

Mortality in very low birth weight (VLBW) infants in the South American NEOCOSUR Neonatal Network: timing and causes

Alberto Toso^a, Catalina Vaz Ferreira^b, Tamara Herrera^b, Luis Villarroel^c, Mariana Brusadin^d, María J. Escalante^e, Daniela Masoli^f, Ivonne D'Aprenont^a, Gonzalo Mariani^e, José L. Tapia^a and NEOCOSUR Neonatal Network^f

- a. Department of Neonatology, School of Medicine, Pontificia Universidad Católica de Chile, Santiago de Chile, Chile.
- b. Department of Neonatology, Centro Hospitalario Pereira Rossell, Universidad de la República, Montevideo, Uruguay.
- c. Department of Public Health, School of Medicine, Pontificia Universidad Católica de Chile, Santiago de Chile, Chile.
- d. Department of Neonatology, Hospital Español de Mendoza, Mendoza, Argentina.
- e. Department of Pediatrics, Hospital Italiano de Buenos Aires, the City of Buenos Aires, Argentina.
- f. South American Neonatal Network (Red Neonatal del Cono Sur, www.neocosur.org).

ABSTRACT

Introduction. Mortality in very low birth weight infants (VLBWIs) has remained at ~26% in the past 16 years in the NEOCOSUR Neonatal Network.

Objective. To determine the cause of death of VLBWIs and its temporality in the 2007-2016 period in the NEOCOSUR Neonatal Network.

Population and methods. Observational, multicenter cohort study; retrospective analysis of data collected prospectively. Newborn infants born between 24 and 31+6 weeks of gestation age with a birth weight between 500 and 1500 g in the 26 sites of the NEOCOSUR Neonatal Network were included. The causes of death were analyzed depending on whether they occurred in the delivery room (DR) or in the neonatal intensive care unit (NICU). The postnatal age at time of death was determined using the Kaplan-Meier test.

Results. A total of 11 753 VLBWIs were included; overall mortality was 25.6%. The prevailing causes of death in the DR were congenital malformations (43.3%), respiratory diseases (14.3%), and prematurity (11.4%). The prevailing causes of death in the NICU were respiratory diseases (24.2%) and infections (24.1%). The average and median age at death were 10.2 and 4 days, respectively. Also, 10.2% of deaths occurred in the DR; 21.5% on day 1, 52% in the first 4 days, and 63.8% in the first week of life.

Conclusions. Important differences were observed in the causes of death of VLBWIs depending on their occurrence in the DR or the NICU. Infectious and respiratory conditions were the most relevant factors following admission to the NICU.

Key words: mortality, very low birth weight infants, preterm newborn infant.

<http://dx.doi.org/10.5546/aap.2022.eng.296>

To cite: Toso A, Vaz Ferreira C, Herrera T, Villarroel L, et al. Mortality in very low birth weight (VLBW) infants in the South American NEOCOSUR Neonatal Network: timing and causes. *Arch Argent Pediatr* 2022;120(5):296-303.

INTRODUCTION

Over the years, mortality in very low birth weight infants (VLBWIs) has remained stable in the NEOCOSUR Neonatal Network, at approximately 26%.¹ Such mortality rate is higher than that reported by other neonatal networks in developed countries. According to data from the Swiss Neonatal Network, the mortality rate was only 11% between 2012 and 2014 in the same group of newborn infants.² The International Network for Evaluating Outcomes (iNeo) groups 10 networks from around the world and describes an overall mortality of 9.1% in VLBWIs born between 24 and 32 weeks of gestational age between 2007 and 2015.³ In addition, the Brazilian Neonatal Network has reported a 30% mortality in VLBWIs.⁴

Given our high mortality rate compared to other networks, it is highly relevant that the NEOCOSUR Neonatal Network member sites know the leading causes of mortality as well as temporality, categorized into deaths in the delivery room (DR) or during the stay in the neonatal intensive care unit (NICU) based on days of life.

Recent advances in perinatal practice have been significant and have helped greatly to survival without major morbidities in this group of preterm infants, including the NEOCOSUR Neonatal Network. Such advances imply an improved antenatal control, a higher rate of antenatal corticosteroid use, and the implementation of non-invasive

E-mail address:
Alberto Toso: aatoso@uc.cl

Funding:
None.

Conflict of interest:
None.

Received: 8-12-2021
Accepted: 1-12-2022

ventilation techniques together with early surfactant administration.^{1,4,7}

Knowing the causes of death in an accurate and reliable manner allows us to improve the quality of clinical practice in the areas with a greater impact on mortality and, this way, helps to reduce it. In addition, an adequate parent guidance, an active resuscitation behavior—mainly in relation to viability thresholds (22–23 weeks of gestational age)—and perinatal care planning depend on an accurate knowledge of perinatal outcomes in each site.

The objective of this study was to determine the leading causes of death in VLBWIs and its temporality in the 2007–2016 period in the NEOCOSUR Neonatal Network.

POPULATION AND METHODS

This was an observational, multicenter cohort study. Data collected prospectively were used to conduct a retrospective analysis of infants born between 24 and 31⁺⁶ weeks of gestational age, with a birth weight of 500–1500 g, in the 26 sites of the NEOCOSUR Neonatal Network in the 2007–2016 period. Only patients born and deceased in the NEOCOSUR sites were included.

NEOCOSUR is a non-profit collaborative network of South American NICUs that monitor VLBWI outcomes. It includes NICUs from Argentina, Brazil, Chile, Paraguay, Peru, and Uruguay. Data are registered prospectively using predefined diagnostic criteria and an online data input system (www.neocosur.org). The following variables were analyzed: mortality, gestational age, birth weight (BW), multiple birth, antenatal exposure to corticosteroids (at least 1 dose), mode of delivery, Apgar score, surfactant use, invasive/non-invasive ventilation, and main neonatal morbidities, e.g. neonatal respiratory distress syndrome, necrotizing enterocolitis, severe intraventricular hemorrhage, and retinopathy of prematurity. Mortality was defined as that occurred prior to discharge, including death in the DR, regardless of the length of hospital stay. Mortality after discharge is not registered in the network's database. Gestational age in full weeks was established according to the best obstetric estimation based on an early antenatal ultrasound and/or the last menstrual period.

Major congenital malformations were defined as the presence of a prenatal structural defect that affects (or may potentially affect) survival.

The primary or leading cause of death was classified based on what was registered in the

NEOCOSUR database. The cause was grouped into specific causes or by body organ system depending on their clinical relevance. The 6 most common causes of death were established: congenital malformations, infections (early sepsis, late sepsis, clinical sepsis, septic shock, infection identified as cause of death), respiratory conditions (pulmonary hemorrhage, air leak, bronchopulmonary dysplasia, hyaline membrane disease), conditions associated with the central nervous system (CNS) (intraventricular hemorrhage, convulsive status epilepticus, hydrocephalus, CNS disease identified as cause of death), prematurity (thus defined in the database as cause of death), and necrotizing enterocolitis. If not included under these 6 categories, the cause was classified as “other”. If the cause of death could not be clearly established according to the database description, it was defined as “unidentified cause”.

The classification and grouping of causes of death was done and reviewed by 4 clinicians members of the NEOCOSUR Neonatal Network based on predefined criteria that were common for the group as a whole.

The causes of death were broken down depending on whether they occurred in the DR or after admission to the NICU. In addition, they were classified based on temporality (days of life) and stratified gestational age (24–27 weeks and 28–31 weeks).

For the descriptive analysis, mean and standard deviation values were used for numerical variables, whereas frequency and proportion values were used for categorical variables. The former were compared using Student's *t* test and the latter, using the χ^2 test. A value of $p < 0.05$ was considered statistically significant.

Postnatal age at death was determined using the Kaplan-Meier test for the entire study period. The causes of death were analyzed for all preterm infants and based on whether they occurred in the DR or following admission to the NICU.

The SPSS 17.0 (Chicago, IL, USA) software was used for analysis.

The study was approved by the Ethics Committee of the School of Medicine of Pontificia Universidad Católica de Chile (ID: 171106002).

RESULTS

A total of 11 753 live newborn infants born between 24 and 31⁺⁶ weeks of gestational age with a BW of 500–1500 g in the NEOCOSUR

sites between January 2007 and December 2016 were included. Overall mortality since birth until discharge from the hospital across the study period was 25.6% (n = 3012). The characteristics of the study population are described in *Table 1*.

Figure 1 shows the causes of death classified as overall, occurring in the DR or occurring after admission to the NICU. The prevailing causes of death in the DR were congenital malformations (43.3%), respiratory diseases (14.3%), and prematurity (11.4%). After admission

to the NICU, the most common causes of death were respiratory diseases (24.2%), followed by infectious diseases (24.1%), and congenital malformations (10.8%). The cause was not identified in 21.6% of all deaths.

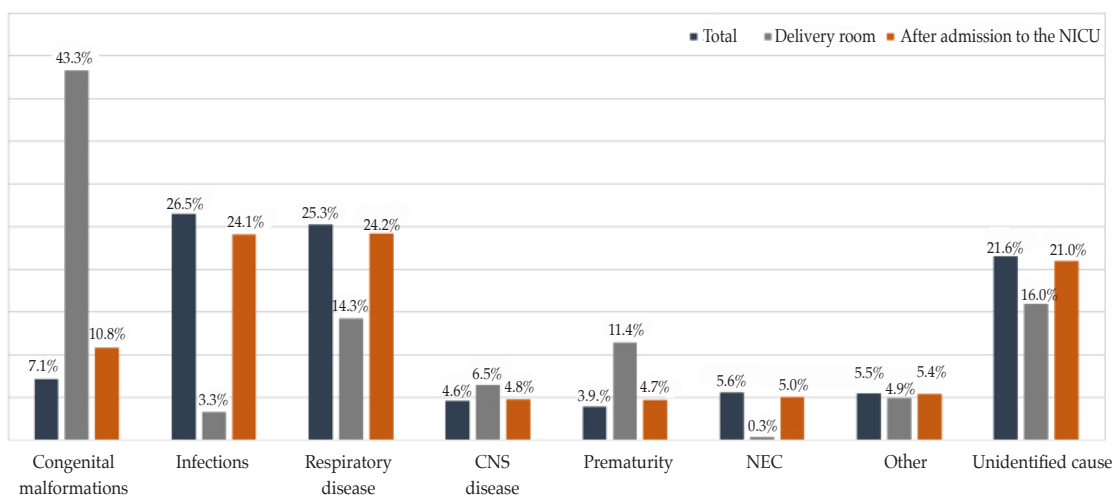
In relation to temporality, the median age at death was 4 days, whereas the average age at death in the study population was 10.2 days (*Figure 2*). If the temporality of deaths in the study population is analyzed in more depth, it is observed that 10.2% of deaths occurred in the

TABLE 1. Characteristics of the study population (n = 11 753) NEOCOSUR Neonatal Network 2007-2016

Gestational age (weeks), mean (SD)	28.0 (2.1)
Birth weight (g), mean (SD)	1054.6 (262.5)
Female sex, n (%)	5540 (47.1)
Multiple pregnancy, n (%)	2402 (20.4)
Antenatal corticosteroids, n (%)	9540 (81.2)
Mode of delivery, n (%)	
Spontaneous vaginal	3254 (27.7)
C-section with labor	5594 (47.6)
C-section without labor	2873 (24.4)
Apgar at 1 min \leq 3, n (%)	2787 (23.7)
Apgar at 5 min \leq 3, n (%)	754 (6.4)
Mortality, n (%)	3012 (25.6)
Death in the delivery room, n (%)	307 (2.6)
Respiratory distress syndrome, n (%)	9774 (83.2)
Mechanical ventilation, n (%)	8243 (70.1)
Necrotizing enterocolitis, n (%)	1402 (11.9)
Intraventricular hemorrhage grade III or IV, n (%)	1222 (10.4)
Retinopathy of prematurity, n (%)	1977 (16.8)

SD: standard deviation; n: number.

FIGURE 1. Causes of death in very low birth weight infants in the NEOCOSUR Neonatal Network between 2007 and 2016 across different periods: Total, delivery room, and after admission to the neonatal intensive care unit



CNS: central nervous system; NEC: necrotizing enterocolitis.

DR; 21.5%, between 1 hour and 1 day of life (after admission to the NICU); 52.1% of patients died in the first 4 days of life and 63.8%, in the first week (Table 2).

The relationship between causality and temporality changes over the first month of life, as shown in Figure 3. Congenital malformations are the prevailing cause of death in the DR compared to respiratory diseases in the first days of life. After the first week of life, infections are the leading cause of death in this population, together with necrotizing enterocolitis.

Figure 4 shows the causes of death by gestational age (24-27 weeks and 28-31 weeks). In the older gestational age group (28-31 weeks), the prevailing cause of death in the DR and during the first 48 hours of life were congenital malformations. However, among infants with a younger gestational age (24-27 weeks), deaths that occurred in the first days of life were mostly related to respiratory diseases.

In both gestational age ranges, deaths due to infections and necrotizing enterocolitis behave

similarly. Infections prevail after the first week of life, whereas necrotizing enterocolitis is more common between the second and the fourth week of life.

DISCUSSION

Overall mortality in VLBWIs was 25.6% in the study period. The average and median age at death were 10.2 and 4 days, respectively. The prevailing causes of death in the DR were congenital malformations, respiratory diseases, and prematurity. After admission to the NICU, the most common causes of death were respiratory diseases, followed by infectious diseases and congenital malformations.

Historically, immaturity and respiratory causes in the first days of life were the leading causes of death in the group of extremely preterm infants. However, Patel et al. have reported a reduction in respiratory diseases as cause of death among extremely preterm infants (between 22 and 28 weeks of gestational age) in the 2000-2011 period according to the

FIGURE 2. Age of very low birth weight infants at time of death. Kaplan-Meier analysis for the entire population

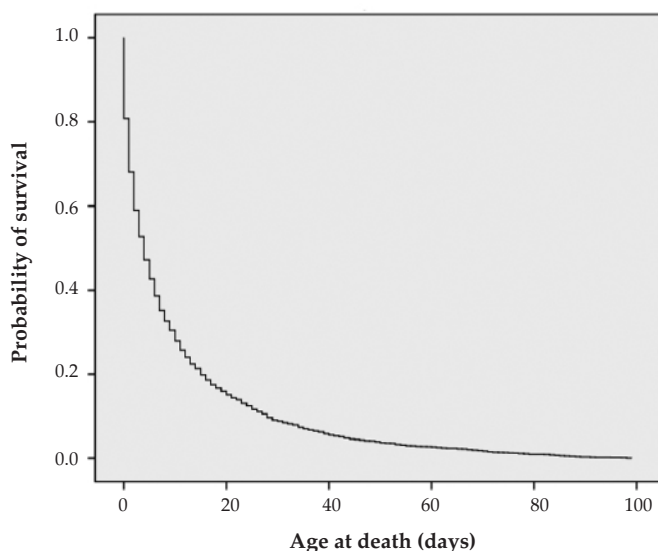
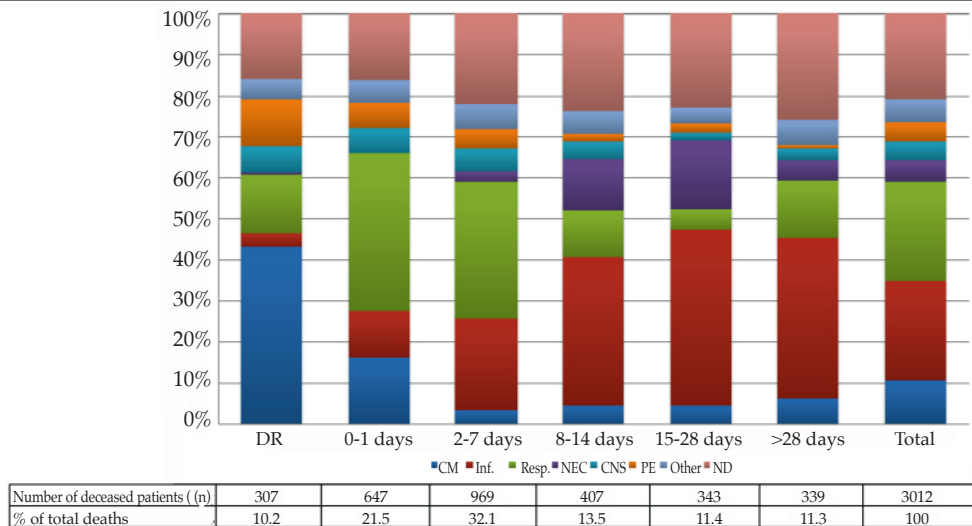


TABLE 2. Causes of death as per temporality in the overall population ($n = 3012$) during the first week of life – NEOCOSUR Neonatal Network 2007-2016

	DR	1 h-1 do	2 do	3 do	4 do	5 do	6 do	7 do	> 7 do
Number of deceased patients (n)	307	647	268	183	163	137	118	100	1089
% of accrued deaths	10.2	31.7	40.6	46.7	52.1	56.6	60.5	63.8	100

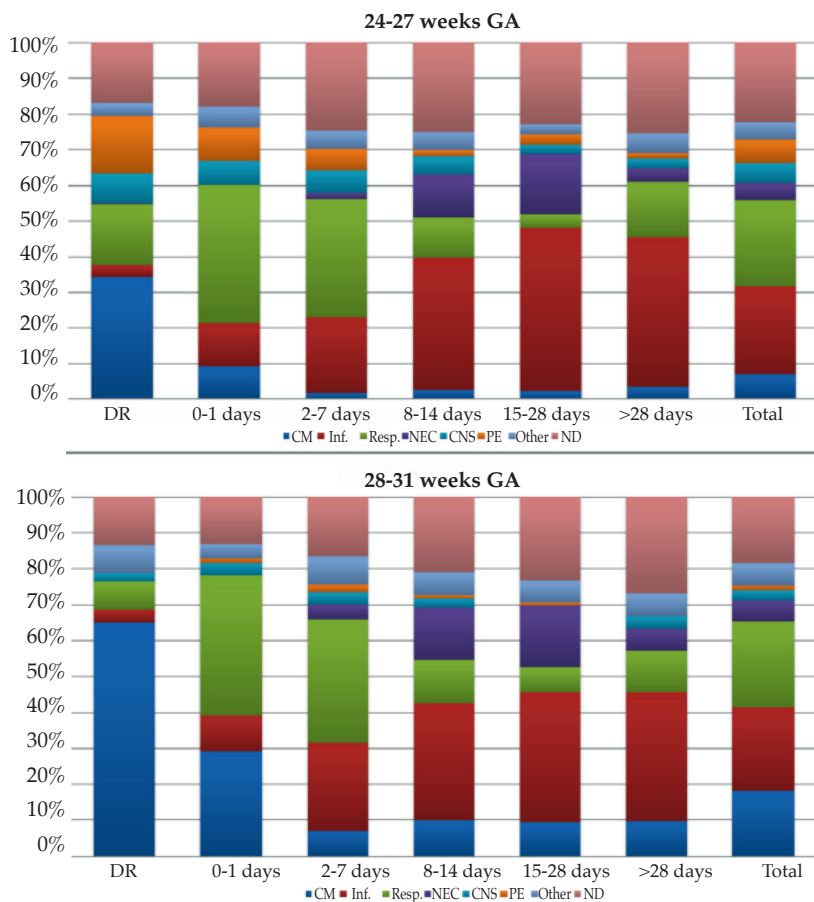
DR: delivery room; do: days old.

FIGURE 3. Causes of death as per temporality in the overall population



DR: delivery room; CM: congenital malformations; Inf.: infections; Resp.: respiratory diseases; CNS: central nervous system; NEC: necrotizing enterocolitis; PE: prematurity; ND: non-determined.

FIGURE 4. Causes of death in very low birth weight infants by gestational age (24-27 weeks [n = 2029] and 28-31 weeks [n = 983]) in the NEOCOSUR Neonatal Network 2007-2016



GA: gestational age; DR: delivery room; CM: congenital malformations; Inf.: infections; Resp.: respiratory diseases; CNS: central nervous system; NEC: necrotizing enterocolitis; PE: prematurity; ND: non-determined.

National Institute of Child Health and Human Development (NICHD) Network (n = 22 248).⁸ In contrast, necrotizing enterocolitis as a cause of death increased. Although other networks have found a recent reduction in the mortality rate of extremely preterm infants, the causes of death are not specified. Data from a study conducted in 2 areas of Croatia (n = 252) point out that immaturity is the most frequent cause of death in the first 3 days of life in VLBWIs born at ≥ 22 weeks of gestational age with a BW < 1500 g; whereas necrotizing enterocolitis is the most common cause after 12 hours of life, followed by infections and, finally, renal conditions. In this study, most deaths occurred in the first 12 hours of life.⁹ A single center study from Korea described the causes of death in preterm infants born between 23 and 26 weeks of gestational age over 2 periods.¹⁰ In the first period (2001-2005, n = 382), the prevailing causes of death were sepsis, air leak, and bronchopulmonary dysplasia (BPD). In the second period (2006-2011, n = 258), the causes of death were intracranial hemorrhage and BPD. A recent study analyzed the causes of death in infants born between 24 and 26⁺⁶ weeks of gestational age in the Netherlands and found that the 3 leading causes were necrotizing enterocolitis, neonatal respiratory distress syndrome, and intraventricular hemorrhage.¹¹

In our study, the main causes of death in the DR were severe congenital malformations and, after admission to the NICU, respiratory diseases and infections, and this is consistent with studies conducted in developing countries.^{9,12}

The analyses of mortality and its causes in other networks are variable. Such variability depends on the target population and excluded patients. For example, the study from the Netherlands excluded patients who died after the first 12 hours of life.¹¹ In our study, we analyzed all deceased patients in the predetermined age, weight, and time group, regardless of their history. This allows to have an actual overview of causes of death in VLBWIs.

Similarly to what has been observed in other networks, prematurity is a cause of death, especially in the DR and in the first days of life.^{8,9} Respiratory conditions prevail in the first weeks of life, whereas infections prevail after the first or second week of life, a period during which necrotizing enterocolitis is also a cause of death.

The analysis of causes of death by gestational age showed that the relevance of congenital malformations as a cause of death in the DR is

higher in the population born at a gestational age between 28 and 31 weeks compared to the group born between 24 and 27 weeks (65.2% versus 34.4%). In addition, as expected, prematurity does not play a relevant role as a cause of death in the group born between 28 and 31 weeks of gestational age, and respiratory causes reduced with an older gestational age. Infections and necrotizing enterocolitis show a similar behavior in both gestational age groups.

Identifying the causes of death also allows to establish potentially modifiable causes, such as respiratory diseases and infections. The subsequent development of quality improvement protocols aimed at reducing infections in the NICU and enhancing respiratory therapies may help to reduce mortality in this group of VLBWIs.

It is also worth noting the large percentage of patients who die in their first week of life, which evidences the relevance of perinatal care to improve survival.

The main limitation of this study, in addition to its retrospective nature, is that a large percentage of causes of death has not been adequately defined. However, the difficulty establishing the cause of death is also common in other networks.⁸ Different factors may contribute to this, resulting in a potential error in the classification of the cause of death.

Thus, in the study by Patel et al., the cause of death was not adequately established in 13.7% of cases.⁸ Another limitation, also recognized by other authors, is that our database does not register the limitation of therapeutic efforts, which may occur since birth. In addition, we may also consider that the fact that the NEOCOSUR Neonatal Network includes selected sites with heterogeneous, public and private NICUs concerned about keeping a prospective data registry is another limitation. For this reason, the collected data may not be entirely extrapolated to the whole region.

In our study, in order to better classify the causes of death, a group of clinicians was specifically trained in this task based on predefined criteria.

Therefore, it is highly necessary to include accurate registries and have clear operating manuals available in relation to causes of death. This way, the actual cause of death of a patient may be better and objectively identified.

The strengths of the study are its multicenter nature and the large group of VLBWIs in whom we especially sought to determine the causes of death and thus contribute to research in a field

that has been little explored in our region.

Another strength is that data collected in this study have allowed to introduce changes in the registry of causes of death in the NEOCOSUR Network in order to standardize and improve mortality diagnoses, reduce the number of unidentified causes due to under-registration, and make better comparisons with the results of other neonatal networks.

CONCLUSIONS

Fifty-two percent of deaths observed in this population of VLBWIs occurred in the first 4 days of life. Congenital malformations were the most common cause of death in the DR, whereas respiratory conditions and infections were the most frequent causes during stay in the NICU. ■

Acknowledgments

We would like to thank all members of the NEOCOSUR Neonatal Network who took part in this study and the Database Unit.

The following members of the NEOCOSUR Neonatal Network helped with this study:

Argentina: Ana Pedraza, Guillermo Colantonio, Gastón Pérez, Jorge Zapata, Fortunato Tomas (Clínica y Maternidad Suizo Argentina, Buenos Aires); Silvia Fernández, Pablo Brener, Gonzalo Mariani, María P. Carrascal, Fernanda Galleti (Hospital Italiano de Buenos Aires); Jorge Tavosnaska, Liliana Roldan, Gladys Saa, Débora Sabatelli, María L. Gendra, María T. Sepúlveda, María F. Buraschi, Graciela Basso (Hospital Juan Fernández, Buenos Aires); Mónica Rinaldi, Daniel Agost (Hospital Lagomaggiore, Mendoza); Claudio Solana, Elio Rojas, Ricardo Nieto, Javier Meritano (Maternidad Sardá, Buenos Aires); Néstor Vain, Lionel Cracco, Edith Martínez, Noemí Jacobi, María San Miguel (Sanatorio de la Trinidad, Buenos Aires); Horacio Roge, Daniel Abdala, Martín Guida, Damián Pretz (Hospital Español de Mendoza, Mendoza); Gabriel Musante, Rodolfo Keller, Carola Capelli, Magdalena Elizalde, Ana Leyla, Romina Acha (Hospital Universitario Austral, Buenos Aires), Luis Ahumada, Mirta Ferreyra, Laura Sánchez, Adriana Mitrano (Hospital Nuestra Señora de la Misericordia, Córdoba).

Brazil: Marynea Do Vale, Vanda M. Ferreira, Silvia Cavalcante de Sousa, Patricia Franco Márquez, Rosangeles Fernández, Lucena Batista, Marília Da Gloria Martins (Hospital Universitario UFMA, São Luís).

Chile: Daniela Masoli, Jorge Fabres, Alberto

Toso, José L Tapia, Álvaro González, Mariela Quezada, Solange Rojas (Hospital Clínico Universidad Católica de Chile, Santiago); Jaime Burgos, María E. Hübner, Rodrigo Ramírez (Hospital Clínico Universidad de Chile, Santiago); Jorge León del Pedregal, Lilia Campos, Aldo Bancalari, Ximena Giacconi, Sergio Treuer, Roxana Aguilar (Hospital Guillermo Grant, Concepción); Jane Standen, Marisol Escobar, Daniela Sandino, Viviana Veas (Hospital Gustavo Fricke, Viña del Mar); Agustina González, Claudia Ávila (Hospital San José, Santiago); Marcela Díaz, Patricia Mena (Hospital Dr. Sótero del Río, Santiago); Dagoberto Pizarro, Rafael Mendizábal, María Caballero (Hospital San Borja Arriarán, Santiago); Rodrigo Donoso, Gerardo Flores, Johanne Jahnsen, Ivian Blanco, Virginia Alpaca, María E. Aguirre, Mauricio Marín, Patricia Álvarez, Jaime García (Hospital Puerto Montt, Puerto Montt); María I. Saldes, Eduardo Ahumada, Montserrat Vásquez, Paula Gajardo (Hospital Van Buren, Valparaíso); Carmen Díaz, Ximena Sandoval, Sergio Farías, Carola Aguirre (Hospital Antofagasta, Antofagasta).

Paraguay: Ramón Mir, José Lacarruba, Larissa Genes, Elizabeth Céspedes, Elvira Mendieta (Departamento de Hospital de Clínicas de Asunción, Asunción); Rosanna Fonseca, Larissa Genes, Leticia Zapata, Sonia Pereira (Hospital San Pablo, Asunción).

Peru: Verónica Webb, Margarita Llontop, Lili Chancafe, Sicilia Bellomo (Hospital Cayetano Heredia, Lima); César García, Oscar Chumbes, Anne Castañeda, Jorge Mucha, Alcides Carrión (Hospital Guillermo Almenara, Lima).

Uruguay: Fernando Silvera, Daniel Borbonet, Catalina Vaz Ferreira, Tamara Herrera, Elsa Arocena, Mey Aguirre (Facultad de Medicina Servicio de Recién Nacidos Pereira Rossell, Montevideo).

Database Unit, Pontificia Universidad Católica, Santiago, Chile: Ivonne D'Apremont, José L Tapia, Mariela Quezada, Solange Rojas, Luis Villarroel, Angélica Domínguez, Claudia Musalem, Guillermo Marshall. José Zubizarreta, PUC Information Technology Management.

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