Death after Birth Asphyxia in the Cooling Era

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In asphyxiated newborn infants treated with hypothermia, 31 of 50 (62%) deaths occurred in unstable infants electively extubated before completing hypothermia treatment. Later deaths occurred after consultation with palliative care (13/19) or clinical ethics (6/19) services, suggesting these decisions were challenging and required support, particularly if nutrition and hydration were withdrawn (n = 4). *(J Pediatr 2020;226:289-93).*

Despite significant advances in the management of neonatal encephalopathy secondary to birth asphyxia, mortality remains high among this population.[1] Approaches for end-of-life decision making typically are based on the foreseen long-term prognosis and quality of life inferred from the clinical examination coupled with the results of ancillary tests.[2] These decisions are influenced by the culture of the local neonatal intensive care units (NICUs) and by the values and beliefs of the health care providers and parental caregivers.[3-7] These cultures, values, and beliefs highly vary across institutions, and decisions usually are made after discussions between parents and the neonatology team, often supported by other health care providers.[8-10] We conducted this study to understand the circumstances around death in a tertiary-level NICU center in asphyxiated newborn infants treated with hypothermia.

Methods

We conducted a retrospective cohort study of near-term and term-asphyxiated newborn infants, who were treated with hypothermia from 2008 to 2017 at a single tertiary-level NICU center. The retrospectively collected database was approved by the institutional research ethics board, who waived the need for informed consent.

The severity of neonatal encephalopathy was assigned according to the modified Sarnat score recorded on admission.[11,12] The presence of seizures, either clinical or subclinical, was documented along with the number of antiepileptic medications required to control the seizures. Brain MRI studies were interpreted by a pediatric neuroradiologist, who was blind to the clinical condition of the infant. The presence and extent of brain injury was recorded using a previously described MRI scoring system.[13] We collected autopsy results when available.

Data were collected on the circumstances of death, including age and location at the time of death, involvement of the palliative care team (a doctor and a nurse), the clinical ethics team (including 1-2 ethicists), and other medical professionals including social workers. We classified the circumstances of death using the category framework developed by Verhagen et al and modified by Lemmon et al: (A) unstable newborn infants who died while receiving cardiopulmonary resuscitation (CPR), (B) unstable ventilated infants who died withholding CPR, (C) unstable infants who died after elective extubation in their parents' arms, (D) physiologically stable infants who died after elective extubation for quality-of-life considerations, and (E) physiologically stable infants who died after withdrawal of artificial nutrition and hydration.[2,6] We used the same definition of physiological instability used by Lemmon et al, which included 2 or more of the following: (1) persistent oxygen desaturation despite 100% oxygen and mechanical ventilation, (2) hypotension despite volume infusion and inotropes, or (3) protracted anuria for 24 hours.[2]

CPR	Cardiopulmonary resuscitation
NICU	Neonatal intensive care unit
MRI	Magnetic resonance imaging

Results

Among 290 asphyxiated newborn infants who were treated with hypothermia during the study period, 17% (50/290) died, and were included in our study (**Figure**). All infants who died displayed evidence of multisystem organ involvement: 78% (39/50) had hypotension requiring volume infusion, inotropic support, or hydrocortisone; 44% (22/50) had persistent pulmonary hypertension requiring nitric oxide (91% [20/22]) and/or extracorporeal membrane oxygenation (9% [2/22]); 60% (30/50) had acute kidney injury; 74% (37/50) had coagulopathy requiring vitamin K, fresh frozen plasma, or cryoprecipitate; 46% (23/50) had thrombocytopenia; 76% (38/50) had hyponatremia; 34% (17/50) had hypoglycemia (59% [10/17]) or hyperglycemia

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P.W. receives research grant funding from the FRSQ Clinical Research Scholar Career Awards Junior 2 and a CIHR Project Grant. The study sponsors had no involvement in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the paper for publication. The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.07.041

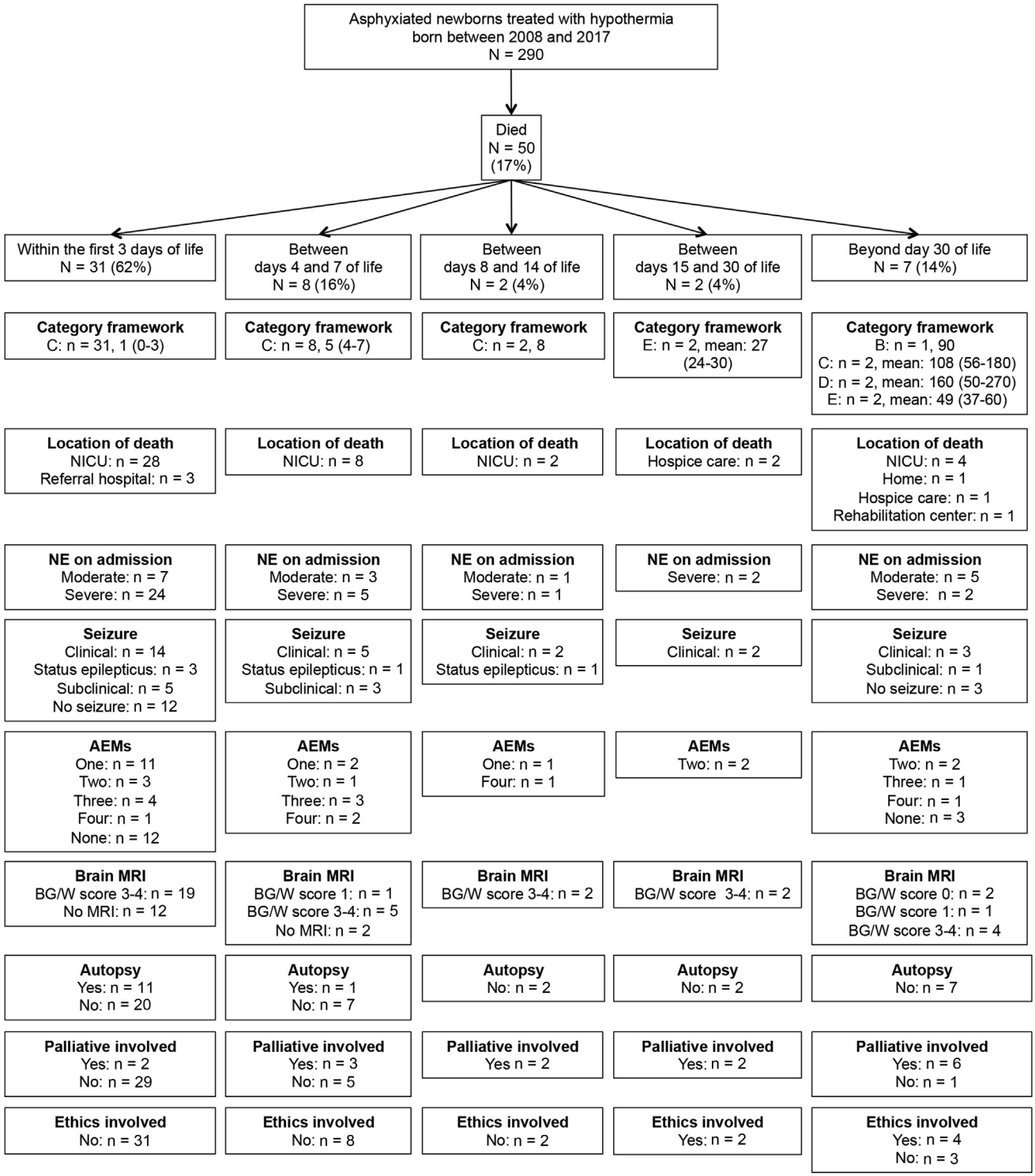

Figure. Flow chart of the study cohort. Infants are grouped by the age at death and vertical panels detail the clinical characteristics and circumstances of death using the category framework described in the methods. *AEM*, antiepileptic medication; *NE*, neonatal encephalopathy severity.

(41% [7/17]); and 1 infant (2%) developed subcutaneous fat necrosis.

Sixty-eight percent (34/50) of the asphyxiated infants who died displayed severe neonatal encephalopathy (modified Sarnat score of 3) on admission. Seventy percent (35/50) of these infants displayed clinical (74% [26/35]) or subclinical (26% [9/35]) seizures (Table); and 14% (5/35) developed status epilepticus. At time of death, 40% (14/35) were

Table. Clinical characteristics

Characteristics	Median (range) or No. (%)
Maternal characteristics	
Maternal age, years	32 (18-40)
First pregnancy	22 (44)
Mode of delivery	
Vaginal delivery	18 (36)
Emergent cesarean delivery	32 (64)
Infant characteristics	
Male	27 (54)
Gestational age, weeks	39.29 (35.29-42.00)
Birth weight, kg	3415 (2025-4450)
10-minute Apgar score	3 (0-7)
Arterial cord pH	6.85 (6.52-7.29)
First blood gas pH	6.91 (6.46-7.36)
Modified Sarnat score on admission	
Mild encephalopathy	0 (0)
Moderate encephalopathy	16 (32)
Severe encephalopathy	34 (68)
Seizures	35 (70)
Clinical	26/35 (74)
Subclinical	9/35 (26)
Brain imaging	
Brain MRI	36 (72)
Type of brain injury:	
BG/W score 0	2/36 (6)
BG/W score 1	2/36 (6)
BG/W score 3	17/36 (47)
BG/W score 4	15/36 (41)

BG/W, basal ganglia/watershed score (13): 0, no brain injury; 1, basal ganglia injury pattern; 2, watershed injury pattern; 3-4, severe extensive brain injury, with 4 corresponding to near-total injury pattern.

being treated with 1 antiepileptic medication, 23% (8/35) with 2 antiepileptic medications, 23% (8/35) required 3 antiepileptic medications, and 14% (5/35) required 4 antiepileptic medications, and 72% (36/50) of the asphyxiated infants who died had a brain MRI. The median age at the time of the MRI was 2.5 days. The majority (88% [32/36]) had extensive brain injury; 6% (2/36) had basal ganglia injury; and 6% (2/36) did not display any injury on the MRI (Table).

None of the infants in our cohort died while receiving CPR, but 1 infant (2%) died during mechanical ventilation while CPR was withheld. The majority (86% [43/50]) were unstable at time of death and were extubated to their parents' arms. Four percent (2/50) were stable and died after an elective extubation for quality-of-life reasons. Eight percent (4/50) were stable and died after nutrition and hydration were withheld (Figure).

Most of the asphyxiated infants (62% [31/50]) died within the first 3 postnatal days before completion of therapeutic hypothermia (Figure). These infants were unstable and were electively extubated, so they could die in their parents' arms. Ninety percent (28/31) died in the NICU and 10% (3/31) were brought back to their original referral hospital to die with their parents. Sixty-one percent (19/31) had an MRI showing extensive brain injury.

A consult was requested with the palliative care team for 30% (15/50) and with the hospital-based clinical ethicist for 12% (6/50) of those who died. The palliative care team and clinical ethics were involved in all cases (8% [4/50]) involving withdrawal of nutrition and hydration. These 4 infants initially presented with severe encephalopathy and displayed extensive brain injury on their MRI and/or autopsy.

Twenty-four percent (12/50) of the asphyxiated infants who died had an autopsy. The histopathologic examination demonstrated brain injury, with evidence of neuronal necrosis and scattered apoptotic glial cells, involving the cortex and the white matter in 100% (12/12), as well as the basal ganglia, cerebellum, and brainstem in 92% (11/12). Forty percent (5/12) of autopsied infants had both brain MRI and brain autopsy, and all had corroborating extensive brain injury on the MRI.

Discussion

In our cohort of asphyxiated newborn infants treated with hypothermia, most deaths happened in the NICU. Most infants in our study died in the first 72 hours, before completion of therapeutic hypothermia. The majority of these infants were unstable at the time of death (88%), and their deaths occurred expectedly as a result of an active decision to withhold CPR, intubation, or hydration/nutrition; for most of them, an elective extubation was performed before death.

Most of the hypothermia trials did not specifically mention the circumstances of death for asphyxiated infants treated with hypothermia. Few studies in the current literature have discussed the circumstances surrounding neonatal deaths.[2,6,8,14-16] Most of these studies were written before the cooling era, whereas hypothermia treatment has modified the prognosis of asphyxiated infants.[2,6,14-16] Few studies have discussed the circumstances around death of asphyxiated infants in the cooling era. For example, Lemmon et al reported that in their center, the majority of infants who died (n = 31) were stable at time of death, and passed away after an elective extubation for quality-of-life reasons (89%) or after nutrition and hydration were withheld or withdrawn (11%).[2] A minority (10%) were unstable and passed away after an elective extubation, reflecting well-described variations in approaches to end-of-life decision-making across institutions and countries.[8] In that study, 40% of infants died after completing hypothermia treatment. Natarajan et al reported the incidence of death in their multicenter data registry (n = 267) and the clinical characteristics of those who died after withdrawal of life support (defined as withdrawal of life-sustaining medical care before death; 88%), without further discussions about the circumstances of death.[17]

Not unexpectedly, the deaths in our cooled cohort predominantly occurred in infants with severe brain injury as assessed by clinical impression, electrophysiologic testing, or neuroimaging. These data suggests that, in the site investigated by the present study, the decision to withdraw intensive care often was made early on based on the postnatal clinical evolution within the first days of life. The first few days of life are known to be a critical period of physiological instability and multiorgan dysfunction, during which withdrawing life-sustaining treatments is likely to be followed

by death; however, a delay in withdrawing life-sustaining care may lead to the survival of severely impaired or disabled children for whom caregivers contemplate a poor quality of life not consistent with their values.[18-21] Arnaez et al performed a survey of end-of-life decisions and palliative care with respect to asphyxiated infants treated with hypothermia, and noted that neonatologists have concerns for missing the early time window to withdraw life-sustaining treatment for these critically ill neonates.[22] A better understanding of individual neonatologists' thresholds for an early prediction of a poor prognosis would be an interesting study for future research.

In the present study, the palliative care or clinical ethics teams were involved in a minority of cases, although at a higher frequency than previously reported.[2] The palliative care or clinical ethics teams always were involved when a decision was made to withdraw nutrition and hydration, which suggests that health care providers and parents may have been comfortable with a decision to electively extubate early on if a prognosis seemed to be guarded, but third-party support was required to withhold or withdraw nutrition and hydration. Although the end is the same, the means to achieve that end may, in practice, have different emotional and moral implications for health care providers and parents.

Clinical guidelines developed by professional societies—such as the American Medical Association's Code of Ethics—have proposed that artificial nutrition and hydration should be considered as a form of treatment similar to more technological treatments such as ventilation.[23-26] In principle, elective extubation and cessation of artificial nutrition and hydration should not be ethically different, but, in practice, caregivers and health care providers have long exhibited an uneasiness with expert views and consensus regarding this topic, notably because of the symbolic and emotional aspects of nutrition and hydration.[27,28] This issue is particularly complex with respect to newborn infants, who need to be fed by a caregiver around the clock, even when neurologically intact. We speculate that withdrawing nonoral artificial nutrition and hydration may have different emotional implications and parental involvement than withdrawal of mechanical ventilation. However, formal qualitative studies of the experience of families and health care providers are needed to determine if withdrawing nonoral artificial nutrition and hydration is more challenging than withdrawing mechanical ventilation. These studies may highlight the unease experienced by health care providers and families in discussing these issues.

In our study, elective withdrawal of ventilation was the most common intervention leading to the death of infants with neonatal encephalopathy secondary to birth asphyxia. These deaths predominantly occurred early on, suggesting that health care providers and parents were able to address these difficult decisions within a short timeframe and successfully reach consensual decisions. However, we demonstrated active support by third parties (palliative care, ethics) in infants who died after withdrawal of nutrition and hydration, suggesting that these decisions may be more challenging than elective extubation. Parents and health care providers need to be supported in making such decisions, and they should feel that they have the appropriate resources to participate in this kind of end-of-life care. ■

We thank Mr Wayne Ross Egers for his professional English correction of the article.

Submitted for publication Jan 16, 2020; last revision received Jul 12, 2020; accepted Jul 13, 2020.

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Data Statement

Data sharing statement available at www.jpeds.com.

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