among 53 infants with definite infection in group I versus 53 infections among 40 infants with definite infection in group II.
*** Group I versus group II, $P < .05$ for days 1 to 14 and days 1 to 42.

TABLE 3. Infection Analysis Adjusted for Center Differences—Group I Versus Group II

Variable	Days 1 to 14		Days 1 to 42	
	Adjusted OR (95% CI)	*P* Value for Homogeneity*	Adjusted OR (95% CI)	*P* Value for Homogeneity
Blood culture performed	0.72 (0.44, 1.18)	.60	0.49 (0.25, 0.97)	.24
Positive blood culture results	2.31 (1.39, 3.84)	.94	1.73 (1.09, 2.76)	.90
LP performed	2.06 (1.32, 3.22)	.24	1.40 (0.91, 2.15)	.39
Positive CSF culture results	1.15 (0.39, 3.36)	.47	2.23 (0.92, 5.43)	.41
Definite infection	1.86 (1.06, 3.26)	.97	1.61 (0.99, 2.63)	.78
Possible/clinical infection	0.65 (0.42, 1.00)	.13	0.80 (0.53, 1.21)	.59

* A nonsignificant *P* value for homogeneity indicates that there are no significant differences across centers in the effect of group I versus group II.

Using a logistic regression model with backward selection, increasing birth weight and C/S remained statistically significant factors associated with reduced risk, whereas randomization to early steroids and H_2 blocker therapy were associated with a significantly increased risk of definite infection. Over the entire study period, the unadjusted factors of increasing gestational age and birth weight and C/S seemed to have a protective effect on the incidence of definite infection. By contrast, being black , having a higher baseline RIS, having had late onset sepsis before randomization, and using H_2 blockers seemed to increase the risk. Adjusting for other covariates, C/S delivery and increasing birth weight were associated with a reduced risk of definite infection, whereas H_2 blocker therapy before randomization was associated with an increased risk.

DISCUSSION

In this randomized controlled trial, we documented that dexamethasone therapy increases bloodstream and/or CSF infection in VLBW infants. Our findings are consistent with a previous report by Yeh et al[15] who reported a significant increase in culture-proven bacteremia or clinical suspicion of sepsis in infants who received a 28-day course of dexamethasone, beginning on the first postnatal day of age. There were notable differences between this trial and the Yeh trial; we studied a smaller, more immature, sicker cohort, began steroids at 2 weeks of age versus 1 day of age, gave a 2-week rather than a 4-week course of steroids, and found a significantly higher rate of culture-documented infection.

The high number of blood cultures performed over the 42-day study period (1481 cultures among 371 infants) is a reminder of how frequently physicians caring for VLBW infants suspect sepsis. This reflects the severity of illness of the cohort and possibly the heightened concern for infection in infants who might be receiving dexamethasone. Although the rates of possible/clinical infection did not differ between groups for the entire study period, for the first 14 days, infants in the placebo arm were more likely to have a diagnosis of possible/clinical infection. A possible explanation is that the infants receiving placebo continued to have more severe respiratory disease over these 2 weeks, and, because exacerbations of respiratory disease may mimic sep-

TABLE 4. Significant Risk Factors* Before Randomization and Subsequent Definite Infections for Study Days 1 to 14 and 1 to 42

Days 1 to 14 (n = 371)	Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI
Risk factor				
Birth weight	0.83	(0.76, 0.91)	0.83	(0.76, 0.92)
Gestational age	0.75	(0.63, 0.89)		
C/S	0.49	(0.28, 0.85)	0.52	(0.29, 0.94)
Group I	1.77	(1.03, 3.04)	1.84	(1.04, 3.25)
Late septicemia/bacteremia	2.33	(1.14, 4.78)		
H_2 blockers	3.03	(1.32, 6.95)	3.12	(1.29, 7.57)
Days 1–42 (n = 371)	Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI
Risk factor				
Birth weight	0.86	(0.80, 0.93)	0.87	(0.80, 0.94)
Gestational age	0.79	(0.69, 0.92)		
C/S	0.53	(0.32, 0.86)	0.56	(0.33, 0.93)
Black race	1.62	(1.01, 2.61)		
Baseline respiratory index score (↑)	1.11	(1.01, 1.21)		
Late septicemia/bacteremia	2.01	(1.03, 3.95)		
H_2 blockers	3.06	(1.38, 6.79)	3.19	(1.38, 7.38)

* Factors evaluated included birth weight, gestational age, race, sex, prenatal care, antenatal steroids, cesarean section delivery, respiratory index score, high frequency ventilation, early and late onset sepsis, urinary tract infection, necrotizing enterocolitis, central venous (surgical and percutaneous) and/or arterial catheter use, assigned treatment group, and therapy with antibiotics, indomethacin, xanthines, and/or H_2 blockers.

sis, they were more likely to be continued on antibiotics despite negative culture results. The diagnosis of possible/clinical infection may reflect true disease unconfirmed by culture or no infection at all. These findings underscore the need for better diagnostic tests to confirm infection in VLBW infants.

Over the first 2 weeks of the trial, positive blood culture results and definite infections were significantly more common among patients receiving steroids, compared with those receiving placebo. Organisms associated with definite infections are presented in detail (Table 2). The high proportion of infections attributable to fungi (26.6%) and Gram-negative organisms (26.6%) is striking. It is curious to consider whether the high rate of serious bacterial infection in this cohort of very sick infants contributed further to their risk of developing CLD.

A striking finding is the significantly increased risk of infection in infants being treated with H_2 blockers before randomization. Note that this is H_2 blocker therapy before study entry, not use initiated because patients might be on steroids. Our data are consistent with a report by Beck-Sague[23] who found that H_2 blocker therapy increased nosocomial infection in a cohort of 376 NICU infants. H_2 blocker use has been associated with an increased risk of nosocomial infection in critically ill children and adults.[24,25] Both natural and drug-induced hypochlorhydria increase the risk of enteric infections.[26,27] Because gastrointestinal colonization may play a role in the pathogenesis of nosocomial infections,[28] it is plausible that hypochlorhydria, induced by these drugs, may change and/or increase small bowel colonization with pathogenic organisms and thereby increase the risk of infection. An alternative explanation is that these medications are markers for infants who have gastroesophageal reflux that may increase the risk of pneumonia/infection.

CONCLUSION

In summary, comprehensive analyses of bloodstream and CSF infections among VLBW infants enrolled in this trial demonstrate that infants who receive a 14-day course of dexamethasone initiated at 2 weeks of age are significantly more likely to have a positive blood culture result and a definite infection while receiving steroids than infants who receive placebo. The decision to treat VLBW infants with dexamethasone must balance potential benefits with the increased risk of serious infections. Nosocomial infections are a major cause of morbidity and mortality among VLBW infants.[16] The widespread use of corticosteroids in neonatal intensive care units may contribute to this important problem.

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APPENDIX

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