Original Article

Very-Low-Birth-Weight Infant Outcomes in 11 South American NICUs

GRUPO COLABORATIVO NEOCOSUR

OBJECTIVE:

To describe and analyze outcomes in very-low-birth-weight (VLBW) infants treated in 11 Neonatal Intensive Care Units (NICUs) from four South American countries. This study is the first of a multination collaboration and can serve as a baseline for future quality and resource utilization efforts.

STUDY DESIGN:

Biodemographic data and multiple outcome measures were prospectively collected from October 1997 until August 1998. A logistic regression model was used to define risk factors in primary outcome measures, death, and bronchopulmonary dysplasia (BPD). Center differences were compared using χ-squared analysis.

RESULTS:

In 385 VLBW infants enrolled, mortality rate was 27%, with a range from 11% to 51% among NICUs. A lower BW, lower gestational age (GA), lack of antenatal steroids (AS), and air leaks (AL) were associated with increased risk of death. A lower BW, lower GA, AL, need for surfactant, necrotizing enterocolitis, and need for intubation were associated with increased risk of BPD.

CONCLUSION:

This study provides actual information about VLBW infants' prognosis in a SA region. Mortality rate variability among NICUs may be explained by differences in population and resources, but also by lack of implementation of proven beneficial therapies such as AS administration.

Journal of Perinatology (2002) **22,** 2–7 DOI: 10.1038/sj/jp/7210591

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INTRODUCTION

The main purpose of this study is to describe the outcome of very-low-birth-weight (VLBW) infants (BW$\leq$1500 g), born at 11 Neonatal Intensive Care Units (NICUs) in four South American (SA) countries. This BW group is important inasmuch as it accounts for 50% of the neonatal mortality, and up to 25% to 30% of the infant mortality in our region.[1,2] VLBW infants outcome has been reported in multicenter studies in developed countries.[3–7] These reports have shown significant outcome variability among centers, probably due to multiple causes including differences in population, in prenatal care, and in the organization and implementation of neonatal care.

In addition, this study may help create a network in the region to serve as a resource for future research and continuous evaluation of outcome. It may also serve for benchmarking purposes for other nonparticipant NICUs.

METHODS

All live inborn infants with BW 500 to 1500 g in the participating centers were eligible for the study. Outborn infants were excluded. Biodemographic data and multiple outcome measures were prospectively collected from October 1997 through August 1998 in the participating NICUs as part of this collaborative multicenter study (three centers participated for a shorter period of time within these dates). Data collection was performed in codified forms with predefined diagnostic criteria.

Hyaline membrane disease was diagnosed according to clinical and radiographic findings. The diagnosis of pulmonary air leak (AL) was confirmed by chest X-ray. Retinopathy of prematurity was diagnosed by examination done by an ophthalmologist, and classified in grades 1 to 5 according to the international classification.[8] Bronchopulmonary dysplasia (BPD) was defined by oxygen requirements at 28 days of life and chronic radiographic changes.[9] Oxygen dependency at 36 weeks postmenstrual age was consigned as a separate diagnosis. The diagnosis of sepsis was confirmed by the isolation of the organism in blood or cerebrospinal fluid. Patent ductus arteriosus was diagnosed clinically and, whenever possible, confirmed by echocardiography. The diagnosis of intraventricular hemorrhage

Table 1 Population Characteristics

BW (g) mean ± SD	1129 ± 226
GA (weeks) mean ± SD	29.6 ± 3.4
Male gender (%)	55
Multiple pregnancy (%)	15
Maternal hypertension (%)	28
Premature rupture of membranes (%)	35
Chorioamnionitis (%)	15
AS (%)	56
Vaginal delivery (%)	39
Apgar <3 at 1 minute (%)	27
Apgar <3 at 5 minutes (%)	7
Intubation at birth (%)	36

was made by cranial ultrasonogram or by autopsy and was classified according to Papile and Bursten.[10] Periventricular leukomalacia was diagnosed by the presence of focal echolucencies in cranial ultrasonogram. Necrotizing enterocolitis (NEC) was confirmed by radiographic (pneumatosis and/or perforation), surgical, or autopsy findings.

Each participating unit managed these VLBW infants according to their usual protocol. However, the following guidelines were suggested so that basic information was uniformly obtained: complete blood count, blood culture, blood sugar, blood gases, plasma electrolytes, and chest X-ray on admission to the NICU. Chest X-ray was repeated according to the infant's condition and at 28 days of life. At least two cranial ultrasonograms were performed at 72 to 96 hours of life and at 3 to 4 weeks of life. The first ophthalmologic evaluation was planned at 4 to 6 weeks of life.

Primary outcome measures were death and BPD. A logistic regression model was used to find factors associated with these measures. A stepwise procedure was used to select those factors that independently contribute to explain the outcome. The effect of each factor was expressed as odds ratio and 95% confidence intervals. A χ-squared analysis was done to find primary outcome differences among the participating NICUs. Secondary outcome measures were the incidence of the main morbidity associated with VLBW, and the utilization of some therapies such as antenatal steroids (AS), surfactant, mechanical ventilation, and also duration of hospitalization.

RESULTS

There were 385 infants with BW 500 to 1500 g, born during the study period at the participating centers. Table 1 shows the biodemographic characteristics of the population. Figure 1 shows data for primary outcomes. Each bar represents each of the participating centers; the last bar shows the total population studied. Mortality rate averaged 27%; there was a broad difference between centers with values in the

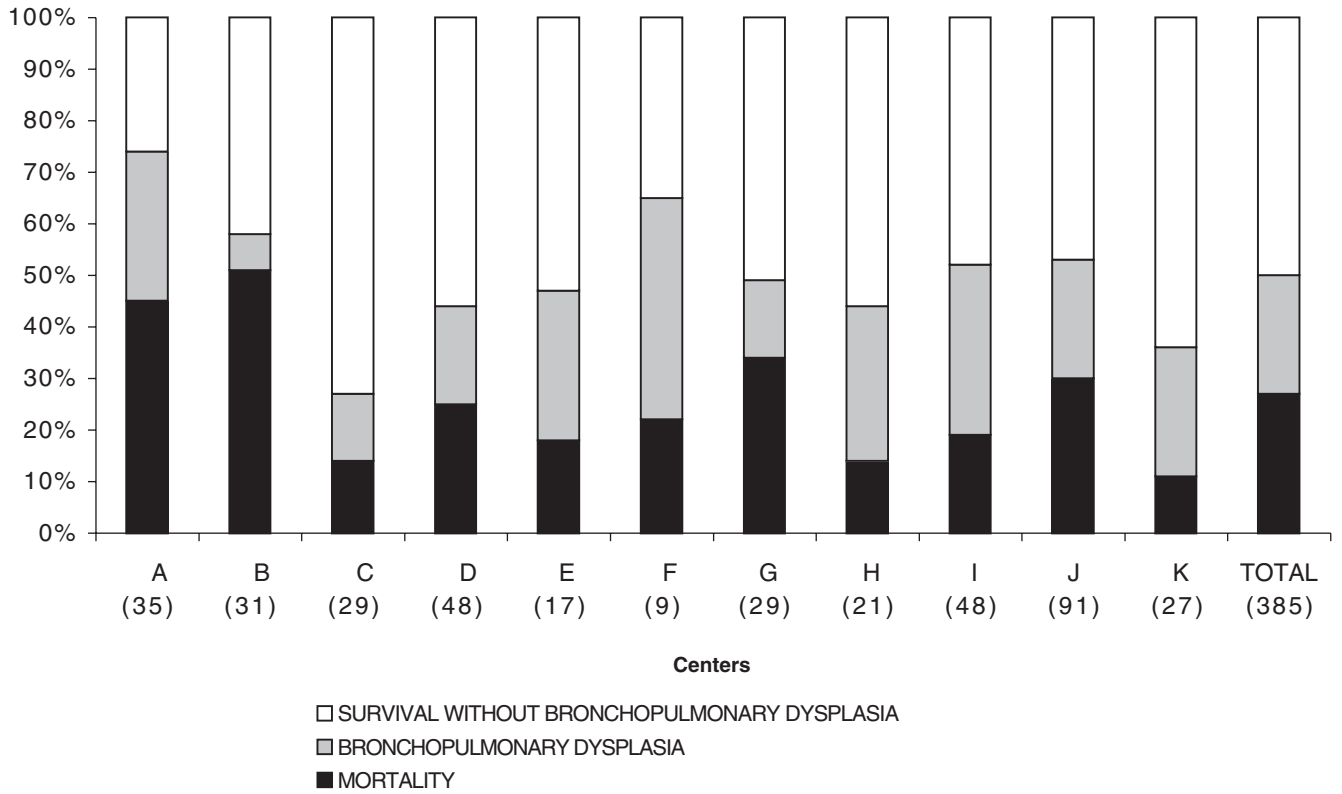

Figure 1. Primary outcome in 385 VLBW infants from 11 South American centers.

Table 2 Risk Factors for Death and BPD

Death	*p*	OR	95% CI	BPD	*p*	OR	95% CI
BW*	<0.01	0.77	(0.66–0.90)	BW*	<0.001	0.76	(0.59–0.98)
AL	<0.01	5.60	(2.61–12.03)	GA†	<0.001	0.54	(0.39–0.74)
AS	<0.01	0.38	(0.22–0.66)	AL	0.02	1.96	(0.38–10.10)
GA†	0.04	0.87	(0.76–0.99)	Intubation at birth	0.01	2.09	(0.83–5.28)
				Surfactant	0.02	4.70	(1.18–18.72)
				NEC	0.001	6.43	(2.37–17.42)

*By 100 g intervals.
†By weekly intervals.
NEC, necrotizing enterocolitis; OR, odds ratio ; CI, confidence interval.

range from 11% to 51% ($p<0.01$). These differences in mortality remained significant after adjusting for BW using logistic regression models ($p<0.001$). BPD had an incidence of 23% with a 7% to 43% range ($p=0.4$). Survival without BPD averaged 50% with a 26% to 73% range. In infants under 1000 g, primary outcome averages were: mortality rate 52% and BPD 62%.

Factors associated with increased risk for death and BPD appear in Table 2. A lower BW, lower GA, lack of AS and AL were significantly associated with increased risk of death. A lower BW, lower GA, AL, need for surfactant, NEC, and need for intubation were significantly associated with increased risk of BPD.

Figures 2 and 3 show specific mortality rate by 100 g BW intervals and by weekly GA intervals, respectively. By BW intervals, mortality decreases steadily with increasing BW up to 1201 g; thereafter, mortality did not change with increases in BW. Mortality was 100% at 22 and 23 weeks' GA, and decreased steadily from 24 through 31 weeks. Mortality rates remained unchanged through 34 weeks and worsened thereafter (infants with severe weight retardation).

Autopsies were performed in 28% of the infants who died. Causes of death were classified as follows: sepsis 20%, extreme prematurity 15%, congenital malformations 11%, pulmonary hemorrhage 8%, hyaline membrane disease 7%, intraventricular hemorrhage 8%,

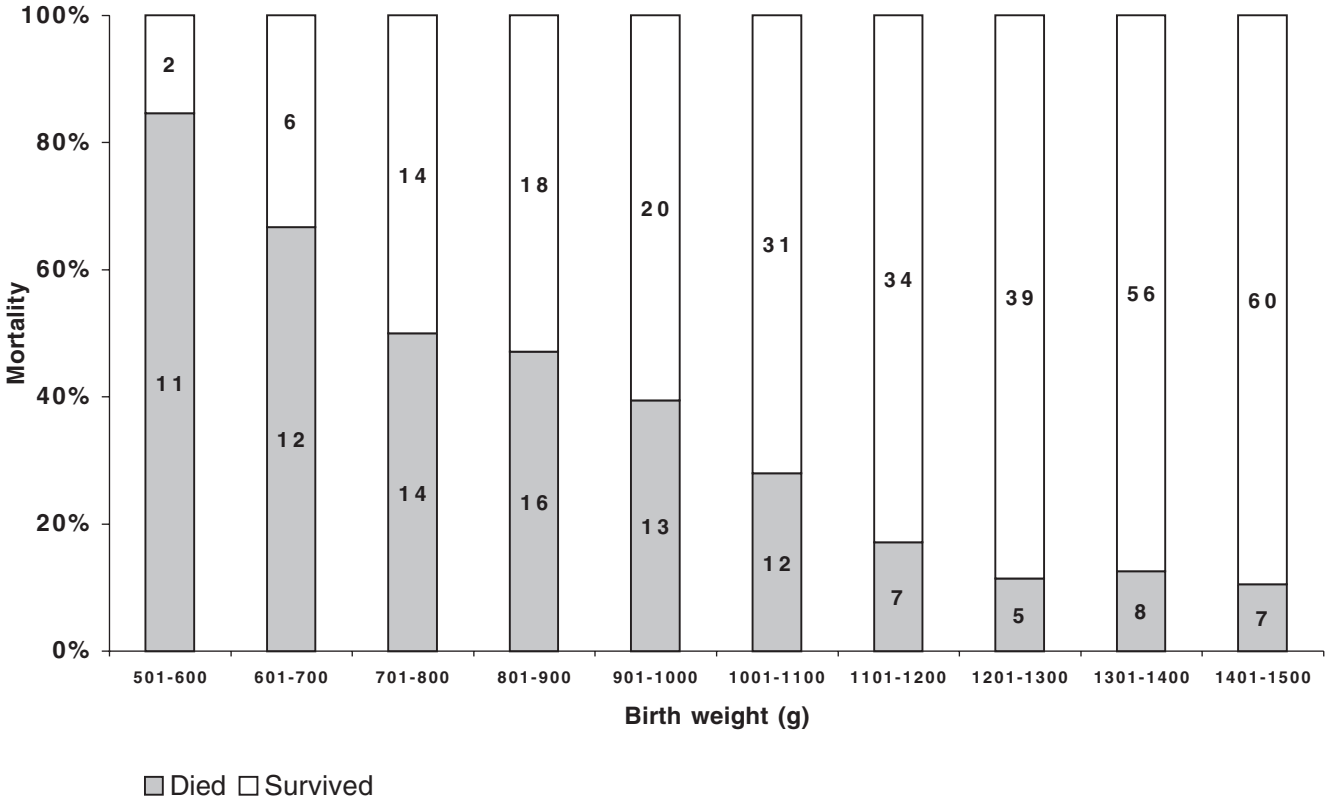

Figure 2. Mortality according to BW.

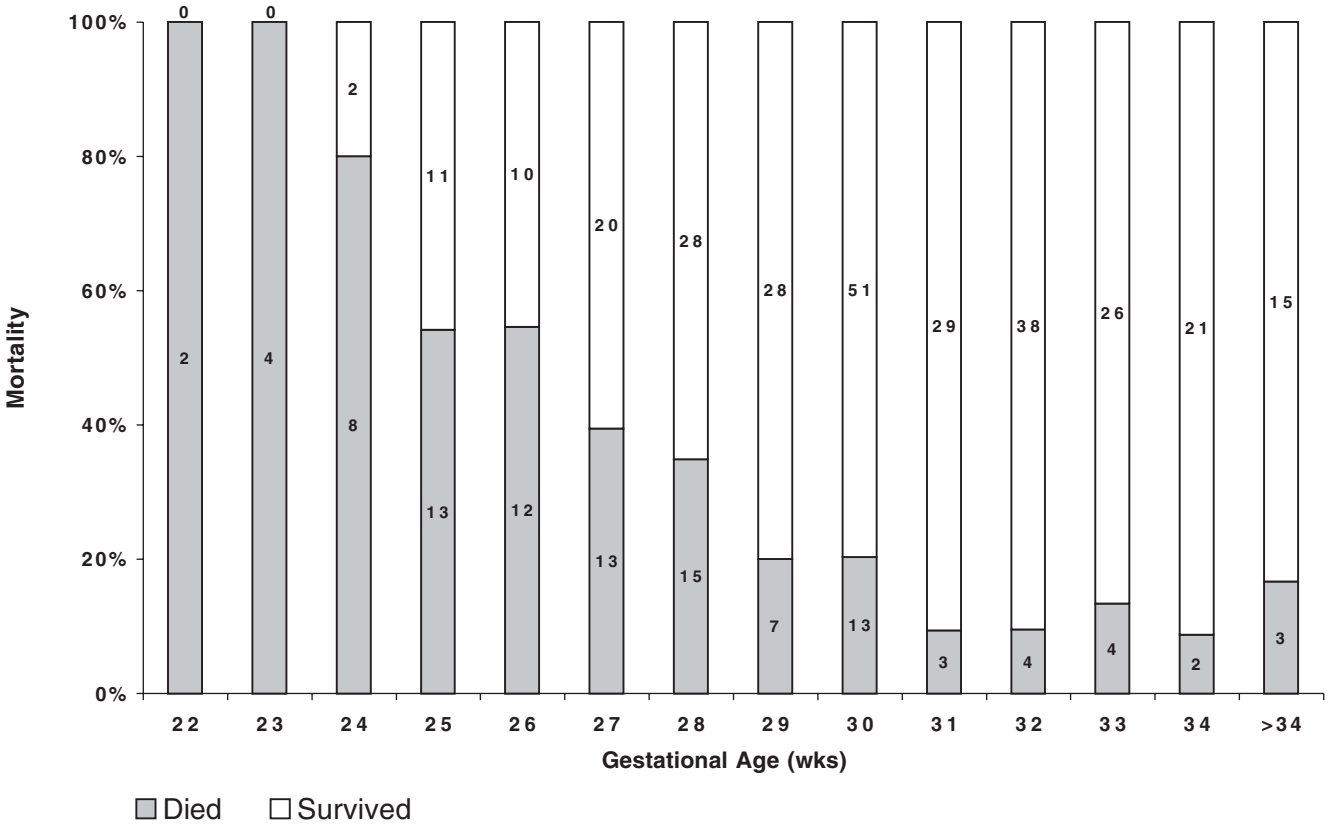

Figure 3. Mortality according to GA.

asphyxia 3%, and NEC 2%. Almost 38% of the deaths occurred in the first 24 hours of life, 49.5% in the first 72 hours, and 80% in the first 11 days of life.

The incidence of commonly associated morbidity in these VLBW infants and its range among centers is shown in Table 3. Ophthalmologic evaluation was performed in 68% of survivors and diagnosis of retinopathy of prematurity was made in 42% of the infants who survived and were evaluated. Of the survivors at 28 days, 6% had a diagnosis of periventricular leukomalacia. In septic infants, the organisms isolated were: coagulase-negative *Staphylococcus* (24), *Klebsiella* (12), *Candida albicans* (12), *Acinetobacter* (10), *Staphylococcus aureus* (10), *Pseudomona aeruginosa* (9), *Enterobacter* (2), group B streptococci (5), *Escherichia coli* (3), and unclassified Gram-positive (1). Twenty-four percent of the infected infants had more than one episode of sepsis.

Table 3 Incidence of Associated Pathology in 385 VLBW Infants

	Average and range among centers (%)
HMD	47 (32–79)
IVH	26 (8–32)
PDA	21 (4–43)
AL	10 (4–33)
Sepsis	24 (11–46)
NEC	10 (0–26)
BPD	23 (7–43)
02–36 weeks	10 (0–33)

HMD, hyaline membrane disease; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; AL, air leaks; NEC, necrotizing enterocolitis; BPD, Bronchopulmonary dysplasia.

Surfactant was administered to 38% of these infants; it was given at an age (mean ± SD) of 7.6 ± 11.9 hours, with a median of 4 hours. At 28 days of age, the weight (mean ± SD) was 1415 ± 344 g and the length was 39 ± 5 cm; at 36 weeks postconceptional age, the weight and length were 1661 ± 364 g and 41 ± 5 cm, respectively; at discharge, the weight was 2157 ± 502 g. Sixty-four percent of the infants received mechanical ventilation, 83% of the 500 to 1000 g group, and 54% of the 1001 to 1500 g group, with a median of 5 days on this therapy: 4 days for the 1001 to 1500 g group, and 15 days for the 500 to 1000 g group. Length of hospital stay had a median of 42 days: 53 days for the infants who survived, and 3 days for those who died; 81 days for survivors under 1000 g, and 46 days for the 1000 to 1500 g survivors.

DISCUSSION

This study describes current prognosis of VLBW infants in a region of South American. The majority of the participating centers are

university-affiliated and about half belong to the Public National Health Service. They vary in size, population served, and resources. Overall, they may constitute an adequate representation of the state of health care in Latin American countries.

There were important differences in mortality rates among NICUs: 11% to 51%. This variability may be explained by differences in population and resources, but also by lack of implementation of proven beneficial clinical practices such as use of AS. AS administration varied from 6% to 71% among centers, and lack of administration was associated with an increased of risk of mortality. The use of this prenatal therapy can and should be increased.[11,12] Surfactant was not completely available in all of the participating centers. Also, surfactant was given rather late, if one considers that randomized trials support the early institution of this therapy (within the first 2 hours of life).[13,14]

Other risk factors for increased mortality in this study were a lower BW, a lower GA, and the presence of AL. The first two are difficult to prevent. However, AL may be at least partly prevented by using high ventilator rate and low tidal volume (low inspiratory pressure) during positive pressure ventilation.[15,16]

Sepsis was the most commonly reported cause of death in our study. This is in agreement with studies that have analyzed causes of death among VLBW infants,[17] so that prenatal or postnatal prevention of infections seems an important issue in improving this group's outcome. Also, our data show that about half of the isolated bacteria in infants with sepsis was Gram-negative, in contrast with published data from high-risk nurseries in the United States where Gram-positive bacteria are much more frequently isolated.[18] This finding may reflect differences in quality of care among units in developed versus emerging countries.

BPD incidence averaged 23%. Two risk factors for BPD were among the expected: a lower BW and GA. The association between AL and subsequent BPD has long been recognized and related to the use of high ventilatory pressures.[19] BPD association with surfactant requirement and with the need for intubation at birth can be explained because these are interventions indicated in the sicker infants. However, there is recent evidence in animal models that a manual ventilation with high tidal volume at birth may damage immature lungs.[20] The association of BPD with NEC is probably also reflecting sicker infants.

With regard to the incidence of morbidities associated with VLBW infants, the numbers are small to analyze center variability. However, this wide difference between centers needs to be carefully assessed in future collaborative studies to help establish reasonable guidelines for the improvement of care in VLBW infants.

The present study is limited because the study population is small and the study period is short. However, a good initial database is presented and can be useful for future research in this region. Average VLBW mortality rate in this study is high compared with rates reported in similar studies in developed countries (27% vs 16% to 18%[5,6]), although three of this study's participating centers showed low comparable rates (11% to 14%). These data indicate that reducing mortality in this BW group of infants in our region is possible and is a challenge that needs to be addressed.

Studying center to center differences, and the possible explanations for these differences, may provide useful information and help in the design of perinatal strategies and/or interventions that will impact on the outcome of VLBW infants in our region.

APPENDIX

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Acknowledgments

We thank Eduardo Bancalari for his advice in preparing this manuscript and Guillermo Marshall (PhD) and Luis Villaroel for statistical assistance.

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