Trends in Perinatal Practices and Neonatal Outcomes of Very Low Birth Weight Infants during a 16-year Period at NEOCOSUR Centers

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Objective To describe trends in mortality, major morbidity, and perinatal care practices of very low birth weight infants born at NEOCOSUR Neonatal Network centers from January 1, 2001, through December 31, 2016.

Study design A retrospective analysis of prospectively collected data from all inborn infants with a birthweight of 500-1500 g and 23-35 weeks of gestation.

Results We examined data for 13 987 very low birth weight infants with a mean birth weight of 1081 ± 281 g and a gestational age of 28.8 ± 2.9 weeks. Overall mortality was 26.8% without significant changes throughout the study period. Decreases in early onset sepsis from 6.3% to 2.8% (P <.001), late onset sepsis from 21.1% to 19.5% (P = .002), retinopathy of prematurity from 21.3% to 13.8% (P <.001), and hydrocephalus from 3.8% to 2.4% (P <.001), were observed. The incidence for bronchopulmonary dysplasia decreased from 17.3% to 16% (P = .043), incidence of severe intraventricular hemorrhage was 10.4%, necrotizing enterocolitis 11.1%, and periventricular leukomalacia 3.8%, and did not change over the study period. Administration of antenatal corticosteroids increased from 70.2% to 82.3% and cesarean delivery from 65.9% to 75.4% (P <.001). The use of conventional mechanical ventilation decreased from 67.7% to 63.9% (P <.001) and continuous positive airway pressure use increased from 41.3% to 64.3% (P <.001). Survival without major morbidity increased from 37.4% to 44.5% over the study period (P <.001).

Conclusions Progress in perinatal and neonatal care at network centers was associated with an improvement in survival without major morbidity of very low birth weight infants during a 16-year period. However, overall mortality remained unchanged. *(J Pediatr 2020;225:44-50)*.

The survival rate of very low birth weight (VLBW) infants has increased worldwide as a result of improved quality of antenatal and postnatal care.[1-3] Increased use of antenatal corticosteroids (ACS), enhanced noninvasive respiratory support, use of surfactant, and a decrease in the use of invasive mechanical ventilation, have been associated with better outcomes in this group of infants.[4] Despite improved survival rates, complications associated with premature birth have been recognized as the leading cause of death among children under 5 years of age throughout the world, accounting for approximately 1 million child deaths each year.[5-10] In addition, surviving infants are at significant risk of long-term sequelae including cognitive delays, neurodevelopmental impairment, and visual and hearing disabilities.[8,11-14] These factors have produced significant concerns for emotional burden for families and their caregivers, as well as financial costs for society.[15-20] Monitoring the burden of VLBW infants is important not only to assess the impact of perinatal care, but also to orient parental counseling and clinical decision making, including targeted strategies to decrease preterm births, and evidence-based clinical guidelines to increase survival free of major morbidity.[21]

To improve the care of VLBW infants, comprehensive reviews on outcomes and interventions comparing different time periods and different neonatal

ACS	Antenatal corticosteroids
BPD	Bronchopulmonary dysplasia
IVH	Intraventricular hemorrhage
LOS	Late-onset sepsis
NEC	Necrotizing enterocolitis
PVL	Periventricular leukomalacia
ROP	Retinopathy of prematurity
VLBW	Very low birth weight

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A list of members of the NEOCOSUR Neonatal Network centers can be found at www.jpeds.com (**Appendix**)

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networks databases have been published.[1,2,4,6,22-26] Variations in neonatal outcomes have been attributed to differences in management, availability of resources, and healthcare policies across centers and regions.[25,27-29] Benchmarking among centers with best performance is useful to determine best clinical practices and identifying potentially optimal approaches that might help improving VLBW infant outcomes.[30]

NEOCOSUR is a voluntary nonprofit collaborative South American neonatal network (6 countries and 30 Neonatal Units from Argentina, Brazil, Chile, Paraguay, Peru, and Uruguay). All participating centers are university affiliated and represent both public and private tertiary-care institutions whose primary mission is the improvement of neonatal care and outcomes in the region. Since 1997, the network has monitored VLBW infants outcomes using standardized collection of data on morbidity and mortality as well as antenatal and postnatal care practices. Demographic information and outcome data are prospectively collected at each network site using predefined diagnostic criteria and online data entry system (www.neocosur.org).

Previous reports from the network have shown mortality rates of approximately 27%.[31,32] The aim of this study was to report changes in neonatal outcomes and identify trends in mortality and morbidity of infants born at 23-35 weeks of gestation and a birthweight of 500-1500 g over a 16-year period. As a secondary objective, we sought to identify changes in the most relevant perinatal and postnatal interventions over the same time period.

Methods

We performed a retrospective analysis of prospectively collected data of VLBW infants born at 14 network centers between 2001 and 2016. All inborn infants with a birth weight of 500-1500 grams and a gestational age of 23-35 weeks were included in the study registry.

Variables examined included mortality, gestational age, birth weight, multiple birth, exposure to ACS and/or antenatal antibiotics, cesarean delivery, Apgar scores, major birth defects, surfactant use, invasive/noninvasive ventilation, and major neonatal morbidities. Mortality was defined as predischarge death, including death in delivery room, independent of length of hospital stay. Postdischarge mortality is not registered. Gestational age in completed weeks was determined by the best estimate based on early prenatal ultrasound examination, last menstrual period, or physical examination of the infant at birth. Major congenital malformations were defined as a structural defect of prenatal origin affecting (or having the potential to affect) health, survival, or cognitive functioning. Exposure to ACS was defined as administration of 1 or more doses of any corticosteroid with proven efficacy to the mother before an anticipated preterm delivery. Multiple birth was defined as twin, triplet, or any higher order gestation.

The main outcomes of interest were changes in mortality rates, major neonatal morbidities, perinatal care practices, and survival without major morbidity throughout the study period. Major neonatal morbidities included (1) bronchopulmonary dysplasia (BPD), defined as oxygen use at 36 weeks postmenstrual age or discharge, whichever came first[33]; (2) patent ductus arteriosus diagnosed clinically and, when available, confirmed by echocardiography, (3) necrotizing enterocolitis (NEC) confirmed by radiologic (pneumatosis and/or perforation) or surgical findings (Bell stages IIA or higher)[34]; (4) early-onset sepsis (≤72 hours) and late-onset sepsis (LOS; >72 hours) confirmed by positive cultures for bacteria, virus, or fungi[35,36]; (5) periventricular leukomalacia (PVL) diagnosed by the presence of intraparenchymal necrotic lesions in the white matter by cerebral ultrasound examination, (6) severe intraventricular hemorrhage (IVH) diagnosed by cerebral ultrasound examination or autopsy as grades III-IV according to the criteria by Papile et al[37], and (7) retinopathy of prematurity (ROP) diagnosed by eye examination performed an ophthalmologist after 28 days of birth and classified in stages 1-5 according to the International Classification.[38] Survival without major morbidity was defined as survival to discharge without NEC (stage IIA or more), severe IVH, PVL, LOS, BPD, or any stage ROP.

Missing data for major morbidities were BPD (2.6%), LOS (7%), severe IVH (3.3%), PVL (5%), and NEC (2.9%), with similar proportions throughout the study periods. Missing values were not imputed except for ROP in infants who died or were discharged home before 28 days of life; in those cases, they were imputed as no ROP.

The study was approved by the Ethical Committee and Institutional Review Board of Pontificia Universidad Católica de Chile, School of Medicine.

Statistical Analyses

Descriptive statistics are shown in 4-year periods (2001-2004, 2005-2008, 2009-2012, and 2013-2016). A logistic regression model was used for categorical outcomes to analyze potential linear trends throughout the 4 study periods. When appropriate, this analysis was performed by adjusting for key prenatal variables such as birth weight, gestational age, Apgar scores at 1 minute, sex, and center. For numerical variables, the linear trend analysis was done using the Jonckheere-Terpstra test. The primary analyses were performed using data from 14 permanent centers of NEOCOSUR's Neonatal Network over 16 years. A P value of less than .05 was considered significant. Analyses were completed using SPSS statistical software version 17.0 (SPSS, Inc, Chicago, Illinois).

Results

Trends in main perinatal results throughout the study period are shown in the **Table**. A total of 13 987 infants were born between 23 and 35 weeks of gestation and weighing 500-1500 g at the 14 permanent network centers during the 2001-2016 study period. We excluded 1473 infants because

they were transferred to other centers. The mean birth weight was 1.081 ± 281 g and did not change significantly over the study period. The mean gestational age decreased from 29.1 weeks to 28.7 weeks of gestation (P <.001). Maternal age increased from 27.7 to 28.8 years (P <.001), and multiple birth increased from 17.1% to 22.3% (P <.001). The incidence of low Apgar scores at 1 and 5 minutes of life (0-3) increased over time (P <.001 and P = .004, respectively), as did the presence of major birth defects (P = .002).

The overall mortality rate remained unchanged over the study period at 26.8% (P = .1); of these deaths, 4.4% occurred in the delivery room. Data regarding postdischarge mortality were not a part of the registry.

The incidence of BPD decreased modestly from 17.3% to 16.0% (P = .04); early-onset sepsis decreased from 6.3% to 2.8% (P <.001) and LOS from 21.1% to 19.5% (P <.001). The rate of persistent ductus arteriosus increased from 29.7% to 45% (P <.001), and severe IVH (grades III-IV) and PVL remained unchanged throughout the study periods, with rates of 10.4% and 3.8%, respectively. The incidence of ROP decreased from 21.3% to 13.8% (P <.001). Rates of NEC remained unchanged at 11.1% during the study period. (Figure 1)

Overall survival without major morbidity increased from 37.4% to 44.5% across the study period (P <.001). A subgroup analysis showed that overall survival rate among infants born between 23 and 25 weeks of gestation decreased from 34% to 24% (P = .004) with a mean of 29% (Figure 2, A), of which only 2% survived without major morbidities (Figure 2, B). In the group of preterm infants born between 26 and 28 weeks of gestation, 70% survived and 23% survived with no major morbidities. A significant upward trend in survival without major morbidities was observed in this group of infants over the last 3 periods of the study (P = .002). Survival rate for infants between 29 and 31 weeks of gestation was 87%; 54% survived without major morbidities with improvement over the study period (P <.001). Survival in the 32 to 35 weeks group remained almost unchanged at 88%; 69% survived without major morbidity.

Administration of at least 1 dose of ACS increased from 70.2% to 82.3% and cesarean delivery from 65.9% to 75.4% (P <.001). Antenatal antibiotic use decreased from 34.9% to 32.9% (P <.001). A total of 8636 infants (65%) received mechanical ventilation throughout the study period, and these rates decreased from 67.7% to 63.9% over the study period (P <.001). Use of continuous positive airway pressure

Table. Main perinatal characteristics and outcomes from the 14 permanent NEOCOSUR's centers, 2001-2016

Mortalities	Global (n = 13 987)	2001-2004 (n = 3163)	2005-2008 (n = 3646)	2009-2012 (n = 3712)	2013-2016 (n = 3466)	*P* value*
Global mortality	26.8	26.3	26.7	27.5	26.8	.107
Death in delivery room	4.4	3.7	4.3	4.6	4.8	.604
Death after admission	22.4	22.6	22.4	22.8	22.0	.072
Maternal characteristics						
Maternal age, years	28.2 ± 7.4	27.7 ± 7.1	27.8 ± 7.4	28.3 ± 7.5	28.8 ± 7.3	<.001
Prenatal steroids	78.0	70.2	77.8	80.8	82.3	<.001
Prenatal antibiotics	34.3	34.9	35.9	33.4	32.9	<.001
Cesarean delivery	71.9	65.9	71.7	74.1	75.4	<.001
Neonatal characteristics						
Birth weight, g	1081 ± 281	1083 ± 280	1079 ± 280	1077 ± 283	1087 ± 280	.519
Gestational age, weeks	28.8 ± 2.9	29.1 ± 2.9	28.7 ± 2.9	28.6 ± 2.9	28.7 ± 2.8	<.001
Male sex	51.2	50.6	51.9	49.8	52.8	.619
1-minute Apgar score of 0-3	22.7	19.8	22.6	23.7	24.3	<.001
5-minute Apgar score of 0-3	7.6	6.3	6.7	8.4	8.8	.004
Multiple gestation	20.3	17.1	19.4	22.1	22.3	<.001
Major birth defects		NA	5.6	7.2	6.3	.002
Respiratory support†	**(n = 13 371)**	**(n = 3045)**	**(n = 3488)**	**(n = 3540)**	**(n = 3298)**	
Surfactant use		NA	55.9	55.2	58.9	.004
Conventional ventilation	64.6	67.7	65.1	62.1	63.9	<.001
NCPAP	57.2	41.3	61.0	60.5	64.3	<.001
Neonatal morbidities†						
Oxygen 36 weeks	16.6	17.3	16.7	16.6	16.0	.043
PDA	40.0	29.7	39.8	44.5	45.0	<.001
Early onset sepsis	3.4	6.3	2.4	2.5	2.8	<.001
Late onset sepsis	20.2	21.1	20.8	19.7	19.5	<.001
IVH G III-IV	10.4	10.2	9.8	10.6	11.0	.767
PVL	3.8	4.2	3.8	3.6	3.6	.143
Hydrocephalus	3.2	3.8	3.6	2.9	2.4	<.001
Global ROP	17.8	21.3	20.4	15.9	13.8	<.001
NEC	11.1	10.4	12.0	11.7	10.2	.937
Survival without major morbidities	40.5	37.4	39.1	40.9	44.5	<.001

NA, information unregistered in period; *NCPAP*, noncontinuous positive airway pressure; *PDA*, persistent ductus arteriosus; *PMA*, postmenstrual age.
Values are mean ± SD or percent.
*Adjusted by gestational age, birth weight, gender, 1-minute Apgar score, and center.
†Excluding deaths in delivery room.

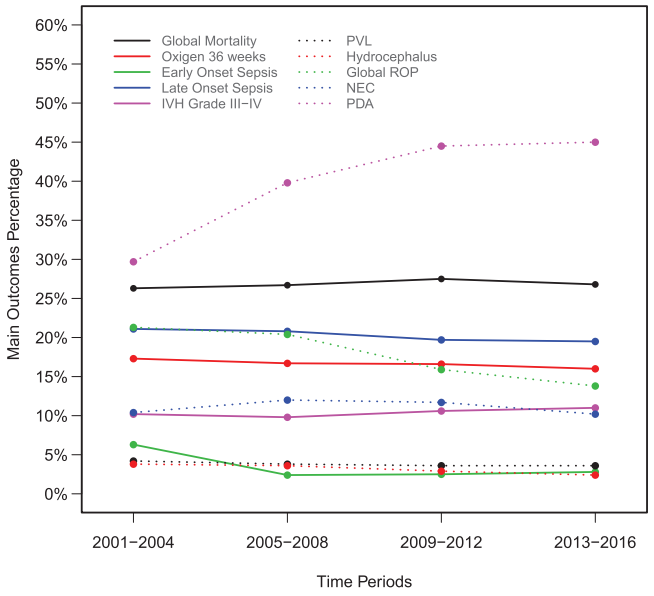

Figure 1. Overall mortality rate and main morbidity incidences in infants born in NEOCOSUR centers. *PDA*, patent ductus arteriosus.

increased from 41.3% to 64.3% (P <.001) and surfactant administration increased from 55.9% to 58.9% (P = .008) (**Figure 3**).

Discussion

In our network, there was a significant improvement in survival without major morbidity throughout the 16-year period of our study, even though overall VLBW mortality remained unchanged.

Internationally, other neonatal networks have reported their outcomes in recent years. A study comparing outcomes for VLBW populations in the Swiss Neonatal Network and the US members of the Vermont Oxford Network showed comparable mortality rates of 11% to 12%,[25] and the Korean Neonatal Network reported an overall survival of 86%.[39] The International Network for Evaluating Outcomes compared 2 periods in more than 150 000 neonates between 24 and 32 weeks of gestation born in 11 high-income countries.[40] They found an overall mortality of 9.1% and observed a reduction in mortality over the 9-year study period from 9.9% to 8.2%. They also reported that the incidence of BPD increased from 23.3% to 27.5%. This same network has also reported significant variation in the survival of very preterm infants across study networks, particularly between 24 and 27 weeks of gestation, ranging from 78 to 93%.[23] Our results compared with neonatal networks from the developed world highlight important differences in mortality rates. There are few published studies regarding VLBW infant outcomes from networks that represent developing or middle-income countries. The Brazilian Neonatal Research Network published in 2015 VLBW outcomes with an overall mortality of 30% and survival without major morbidity of 47%.[41]

We do not have a clear explanation for our unchanged mortality rate over time despite the improvement in some of the evidence-based practices. We noted survival in the gestational age range of 23-25 weeks decreased from 34% to 24%. In contrast, there was a trend for increased survival in infants between 26 and 35 weeks gestational age. Possible factors could include a slightly lower gestational age, increased birth defects, and lower Apgar scores over the study

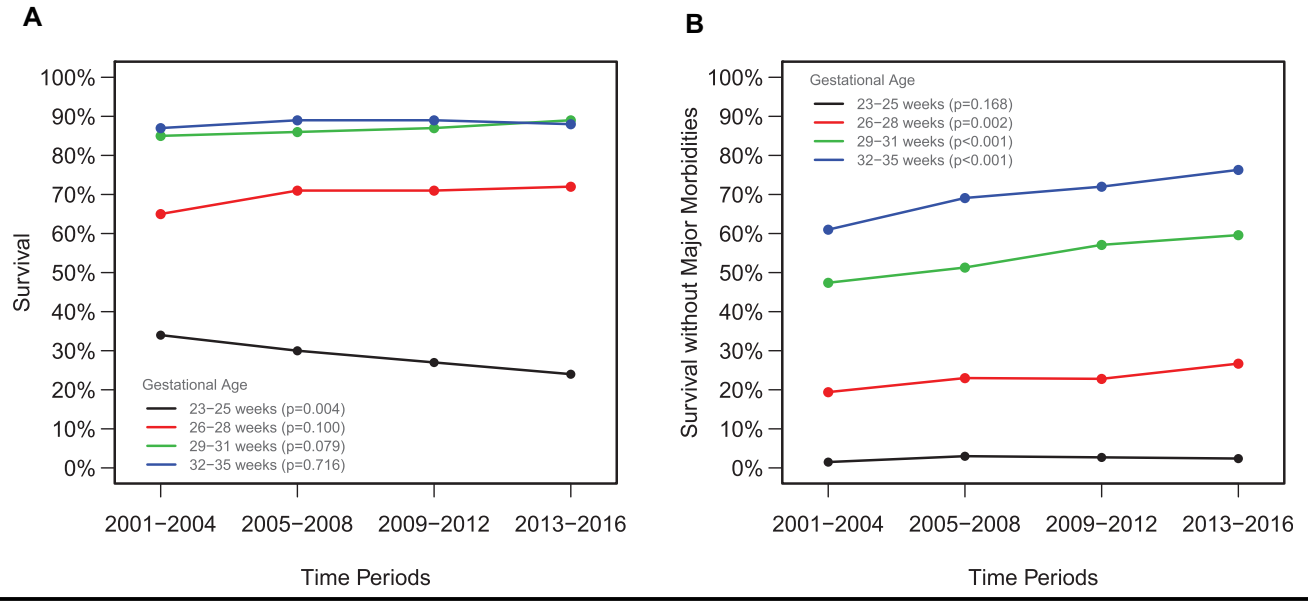

Figure 2. Trends in, **A,** survival and, **B,** survival without major morbidity at different gestational ages in infants born in NEOCOSUR centers.

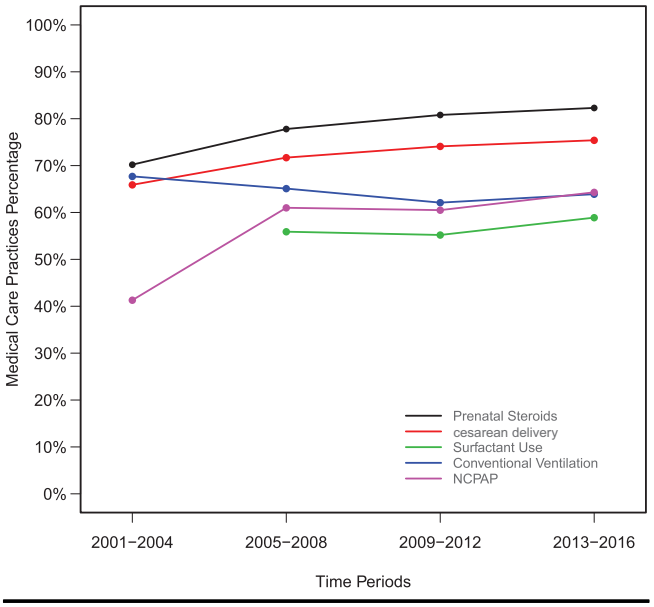

Figure 3. Trends in perinatal care practices in infants born in NEOCOSUR centers. *NCPAP, noncontinuous positive airway pressure*.

period. There was also increased surfactant use, despite a decrease in invasive ventilation. Maternal age increased, as well as multiple births. We have previously reported that training of medical and nursing staff is variable among centers and may influence outcomes.[42] Our study shows a significant increase in ACS administration and in the use of continuous positive airway pressure, with a significant decrease in the proportion of patients that receive invasive respiratory support during neonatal intensive care unit stay. These findings reflect better adherence to international recommendations and guidelines for perinatal management.[43,44]

Our finding of a modest but significant decrease in BPD incidence over time may be associated with some of the observed changes in care practices. A wide variability in the rate of BPD ranging from 10.2% to 24.8% has been reported in infants born at 24-32 weeks of gestation across European regions, attributed mainly to the degree of immaturity of the different populations.[45] A retrospective analysis of 27 205 VLBW infants from the Spanish SEN1500 network in 2 consecutive periods (2002-2006 and 2007-2011) showed only a moderate increase in survival without BPD from 26.6% to 31.6% among infants born at 23 to 26 weeks of gestation, despite significant increases in prenatal steroid administration and noninvasive respiratory support in the delivery room and neonatal intensive care unit.[4] Other factors that may influence the incidence of BPD, such as oxygen saturation targets, ventilation modes, fluid volumes, and nutritional practices were not included in our analyses because this information is not collected in the database.

We observed a significant increase in the incidence of patent ductus arteriosus from 29.7% to 45.0%, possibly because of better screening practices and diagnosis with functional echocardiography. The NICHD reported in 2010 a 46% incidence of patent ductus arteriosus in VLBW infants born in its centers.[5]

The proportion of infants diagnosed with ROP in our study decreased from 21.3% to 13.8%, in contrast with the frequency reported by Stoll et al of 60% of infants with all stages of ROP.[1] However, this study included infants less than 29 weeks gestational age. Our decreasing incidence of ROP may be due to improved use and strict monitoring of supplemental oxygen after birth.[46]

Despite a significant increase in ACS administration and the rate of cesarean delivery, no changes were observed in the incidence of severe IVH. However, rates of hydrocephalus decreased significantly, which might be attributed to improved quality of postnatal care as reflected by the improved survival without major morbidity. PVL rates remained stable throughout the study periods. The overall incidence of severe IVH (10.4%), NEC (11.1%), and PVL (3.8%) agree with those reported for VLBW infants in other networks.[1,6,25]

Both early-onset sepsis and LOS decreased significantly during the study period. The decrease in LOS might be attributed to better care of central lines and other invasive devices, as well as better adherence to hygiene protocols. Because LOS has been associated with an increased risk of neurodevelopmental impairment, we hypothesize that decreased rates of LOS might be associated with the increase in survival without major morbidities.

Survival without major morbidities improved over time, especially in the subgroup of infants between 29 and 35 weeks of gestation. The most dramatic difference in survival was between the group of infants of 23-25 weeks of gestation (29%) and 26-28 weeks of gestation (70%). Efforts should be directed to the group of 23-25 weeks gestational age, where survival without major morbidities was as low as 2%. We believe that not only improvement in mortality rate is pivotal, but that survival without major morbidities is also of great importance when evaluating effectiveness of new strategies or interventions.

Limitations of this study include missing data for some morbidities and its retrospective nature. In addition, our database only recently began including feeding practices (such as use of human milk or formula), which are known to have an influence in neonatal outcomes. We believe this topic is of special interest, because disseminating knowledge obtained in regional centers may facilitate and enhance parental counselling. This study paves the way to further care quality improvement provided by NEOCOSUR centers in the South American region.

In conclusion, progress in perinatal practices and neonatal care at NEOCOSUR network centers was accompanied by an improvement in survival of VLBW infants without major morbidity over a 16-year period. However, no changes were observed in overall mortality. The results of 16 years of experience in our network show that progress in care to

date is still insufficient to decrease mortality and burden in the VLBW infant population. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Neonatal Seizures: 50 Years of Progress

Freeman JM. Neonatal seizures–diagnosis and management. J Pediatr 1970;77:701-8.

One-half century ago, John Freeman presented in *The Journal* a review of neonatal seizures, listing the major causes, presentations, diagnostic approaches, and treatments of the different etiologies. A high initial mortality of about 40% after neonatal seizures in 2 unselected and 25% in 1 selected series was found. Intracranial hemorrhage accounted for approximately 50% of deaths, both in term and preterm children at the time, and accounted for 60%-80% of postmortem identified causes of seizure-related deaths. In a series of deaths excluding preterm infants, 20% were due to birth trauma and anoxia. In the current literature, mortality has decreased to approximately 20%.[1]

The list of etiologies for neonatal seizures still encompasses the same causes as it did 50 years ago. Hypoxic-ischemic encephalopathy is now the most common reason in the term, and intraventricular hemorrhage in the preterm neonate. However, routine cranial ultrasound examination was not introduced in the neonatal intensive care units until around 1980, and the latter would therefore likely have been diagnosed post mortem 50 years ago. There is a greater chance of both identifying and treating infants with hypoxic-ischemic encephalopathy today. There is a much better understanding of the metabolic causes of seizures today, and the field of genetics has identified several genetic epilepsy syndromes accounting for approximately 15% of all seizures in the neonatal population, with specific presentations and treatment options.[2] The higher rate of diagnosed seizures today is, to a large extent, due to the introduction of the amplitude integrated electroencephalogram, and the more widespread use of full electroencephalograms with simultaneous video recordings. Reading Freeman's review reminds us of the immense progress that has been made in the field of neonatal seizures in the last 50 years, and also the fact that we still have neither the optimal diagnostic tools nor the optimal treatment options for this group of patients.

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Appendix

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