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Robert Hsiao, MD, and Said A. Omar, MD

ABSTRACT. *Background.* **Leukemoid reaction (LR) is defined as an absolute neutrophil count (ANC) of >30 × 10^3/mm^3. No previous study has systemically examined the clinical and prognostic significance of this phenomenon in extremely low birth weight (ELBW) infants.**

Objective. **The purpose of this study was to examine the effect of LR in morbidity, mortality, and long-term developmental outcome in ELBW infants.**

Method. **Infants with gestational age of ≤30 weeks and birth weight ≤1000 g were included in the study (n = 152). The medical records were reviewed for the clinical characteristics and long-term developmental outcome of these infants. Serial complete blood cell count and ANC were calculated on day 1 and weekly thereafter until discharge. LR was defined as an ANC of >30 × 10^3/mm^3.**

Results. **LR was detected in 17% of the study infants (26 of 152). ANC increased postnatally in LR (n = 26) and no-LR (n = 126) infants during hospitalization, peaked in the second week of life (43 ± 3 vs 14 ± 1 × 10^3/mm^3), and remained significantly higher in LR infants during the first 5 weeks of life. LR occurred more frequently during the first 2 weeks of life and lasted for 3 ± 1 days. There was no significant difference between the LR and no-LR infants in gestational age, birth weight, delivery mode, gender, Apgar scores, or incidence of respiratory distress syndrome, patent ductus arteriosus, necrotizing enterocolitis, intraventricular hemorrhage, and retinopathy of prematurity. LR infants required a significantly longer duration of ventilatory support (36 ± 4 vs 21 ± 2 days), longer duration of oxygen requirement (58 ± 6 vs 40 ± 3 days), and had a higher incidence of bronchopulmonary dysplasia (BPD) (54% vs 25%) compared with no-LR infants. Furthermore, the length of hospitalization was significantly longer in LR infants (69 ± 6 vs 54 ± 3 days). There was no significant difference between the groups in developmental outcome at 2 years of age including receptive/expressive language, fine/gross motor skills, and hearing. Incidence of abnormal neurodevelopment outcome was also similar between LR and no-LR infants.**

Conclusions. **LR in ELBW infants is associated with a prolonged need for ventilatory and oxygen support, a higher incidence of BPD, and a tendency for lower mortality. The findings from our study suggest that LR is associated with conditions known to have an excess of proinflammatory cytokines. Additional prospective study is needed to understand the relationship between LR, proinflammatory cytokines, and development of BPD.** *Pediatrics* **2005;116:e43–e51. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1379;** ***leukemoid reaction, absolute neutrophil count, extremely low birth weight infants, bronchopulmonary dysplasia.***

ABBREVIATIONS. LR, leukemoid reaction; ANC, absolute neutrophil count; ANS, antenatal corticosteroids; BPD, bronchopulmonary dysplasia; ELBW, extremely low birth weight; CBC, complete blood cell; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; PNS, postnatal corticosteroids; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; LOH, length of hospitalization; IL, interleukin; G-CSF, granulocyte colony-stimulating factor.

Improvement in neonatal care has led to increased survival of premature infants with lower gestations at the cost of higher morbidity.[1–4] The majority of morbidities occur as the result of immature adaptation to postnatal life, which can involve all major organs (including the hematologic system), with an increased prevalence of early- and late-onset neutropenia and neutrophilia.[5] Neutrophilia with leukocyte a count of ≥50 × 10^3/mm^3 associated with nonmalignant conditions has been described previously as leukemoid reaction (LR).[6] Earlier studies of LR were done in an adult population. Holland and Maurer[7] described the first case series of LR in a pediatric population, which included only 1 premature infant. A number of case reports have subsequently described the presence of neonatal LR.[8,9] Because of differences in leukocyte and absolute neutrophil counts (ANCs) between the adult and infant populations, the LR during infancy has been defined as an ANC of >10 SD above the mean for gestational age or >30 × 10^3/mm^3 during the first week of life.[10–12]

Neonatal LR has been described in a number of case reports in association with various clinical conditions including prematurity, chromosomal anomalies, exposure to antenatal corticosteroids (ANS), severe anemia, infections, and bronchopulmonary dysplasia (BPD).[8,9,13–20] In the recent clinical studies by Calhoun et al[10] and Rastogi et al,[21] LR occurred in 1.3% to 15% of infants admitted to neonatal intensive care units, with no significant association demonstrated between LR and maternal and neonatal variables. In addition, Zanardo et al,[20] in a retrospective case-controlled study of preterm infants with gesta-

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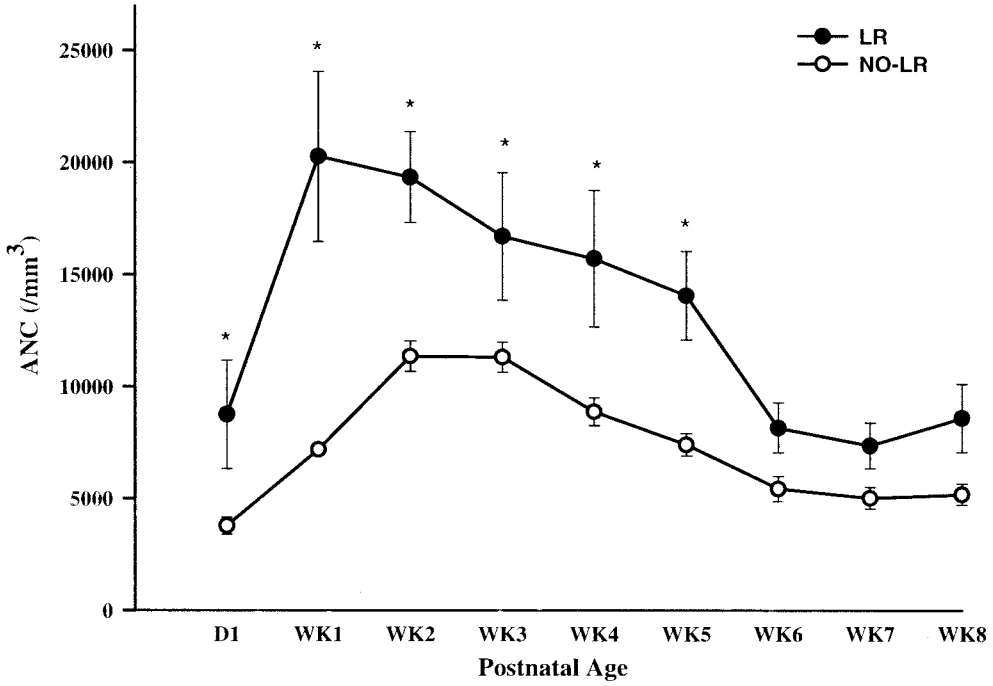

Fig 1. ANCs ($\times 10^3/mm^3$) of the LR and no-LR infants. Error bars represents mean ± SEM. * $P < .05$ versus no-LR infants.

tional age of <32 weeks, showed that BPD was associated with higher incidence of LR (5 of 50 vs 0 of 50; $P = .001$). No previous study has systemically examined the clinical and prognostic significance of neonatal LR in extremely low birth weight (ELBW) infants. In this study, we evaluated the relationship between LR and the mortality, morbidity, and long-term neurodevelopmental outcome in ELBW infants.

METHODS

All appropriate-for-gestational-age premature infants with birth weight ≤1000 g and gestation age of ≤30 weeks who were admitted consecutively to the neonatal intensive care unit at Sparrow Regional Children's Center (Lansing, MI) between January 1993 and December 1999 were eligible for the study. Infants with congenital/chromosomal anomalies or who were transported to other centers were excluded from the study. The study was approved by the University Committee on Research Involving Human Subjects of Michigan State University and the institutional review boards of the Sparrow Health System. No parental consent was obtained because of the retrospective nature of the study.

Complete blood cell (CBC) count and differential were done routinely on day 1, weekly, or more frequently as clinically indicated in all ELBW infants during their hospitalization. A CBC count may be done more frequently if an infant has neutropenia or neutrophilia until resolution of the condition(s). All blood samples for CBC counts were drawn from either an umbilical catheter or a peripheral puncture (if an umbilical catheter was no longer present). The majority of the CBC values in the study infants after the third week of life were obtained from heel sticks. White blood cell counts were performed by using a Coulter Counter-Stks Analyzer (Beckman Coulter Inc, Miami, FL), with differentials cell counts analyzed automatically. Each specimen was then verified by a manual differential done by laboratory technicians reviewing the individual smears. The ANC was determined by multiplying the total white blood cell count by the percentage of neutrophils. Neutrophils were corrected for the nucleated red blood cells. LR was defined as an ANC of $>30 \times 10^3/mm^3$.[10–12]

Maternal medical records were reviewed retrospectively for pregnancy and delivery characteristics including, age, gravida, parity, mode of delivery, course of delivery, timing of rupture of membrane, maternal-fetal conditions, chorioamnionitis, and perinatal infections. Medical records of the eligible premature infants were reviewed retrospectively for gestational age, birth weight, gender, Apgar score, patent ductus arteriosus (PDA), respiratory distress syndrome (RDS), early- and late-onset sepsis, exposure to ANS and postnatal corticosteroids (PNS), surfactant use, number of surfactant doses, type of ventilator use, ventilation index, oxygenation index (OI), alveolar-arteriolar oxygenation gradient, score of neonatal acute physiology II, ventilatory support, oxygenation requirement, BPD, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), length of hospitalization (LOH), and discharge status.

Chorioamnionitis was defined based on a positive culture from the amniotic fluid. In the absence of a positive culture, chorioamnionitis was defined in the presence of organisms on Gram-stain, sheets of leukocytes, or low glucose in the amniotic fluid in the presence of any 2 of the following clinical symptoms: maternal fever, leukocytosis, uterine tenderness, pus from the cervix, and fetal tachycardia. RDS was diagnosed if infants had clinical respiratory distress and compatible radiologic findings.[22] IVH was graded prospectively by using Papile's classification of cranial ultrasound finding of blood in the germinal matrix or ventricular system with or without ventricular and parenchymal extension.[23] PDA was diagnosed clinically and confirmed by echocardiogram. NEC was defined as more severe than stage 3 according to Modified Bell's Staging System for NEC.[24] BPD was prospectively diagnosed by the attending neonatologist for infants who required supplemental oxygen as their usual daily therapy at 36 weeks' postconceptional age in association with radiographic evidence of persistent parenchymal lung disease.[25] ROP was classified by using the international classification of ROP.[26]

Early-onset sepsis in newborn infants was diagnosed clinically within the first 72 hours of life based on the signs and symptoms of infection such as meconium aspiration, poor peripheral circulation, respiratory distress, cyanosis, lethargy, irritability, increased or new apnea or bradycardia episodes, tachypnea, fever, hypothermia, poor feeding, abnormal glucose metabolism, and signs of localized infection, accompanied by abnormal laboratory studies such as neutropenia with an ANC of $<1500/mm^3$, high band count, high C-reactive protein (≥1 mg/dL), and/or radiographic evidence of pneumonia on chest radiograph. In addition to the above-mentioned clinical signs and symptoms, culture-positive early-onset sepsis was diagnosed if ≥1 specimen drawn from blood, trachea, urine, or spinal fluid were positive within the first 72 hours of life. Late-onset sepsis was likewise diagnosed beyond the first 72 hours of life.

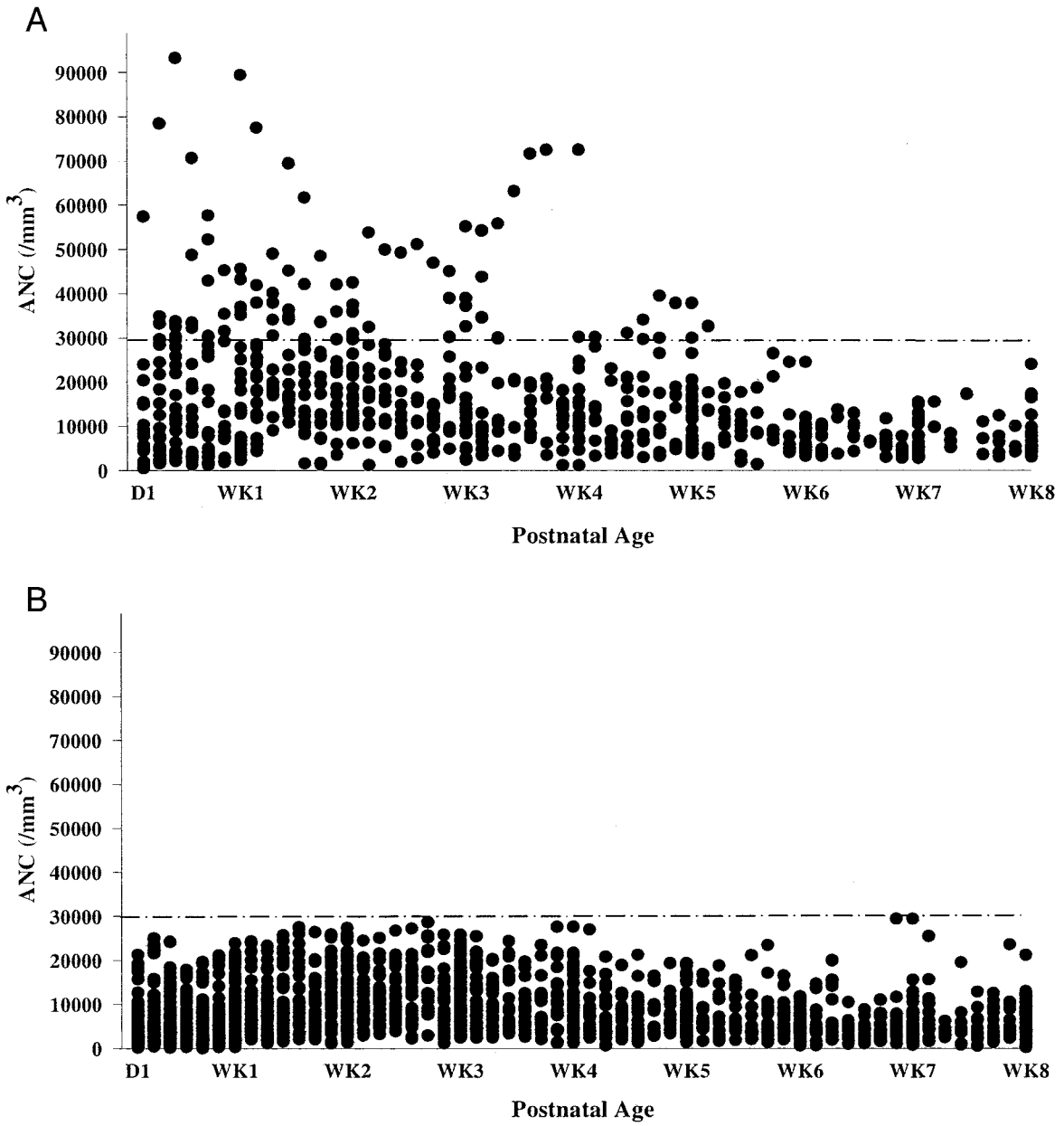

Fig 2. Scatter plots of ANC of the study infants with (A) and without (B) LR.

In our institution, premature infants are seen and examined in the Developmental Assessment Clinic during the first 3 years of life. The 2-year assessment consisted of a detailed medical history obtained from the family, a clinical examination including developmental and neurologic assessment, a classification of the degree and type of disability, language evaluation, a functional classification of hearing disability, and growth assessment. Development and speech were assessed with the use of the Bayley Scale of Infant Development administered by a licensed psychologist. Neurologic assessments were performed by a trained physical therapist at Developmental Assessment Clinic. The muscle tone, reflexes, gait, and movement were examined. Infants were classified as normal, suspicious, or abnormal in accordance with previous publications on neurologic developmental assessment.[27]

Statistical Analysis

Data are presented as mean ± SEM unless otherwise stated. The Student's *t* and Mann-Whitney rank-sum tests were used for statistical analysis of continuous data. Fisher's exact test was used for ordinate data when appropriate. Two-way analysis of variance with a repeated measure of 1 factor was used for analysis of postnatal ANC changes. A P value of $<.05$ was considered statistical significant.

RESULTS

One hundred fifty-two ELBW infants admitted to our neonatal intensive care unit during the study period were included in the study. LR was observed in 17% (26 of 152) of the study infants. These infants were divided into 2 groups: those with LR ($n = 26$) and those without LR ($n = 126$.) LR occurred most frequently in the first 2 weeks of life, with the onset on day 14 ± 2 (median: day 11; range: days 1–33) and lasted for 3 ± 0.6 days (median: 2 days; range: 1–13 days). In both the LR and no-LR groups, ANC increased postnatally and remained consistently higher than the no-LR group during the first 5 weeks of life (Fig 1). ANC use peaked around the second week of life for both groups (day 14 ± 2 vs 12 ± 1),

TABLE 1. ANC Characteristics of the Study Population

	LR (n = 26 [17%])	No LR (n = 126 [83%])	P
Onset of LR, d	13 ± 2	NA	
Median (range)	11 (1–33)	NA	
Day of ANC peak	14 ± 2	12 ± 1	.2
Median (range)	11 (1–33)	11 (1–63)	
Peak ANC, × 10^3/mm^3	43 ± 3	14 ± 1	<.001
Median (range)	38 (30–93)	15 (0.3–29)	
Duration of LR, d	3 ± 1	NA	
Median (range)	2 (1–13)	NA	

Data are presented as mean ± SEM; the 2 groups were compared by the Student's t, χ^2, and Mann-Whitney rank-sum tests. NA indicates not applicable.

with peak values of 43 ± 4 × 10^3/mm^3 and 14 ± 1 × 10^3/mm^3, respectively ($P < .001$), as seen in Fig 2 and Table 1.

The maternal, perinatal, and neonatal characteristics of the study infants are displayed in Tables 2 and 3. The LR and no-LR infants were comparable in regard to baseline maternal, perinatal, and neonatal characteristics (Tables 2 and 3). The LR group tended to have a lower mortality rate when compared with no-LR group (27% vs 34%; $P = .63$). Fifty-eight infants expired during the course of hospitalization. LR was observed in 7 of the expired infants. Five of the 7 expired LR infants recovered from LR for 11 ± 5 days (median: 8 days; range: 1–30 days) before death. LR infants tended to have a higher exposure to ANS (73% vs 64%; $P = .53$) and PNS (84% vs 66%; $P = .08$) when compared with the no-LR infants. There was no significant difference in the number of ANS courses between the 2 groups.

LR infants tended to have a higher incidence of early-onset (54% vs 33%; $P = .07$) and late-onset sepsis (50% vs 39%; $P = .22$) compared with no-LR infants. The majority of sepsis cases were diagnosed based on the clinical assessment. Early- and late-onset sepsis did not occur concurrently with LR except for 7 and 3 infants, respectively. None of these infants experienced repeated episodes of LR with early- and late-onset sepsis. Eight LR infants did not experience any septic episode during the course of hospitalization.

Infants in the LR group had a significantly longer duration of ventilatory support (36 ± 4 vs 21 ± 2 days; $P < .001$), longer oxygen requirement (58 ± 6 vs 40 ± 3 days; $P = .01$), and a higher incidence of

TABLE 2. Maternal and Perinatal Characteristics of the Study Population

Characteristic	LR (n = 26 [17%])	No LR (n = 126 [83%])	P
Age, y	24 ± 1	26 ± 0.5	.21
Median (range)	24 (15–34)	27 (15–39)	
Gravida			.93
Median (range)	2 (1–6)	2 (1–8)	
Parity			.78
Median (range)	0 (0–4)	0 (0–4)	
Mode of delivery			.86
Cesarean section	17 (65)	43 (34)	
Vaginal delivery	9 (35)	83 (66)	
Rupture of membranes			.68
Spontaneous	10 (38)	57 (45)	
Artificial	16 (62)	69 (55)	
Time of rupture of membranes prior to delivery			.14
≤24 h	17 (65)	102 (81)	
>24 h	9 (35)	24 (19)	
Onset of labor			.81
Spontaneous	21 (81)	101 (80)	
Induction	3 (11)	11 (9)	
No labor	2 (8)	14 (11)	
Length of labor			.34
≤24 h	19 (73)	105 (83)	
>24 h	7 (27)	21 (17)	
Gestational diabetes mellitus	0 (0)	5 (4)	.66
Pregnancy-induced hypertension	0 (0)	2 (1)	.77
Preeclampsia			1.0
Mild	0 (0)	17 (13)	
Severe	0 (0)	3 (2)	
Infections			.41
Chorioamnionitis (clinical)	2 (8)	3 (2)	
Other infections	4 (15)	21 (17)	

Numbers represent n (%) unless otherwise specified; the 2 groups were compared by using the Student's t, Mann-Whitney rank-sum, and χ^2 tests.

TABLE 3. Neonatal Characteristics of the Study Population

Characteristic	LR (n = 26 [17%])	No LR (n = 126 [83%])	P
Gestational age, wk	25 ± 0.3	26 ± 0.1	.29
Median (range)	26 (23–28)	26 (23–28)	
Birth weight, g	751 ± 30	764 ± 13	.62
Median (range)	731 (508–964)	779 (438–992)	
Gender			.45
Male	17 (65)	78 (62)	
Female	9 (35)	48 (38)	
Apgar score*			
1 min	4 (3/6)	4 (2/6)	.53
5 min	7 (5/8)	7 (5/8)	.92
PDA	20 (77)	78 (62)	.22
RDS	24 (92)	117 (93)	.75
Early-onset sepsis	14 (54)	41 (33)	.07
Late-onset sepsis	13 (50)	44 (39)	.22
ANS	19 (73)	81 (64)	.53
Number of courses	0.69 ± 0.15	0.89 ± 0.12	.85
Median (range)	0.5 (0–3)	0.5 (0–6)	
PNS	16 (84)	51 (66)	.08
NEC	1 (4)	4 (3)	.67
IVH	8 (31)	30 (24)	.62
Grade I–II	5 (19)	17 (14)	
Grade III–IV	3 (12)	13 (10)	
PVL	6 (23)	16 (13)	.29
ROP	16 (62)	58 (46)	.22
Mortality	7 (27)	43 (34)	.63
LOH, d	69 ± 6	54 ± 3	.01
Median (range)	78 (8–102)	63 (1–146)	

Numbers represent n (%) unless otherwise specified; the 2 groups were compared by using the Student's t, Mann-Whitney rank-sum, and χ^2 tests.
* Median (25th percentile/75th percentile).

BPD (54% vs 25%; P = .01) compared with the no-LR group despite similar baseline pulmonary characteristics and severity of illness on presentation (Table 4). The significance of pulmonary outcome remained even after excluding infants who expired before discharge, with prolonged ventilatory days (40 ± 4 vs 27 ± 2 days; P = .01) and oxygen requirements (70 ± 6 vs 55 ± 3 days; P = .03). Furthermore, in a separate analysis with exclusion of infants with concurrent LR and early-onset sepsis, the remaining LR infants continued to show significantly longer ventilatory days (37 ± 4 vs 21 ± 2 days; $P < .001$), longer oxygen requirements (60 ± 7 vs 39 ± 3 days; P = .004), and a higher incidence of BPD (68% vs 25%; $P = < .001$)

TABLE 4. Pulmonary Baseline Characteristics and Outcome of the Study Population

Characteristic	LR (n = 26 [17%])	No LR (n = 126 [83%])	P
Score of neonatal acute physiology II	26 ± 4	25 ± 1	.66
Median (range)	23 (0–74)	26 (0–61)	
RDS	24 (92)	117 (93)	.75
Surfactant	20 (77)	113 (90)	.14
No. of doses	2.2 ± 0.3	2.2 ± 0.1	.91
Median (range)	2.5 (0–5)	2 (0–6)	
Ventilators			
Conventional	23 (88)	114 (90)	.96
High-frequency oscillatory ventilation	3 (12)	18 (14)	.95
Continuous positive airway pressure	2 (8)	8 (6)	.86
Ventilation index	15 ± 4	19 ± 2	.12
Median (range)	4 (0–64)	15 (1–115)	
Pao_2/fraction of inspired oxygen ratio	1 ± 0.2	1 ± 0.1	.13
Oxygenation index	6 ± 1	5 ± .4	.61
Median (range)	4 (0–25)	3 (0–22)	
Alveolar-arteriolar oxygenation gradient	267 ± 440	252 ± 15	.7
Median (range)	81 (0–616)	235 (0–632)	
Ventilator support, d	36 ± 4	21 ± 2	<.001
Median (range)	32 (8–81)	15 (1–74)	
Oxygen requirement, d	58 ± 6	40 ± 3	.01
Median (range)	51 (8–101)	37 (1–120)	
BPD	14 (54)	32 (25)	.008

Numbers represent n (%) unless otherwise specified; the 2 groups were compared by Student's t, Mann-Whitney rank-sum, and χ^2 tests. Ventilation index, Pao_2/fraction of inspired oxygen, oxygenation index, and alveolar-arteriolar oxygenation gradient are values obtained from the study population during the first 24 hours of life.

compared with the no-LR group (Table 5). There was no significant difference demonstrated between the groups in the incidence of NEC ($P = .67$), IVH ($P = .62$), PVL ($P = .29$), and ROP ($P = .22$), as seen in Table 3. The LOH of LR infants was significantly longer compared with no-LR infants (69 ± 6 vs 54 ± 3 days; $P = .01$).

Table 6 summarizes the results of developmental evaluation of the study infants at ~2 years of age (19–30 months). There was no significant difference observed between the LR and no-LR groups in the incidence of growth impairment (defined as growth parameters <10% in weight, length, or head circumference), abnormal hearing or language, and neurodevelopmental and neuromotor evaluation (fine and gross motor), as seen in Table 6.

DISCUSSION

LR was observed in 26 ELBW infants, with an overall incidence of 17% of the study infants, which is consistent with the incidence of 1.3% to 15% published in the recent studies of LR in term and preterm infants.[10,20,21] In our study, no predictable relationship was observed between the various maternal, perinatal, and neonatal characteristics of ELBW and LR, which is in general agreement with the finding previously described in very low birth weight infants by Rastogi et al.[21]

The value for LR was defined as >10 SD above the mean for gestational age, which was chosen in accordance with definition used previously by Calhoun et al.[10] The definition utilizes the normal reference range published by Manroe et al[12] and Mouzinho et al.[11] There are some limitations for using the similar definition in our study. First, the reference range of Manroe et al and Mouzinho et al were compiled by using data from before 1991.[11,12] There have been several advances in the care of preterm infants since that time, with a significant increase in the survival of ELBW infants. The reference data before 1991 may not be adequately powered to represent this particular population of preterm infants. Furthermore, in the updated reference range published in 1994 by Mouzinho et al,[12] the authors pointed out a significant trend of change in ANC distribution when compared with that of previous publications. They stated that the distribution of ANC is broader, but also the rise and fall after birth occurs more gradually and at a later time point. These observations suggested that there is a birth weight and/or gestational age–dependent effect on the distribution of ANC.[12] With increasing survival of preterm infants of lower gestations, there is a likelihood that the above-mentioned trend will continue to escalade with peak ANC delayed beyond the first 60 hours of life and return to baseline at a much later time than previously observed. In our recent publication on late-onset neutropenia in very low birth weight infants, the peak ANC was noted to occur around the second week rather than within the first 60 hours of life and returned to baseline around the fifth to sixth week of life.[28] A similar trend for delayed peak ANC and recovery to baseline was also observed in our unpublished data on the reference range of ANC in ELBW infants.[29] Therefore, based on our findings and those from previous publications, the 30 000/mm^3 level was used to define LR for the duration of the hospitalization in our study infants.

Inflammatory cytokine activation and cell recruitment occur early in the inflammatory response that persists over the first weeks of life in premature infants. The imbalance of anti-inflammatory cytokines (eg, interleukin [IL] 10) and proinflammatory cytokines (eg, IL-8, tumor necrosis factor α, IL-1, IL-6, etc) has been implicated in the activation of inflammatory cascade associated with prematurity, RDS, cerebral white matter damage, IVH, NEC, BPD, and cerebral palsy.[30–39] Various inflammatory cytokines are capable of initiating or stimulating production of granulocyte colony-stimulating factor (G-CSF) by several cell lines, including monocytes, macrophages, and epithelial and endothelial cells.[40–45] G-CSF can accelerate the production of neutrophils, stimulate the activation of neutrophils, including respiratory burst activity, and produce a leukemoid-like reaction when administered in a sufficiently high dose.[46,47] In a prospective series, Calhoun et al[10] observed that neonatal LR was the result of a transient acceleration in neutrophil production and was associated with elevated serum G-CSF in 30% of the study infants.

Growing evidence suggests that early activation and transendothelial migration of neutrophils has been found to be an important contributing factor in the pathogenesis of severe RDS and its progression to BPD in premature infants.[48] Large numbers of inflammatory cells, predominantly neutrophils, were found in the bronchoalveolar specimens of preterm infants in various stages of developing BPD shortly after the initiation of mechanical ventilation.[49–52] The

TABLE 5. Pulmonary Outcome of the Study Population Without Concurrent Early-Onset Sepsis

Characteristic	LR ($N = 19$)	No LR ($n = 126$)	P
RDS	18 (95)	117 (93)	.85
Ventilator support, d	38 ± 4	21 ± 2	<.001
Median (range)	33 (15–81)	15 (1–74)	
Oxygen requirement, d	61 ± 7	40 ± 3	.007
Median (range)	66 (15–100)	37 (1–120)	
BPD	12 (63)	32 (25)	.002
LOH, d	70 ± 7	54 ± 3	.02
Median (range)	80 (15–100)	63 (1–146)	

Numbers represent n (%) unless otherwise specified; the 2 groups were compared by using the Student's t, Mann-Whitney rank-sum, and χ^2 tests.

TABLE 6. Neurodevelopmental Outcome of the Study Population at 24 Months of Age

	LR (n = 19 [19%])	No LR (n = 82 [81%])	P
Neurodevelopment impairment	4 (21)	18 (22)	.82
Language impairment			
Receptive	4 (21)	13 (16)	.84
Expressive	1 (5)	10 (12)	.64
Neuromotor impairment	5 (26)	9 (11)	.17
Fine motor	5 (26)	7 (9)	.08
Gross motor	3 (16)	8 (10)	.72
Hearing impairment	2 (11)	4 (5)	.69
Weight, <10th percentile	4 (21)	27 (33)	.46
Length, <10th percentile	3 (16)	25 (30)	.31
Head circumference <10th percentile	3 (16)	22 (27)	.48

Numbers represent n (%); the 2 groups were compared by using the χ^2 test.

elevated neutrophil count in airway secretions persisted for weeks in those infants who eventually developed BPD. The appearance of LR may represent a hematologic response from a unique group of premature infants with a genetic susceptibility for heightened response to the perinatal stress by increased production of inflammatory cytokines. The increased circulating neutrophils can readily migrate into various organs, including lung, through a complex interaction between endothelial cells and neutrophils facilitated by the presence of various inflammatory cytokines and local chemotactic and chemokinetic factors. Neutrophils are important in the immune response and repair process, but they may also cause localized tissue injury that leads to subsequent chronic inflammatory changes. Alternatively, the presence of LR in the study infants may be a reflection of the severity of neonatal lung disease and associated chronic lung changes in the early phase of inflammation. However, the likelihood of later speculation is low because of the similar baseline perinatal and pulmonary characteristics and severity of illness between the LR and no-LR groups.

With the exception of pulmonary sequelae, the association of LR and prematurity-associated short- and long-term morbidities cannot be demonstrated in our current study or any previous publication to date.[10,20,21] Absence of the relationship between LR and other prematurity-associated morbidities may attribute to the relatively low incidence and multifactorial nature of various events examined. The potential association can only be demonstrated with a carefully designed prospective study with an adequate sample size and particular attention to monitor and control various potential contributing factors that may lead to changes in the incidence of prematurity-associated morbidities.

The absence of association between LR and sepsis in preterm infants has been described previously by Rastogi et al.[21] However, ELBW infants with LR in our study population have demonstrated an increased tendency for a higher incidence of early- and late-onset sepsis. When we analyzed the diagnosis of each septic episode separately, a significant portion of septic episodes was diagnosed based on risk factors and clinical presentation rather than by cultures. However, because of the relatively low yield of the current culture method and low sensitivity of the currently available diagnostic hematologic and biochemical markers for neonatal sepsis evaluations, the diagnosis of sepsis, particularly early-onset sepsis, will inevitably rely on the clinical assessment of the physician, with emphasis on risk factors and clinical presentation. Therefore, the precise relationship between LR and early- or late-onset sepsis cannot be determined because of the retrospective design of the current study. On the other hand, the observed tendency between LR and sepsis in our study may provide added evidence to the earlier-stated speculation that the affected infants may represent a subgroup of premature infants with an exaggerated response to perinatal stress.

Administration of ANS to pregnant mothers is a widely accepted obstetric practice before delivery of premature infants at risk for RDS. Corticosteroids are known to increase the leukocyte count by accelerating the release of neutrophils from bone marrow and decreasing egress from the circulation. The drug activity is detectable in cord blood as early as 1 hour after administration but undetectable by 72 hours.[53,54] In this study, the LR and no-LR groups had similar exposure to ANS and exhibited a similar pattern of ANC changes, with the peak values occurring around the second week of life, which is beyond the theoretical range of ANS effect as observed in previous clinical studies.[51,52] Therefore, the contribution of ANS to the occurrence of LR is limited, if any. The lack of association between ANS and LR in the current observation provided added evidence to the kinetic study by Calhoun et al,[10] which concluded that the responsible mechanism for LR is increased neutrophil production rather than corticosteroid-induced leukocytosis.

On the other hand, the relationship between the intravenously administered systemic PNS and LR is less clear. No significant difference in the overall exposure to PNS between the 2 groups was observed (84% vs 66%; P = .08). There were 3 infants in the LR group that demonstrated a LR within 2 weeks before or after the administration of PNS. The effect of PNS exposure on the occurrence of LR cannot be eliminated in those cases. The significance of this association remains to be determined by future kinetic study on the effect of corticosteroids on the occurrence of LR.

In our study, there was a tendency for lower mor-

tality in infants with LR compared with their no-LR counterparts, as reported previously by Rastogi et al.[21] LR may be a manifestation of the immature inflammatory cascade activated in response to perinatal or neonatal insult and stress. Its presence in ELBW premature infants may confer a survival advantage at the expense of increased risk for morbidities, such as an increased demand for ventilation and/or oxygen support and a higher incidence of BPD.

CONCLUSIONS

LR in ELBW infants is associated with a prolonged need for ventilatory support and oxygen requirement, higher incidence of BPD, and a tendency for lower mortality. The findings suggest that LR may be associated with an excess of proinflammatory cytokines. Additional prospective study is needed to understand the relationship between LR, proinflammatory cytokines, and development of BPD.

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