

## Hypothermia and Early Neonatal Mortality in Preterm Infants

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**Objective** To evaluate intervention practices associated with hypothermia at both 5 minutes after birth and at neonatal intensive care unit (NICU) admission and to determine whether hypothermia at NICU admission is associated with early neonatal death in preterm infants.

**Study design** This prospective cohort included 1764 inborn neonates of 22-33 weeks without malformations admitted to 9 university NICUs from August 2010 through April 2012. All centers followed neonatal International Liaison Committee on Resuscitation recommendations for the stabilization and resuscitation in the delivery room (DR). Variables associated with hypothermia (axillary temperature <36.0°C) 5 minutes after birth and at NICU admission, as well as those associated with early death, were analyzed by logistic regression.

**Results** Hypothermia 5 minutes after birth and at NICU admission was noted in 44% and 51%, respectively, with 6% of early neonatal deaths. Adjusted for confounding variables, practices associated with hypothermia at 5 minutes after birth were DR temperature <25°C (OR 2.13, 95% CI 1.67-2.28), maternal temperature at delivery <36.0°C (OR 1.93, 95% CI 1.49-2.51), and use of plastic bag/wrap (OR 0.53, 95% CI 0.40-0.70). The variables associated with hypothermia at NICU admission were DR temperature <25°C (OR 1.44, 95% CI 1.10-1.88), respiratory support with cold air in the DR (OR 1.40, 95% CI 1.03-1.88) and during transport to NICU (OR 1.51, 95% CI 1.08-2.13), and cap use (OR 0.55, 95% CI 0.39-0.78). Hypothermia at NICU admission increased the chance of early neonatal death by 1.64-fold (95% CI 1.03-2.61).

**Conclusion** Simple interventions, such as maintaining DR temperature >25°C, reducing maternal hypothermia prior to delivery, providing plastic bags/wraps and caps for the newly born infants, and using warm resuscitation gases, may decrease hypothermia at NICU admission and improve early neonatal survival. (*J Pediatr* 2014;164:271-5).

Preterm infants are susceptible to hypothermia shortly after birth. Lupton et al<sup>1</sup> found that 47% of 5277 very low birth weight (VLBW) infants had a body temperature <36°C on admission to the neonatal intensive care unit (NICU). Adjusted analyses showed that admission temperature was inversely related to intrahospital mortality, with a 28% increase in mortality per 1°C decrease in body temperature. Moderate and severe hypothermia were associated with the risk of death before hospital discharge in a population-based cohort of 8782 VLBW infants in California NICUs in 2006 and 2007.<sup>2</sup> Neither study reported the practices applied to maintain normal body temperature from birth to NICU admission. According to McCall et al,<sup>3</sup> plastic wraps or bags and plastic caps are effective in reducing heat losses in infants born at <28-29 weeks' gestation, but it is unclear whether they reduce the risk of death.

The Neonatal Task Force of the International Liaison Committee on Resuscitation recommended in 2010 Consensus on Science that "newborn infants of <28 weeks' gestation should be completely covered in a polythene wrap or bag up to their necks without drying immediately after birth and then placed under a radiant heater and resuscitated or stabilized in a standard fashion. Infants should be kept wrapped until admission and temperature check. Hyperthermia should be avoided. Delivery room (DR) temperatures should be at least 26°C for infants of <28 weeks' gestation."<sup>4</sup> However, all of these recommendations have low levels of evidence regarding their efficacy and effectiveness in reducing neonatal mortality.

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DR	Delivery room
NICU	Neonatal intensive care unit
VLBW	Very low birth weight

Our goal is to evaluate intervention practices associated with hypothermia at 5 minutes after birth and at NICU admission and to determine whether hypothermia at NICU admission is associated with early neonatal death in preterm infants.

## Methods

We conducted a multicenter prospective cohort study of infants born at gestational ages of 23<sup>0/7</sup> to 33<sup>6/7</sup> weeks without congenital anomalies and admitted at 9 centers of the Brazilian Network on Neonatal Research between August 2010 and April 2012. All of the centers are level III public university hospitals and serve as referral centers for high-risk pregnancies. All of the hospitals have NICU beds and the staff, equipment, and infrastructure required to treat critically ill neonates. The study was approved by the institutional review boards of each institution, and informed consent was signed by the mother of each enrolled neonate.

At each NICU, 1 neonatologist prospectively collected maternal and neonatal data in a Web-based data system specially designed for the study. Gestational age was defined by the hierarchy of obstetric measures (last menstrual period, followed by first trimester ultrasonography) and a neonatal exam.<sup>5</sup> The centers followed the Neonatal Resuscitation Program of the Brazilian Pediatric Society guidelines for stabilization and resuscitation at birth according to the International Liaison Committee on Resuscitation Consensus on Science and Treatment Recommendations.<sup>4,6</sup> All of the centers used the same types of digital environmental (Termômetro Digital 7665; Incoterm, Porto Alegre, Brazil) and individual thermometers (Medflex; Incoterm, Porto Alegre, Brazil). DR temperature was registered at birth. Axillary maternal temperature was assessed up to 20 minutes before delivery; axillary neonatal temperature was measured 5 minutes after birth and at NICU admission. Both maternal and neonatal hypothermia were defined as a body temperature  $<36.0^{\circ}\text{C}$ . The neonatal thermal care practices analyzed were the following: use of a plastic bag or wrap; use of a linen or woolen cap; use of heated gases for ventilation; and use of a transport incubator. Care of all newly born infants was given under radiant heaters in the DR, and exothermic mattresses were not used.

The main outcomes were hypothermia 5 minutes after birth, hypothermia at NICU admission, and death by 6 days after birth. Stepwise logistic regression was applied to evaluate the variables associated with these outcomes. For hypothermia 5 minutes after birth, maternal and neonatal characteristics at birth and variables related to neonatal thermal care in the DR were considered to be independent variables. For hypothermia at NICU admission, variables related to thermal care during transport from the DR to the NICU were also included. For early neonatal death, maternal and neonatal characteristics at birth, hypothermia at NICU admission, and neonatal morbidity were evaluated as independent variables. Variables with a value of  $P < .20$  in the univariate analysis were included in the initial model. The fitness

of the model was assessed by use of the Hosmer-Lemeshow test. We calculated that a study population of 1660 patients would be required to detect a difference of 3% in early neonatal mortality (exposed, 8%; nonexposed, 5%) considering a  $\beta$  error of 20%, an  $\alpha$  error of 5%, and a ratio of exposed/nonexposed to hypothermia at NICU admission of 1:1.

## Results

During the study period, 1955 inborn preterm infants with gestational ages of 23-33 weeks and without congenital anomalies satisfied our inclusion criteria, and 1764 (90%) were enrolled in the study. Enrollment varied from 115 to 262 neonates per center. Axillary temperature at 5 minutes after birth was measured in 1374 neonates, and hypothermia was noted in 44% (median  $36.0^{\circ}\text{C}$ ; 25th-75th percentiles  $35.5^{\circ}\text{C}$ - $36.4^{\circ}\text{C}$ ). Axillary temperature at NICU admission was measured in 1764 neonates at an average of 32 minutes after birth, and hypothermia was noted in 51% (median  $35.9^{\circ}\text{C}$ ; 25th-75th percentiles  $35.3^{\circ}\text{C}$ - $36.4^{\circ}\text{C}$ ).

Hypothermia 5 minutes after birth and at NICU admission varied among centers from 13% to 62% ( $P < .001$ ) and from 25% to 75% ( $P < .001$ ), respectively (Figure). Hypothermia at 5 minutes after birth and at NICU admission was inversely related to gestational age ( $P < .001$ ), but 35% of neonates with gestational ages of 32 and 33 weeks were hypothermic at 5 minutes, and  $\approx 40\%$  were hypothermic at NICU admission. Early neonatal death occurred in 6% of the 1764 neonates, varying among centers between 4% and 9% ( $P = .478$ ).

Maternal and neonatal characteristics, including thermal neonatal care practices, in infants with and without hypothermia at 5 minutes after birth and at NICU admission are shown in Table I. Median DR temperature was  $24.8^{\circ}\text{C}$  (25th-75th percentiles  $23.7^{\circ}\text{C}$ - $25.8^{\circ}\text{C}$ ); median maternal axillary temperature was  $36.2^{\circ}\text{C}$  (25th-75th percentiles  $35.8^{\circ}\text{C}$ - $36.6^{\circ}\text{C}$ ); 9 mothers had temperature  $\geq 38^{\circ}\text{C}$  at an average of 18 minutes prior birth; and median transport incubator temperature was  $36.1^{\circ}\text{C}$  (25th-75th percentiles  $35.0^{\circ}\text{C}$ - $37.0^{\circ}\text{C}$ ). Among the 1764 neonates, 9 (0.5%) had hyperthermia ( $\geq 38.0^{\circ}\text{C}$ ) at NICU admission. DR temperature  $<25^{\circ}\text{C}$ , administration of cold air during positive pressure ventilation, and endotracheal intubation soon after birth were associated with hypothermia at 5 minutes of life and at NICU admission (Table I). The following practices were also associated with hypothermia at NICU admission: absence of cap, transport from DR to NICU with cold air, and temperature of the transport incubator  $<35^{\circ}\text{C}$ .

Demographic and clinical characteristics of the patients, according to early neonatal mortality, are shown in Table II. Male sex, gestational age  $<28$  weeks, birth weight  $<1000$  g, 1-minute Apgar score  $<4$ , 5-minute Apgar score  $<7$ , hypothermia at NICU admission, Neonatal Acute Physiology, Perinatal Extension, Version II score  $>40$ , respiratory distress syndrome, air leaks, and grades III/IV

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