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Original Articles

Withdrawal of Life-Support in Neonatal Hypoxic-Ischemic Encephalopathy

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ABSTRACT

PURPOSE: We describe the frequency and timing of withdrawal of life-support (WLS) in moderate or severe hypoxic-ischemic encephalopathy (HIE) and examine its associations with medical and sociodemographic factors.
PROCEDURES: We undertook a secondary data analysis of a prospective multicenter data registry of regional level IV Neonatal Intensive Care Units participating in the Children's Hospitals Neonatal Database. Infants ≥36 weeks gestational age with HIE admitted to a Children's Hospitals Neonatal Database Neonatal Intensive Care Unit between 2010 and 2016, who underwent therapeutic hypothermia were categorized as (1) infants who died following WLST and (2) survivors with severe HIE (requiring tube feedings at discharge).
RESULTS: Death occurred in 267/1,925 (14%) infants with HIE, 87.6% following WLS. Compared to infants with WLS (n = 234), the survived severe group (n = 74) had more public insurance (73% vs 39.3%, $P = 0.00001$), lower household income ($37,020 vs $41,733, $P = 0.006$) and fewer [20.3% vs 35.0%, $P = 0.0212$] were from the South. Among infants with WLS, electroencephalogram was performed within 24 hours in 75% and was severely abnormal in 64% cases; corresponding rates for MRI were 43% and 17%,

Data were collected from all the participating institutions of the Children's Hospitals Neonatal Consortium (see Appendix).

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respectively. Private insurance was independently associated with WLS, after adjustment for HIE severity and center.

CONCLUSIONS: In a multicenter cohort of infants with HIE, WLS occurred frequently and was associated with sociodemographic factors. The rationale for decision-making for WLS in HIE require further exploration.

Introduction

Perinatal hypoxic-ischemic encephalopathy (HIE) is associated with a 25% case fatality rate during the initial month of life.[1] Therapeutic hypothermia (TH) for perinatal HIE has led to a significant reduction in mortality; current rates range from 9% to 25%, with the vast majority (75% to 90%) of deaths being preceded by withdrawal of life sustaining therapies.[2–4] In other critically-ill neonatal populations including extremely preterm neonates, the decision to withdraw life support (WLS) is associated with sociodemographic characteristics of the family and health care team, the clinical status and the prognosis for quality of life.[5–8] Despite its frequent occurrence, the associations of WLS in HIE have not been systematically investigated in the era of widespread TH. Given recent approaches of integrated neurocritical care in the NICU, it is unclear whether the decision for WLS is based on prognostic neuroimaging and electroencephalogram (EEG) findings or is primarily determined by family and physician preferences. Understanding factors that drive decision-making for WLS is important, as wide variation in WLS rates (5% to 100%) in severe HIE has been noted between centers.[7]

The Children's Hospitals Neonatal Database (CHND) was established to assess disease-specific outcomes in regional Neonatal Intensive Care Units (NICUs) across North America.[9] We previously reported short-term outcomes and intercenter cost-variation of care in a large cohort of infants with HIE at participating sites.[3,10] The goal of the current study was to describe the frequency and timing of WLS in moderate or severe HIE, and to examine its associations with medical and sociodemographic factors, using CHND data. We hypothesized that, in addition to evidence of severe brain injury by clinical, neuroimaging and EEG criteria, sociodemographic factors such as race, geographic birth location, and insurance would be associated with WLS in HIE.

Material and methods

Data source

The multicenter CHND prospectively captures clinical data on all infants admitted to any of the participating 33 regional NICUs with more than 400 admissions per year or more than 25 beds and with greater than a 50% outborn population.[9] Data from 27 participating sites were included in the current study. Trained data abstractors at each site follow a detailed manual of operations with stringent definitions and demonstrate greater than a 90% intrasite concordance in abstraction annually. The Institutional Review Board at each participating institution approved participation in CHND.

Study population

Infants ≥36 weeks' gestational age, greater than 1800 grams birth weight, with HIE defined by either National Institute of Child Health and Human Development (NICHD) or Vermont Oxford Network criteria who underwent TH were identified.[11,12] Infants were excluded if they were admitted after two days of life, or had a "non-perinatal" hypoxic-ischemic event. WLS was defined as active withdrawal of life-sustaining medical care prior to death. Infants with HIE who died following WLS were compared with a "high risk" group of surviving infants with severe HIE who required gastrostomy or nasogastric tube feedings at discharge ("survived severe"). Severe HIE was defined in the CHND as worst stage of encephalopathy during the first seven days following birth based on the infant's level of consciousness (stupor or coma) and nonresponse to arousal or by NICHD examination criteria.[11] Reported rates of death or disability in severe HIE are 78%, compared to 45% in moderate HIE[2]; gavage or gastrostomy tube feedings at discharge has been shown to be independently associated with death or disability in HIE.[13,14] In a previous study, families of 94% of infants with severe HIE had treatment-limitation discussions.[15] Therefore, the comparison group was selected based on the rationale that infants with severe HIE and adverse short-term outcome would have been likely to be considered for WLS by providers and families.

Clinical data and outcomes

Demographic and socioeconomic data included maternal age, race and ethnicity, postal zip code, birth location, and type of insurance (public versus private). Household income was estimated based on median income within the maternal postal zip code, based on US census statistics. Geographic birth regions were classified as West, South, Northeast, and Midwest based on US census Bureau data (Geographic Terms and Concepts - Census Divisions and Census Regions. https://www.census.gov/geo/reference/gtc/gtc_census_divreg.html). Birth characteristics, medical comorbidities and results of neurodiagnostic studies were obtained. Amplitude integrated EEG background activity within six hours of age was classified as normal, moderately, or severely abnormal. Full-scale EEG within 24-hours of age was reviewed. Findings on magnetic resonance imaging (MRI) were described as deep gray matter injury, global brain injury, normal or other findings. We also evaluated surrogate measures of "stability" such as resuscitation outside of delivery room and receipt of extracorporeal membrane oxygenation and inhaled nitric oxide. Mortality-related details such as whether a "do not resuscitate (DNR)" order was in place, whether resuscitation was performed within six hours of death, and the documented single most probable cause of death were abstracted.

Statistical analysis

Descriptive statistics included mean, SD, median, interquartile range or counts (%), as appropriate. Statistical comparisons between the groups were performed using chi-square test and Wilcoxon-Rank Sum Tests. Logistic regression analysis was performed to evaluate the predictors of WLST in HIE, including severity of HIE, seizures at 24 hours, center (random effect) and variables found to be significantly different between groups on initial comparisons as

covariates. As household income and insurance status were expected to be collinear, and as the former was not derived from patient level data, only insurance was included. The interaction between socioeconomic variables such as maternal race and insurance was tested and included only if significant. *P* value <0.05 was taken as statistical significance.

Results

A total of 1925 infants born ≥36 weeks' gestational age and greater than 1800 grams weight with perinatal HIE who underwent TH were admitted to CHND NICUs between June 1, 2010 and December 31, 2015. Death during hospitalization occurred in 267 (14%) infants, 234 (87.6%) following WLS and 33 (12.4%) without WLS. Rates of death following WLS varied from 3% to 35% across centers. Among those who died following WLS, 134 (57.3%) infants had a documented DNR status while seven (3%) underwent resuscitation within six hours before death. Cause of death was coded as central nervous system injury in 177 (75.6%), respiratory failure in 17 (7.3%), infection in two (0.9%), massive hemorrhage or coagulopathy in two (0.9%), multisystem failure in 27 (11.5%), and others in nine (3.9%) infants. Figure 1 shows the ages at death in the WLS group.

Among infants who died following WLS, 206 (88%) infants had severe HIE and 28 (12%) had moderate HIE. The survived severe comparison group included 74 infants with severe HIE who required tube feedings at discharge. Table 1 summarizes demographic, birth, and neonatal characteristics of the two groups. We noted a higher proportion of public insurance, lower median household income, and lower proportion in the South in the survived severe group, compared to the WLS group. Racial differences in the WLS and survived severe groups did not reach statistical significance ($P = 0.08$).

Table 2 is a comparison of neurodiagnostic studies between the WLS and survived severe groups. Of note, a quarter of infants in the WLS group did not have EEG or aEEG within 24 hours of life and 56.8% did not undergo brain MRI prior to death. Among those with continuous EEG, EEG seizures during TH were more frequent in the survived severe group. aEEG or EEG within 24 hours of age was more often severely abnormal as was global brain injury on MRI in the WLS group, compared to the survived severe group.

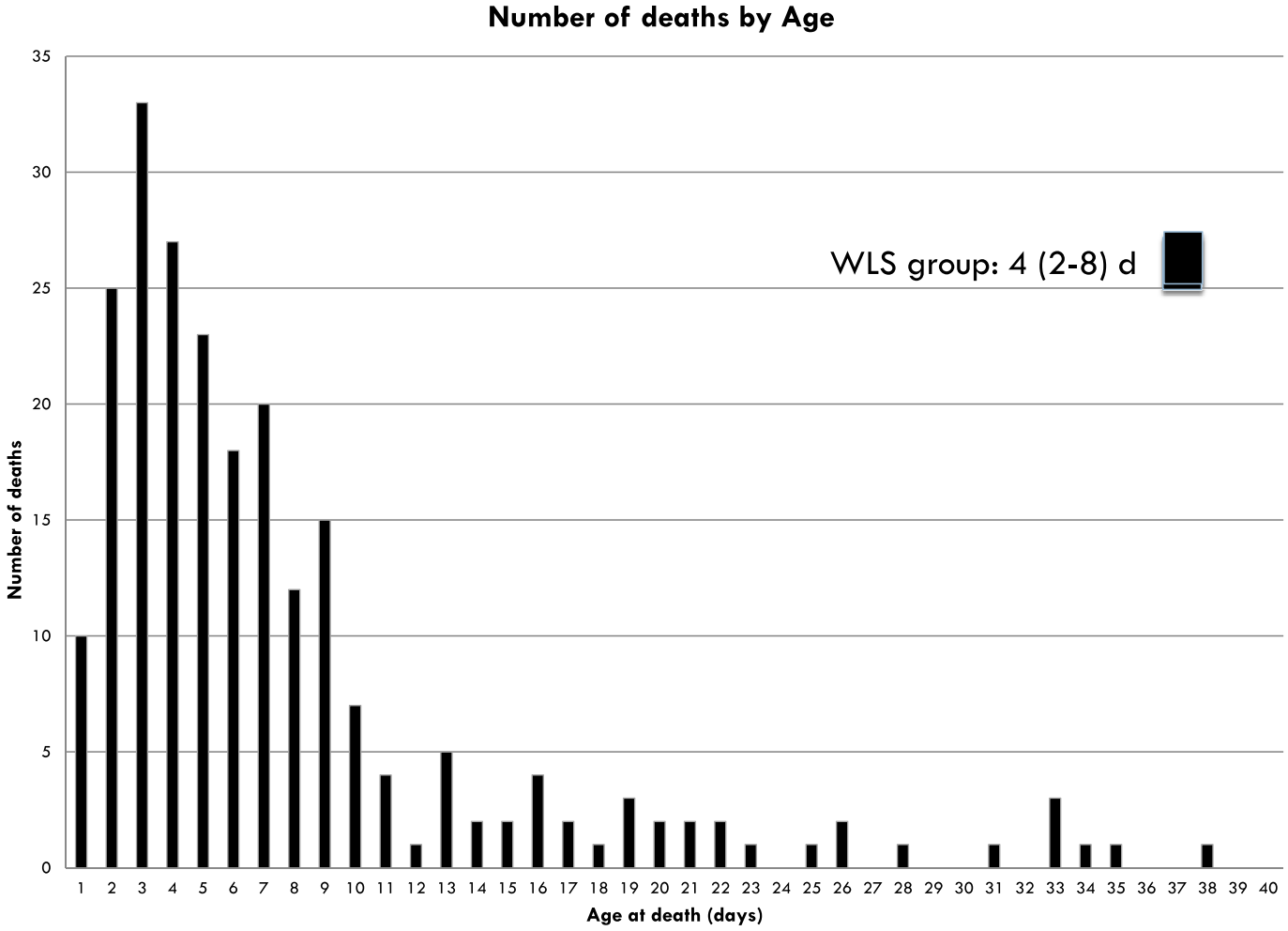

FIGURE 1. Ages at death of infants in the WLS group.

TABLE 1. Demographic and Clinical Characteristics of the Study Population

Characteristic Median [IQR]	WLST (n = 234)	Survived Severe (n = 74)	*P* value
Gestational age (weeks)	39 [38, 40]	39 [37, 40]	0.453
Birth weight (grams)	3324.5 [2950, 3740]	3375.5 [2977, 3950]	0.420
LGA >90th per centile (n,%)	32 (13.68)	18 (24.32)	0.406
Female gender (n, %)	105 (44.87)	28 (37.84)	0.346
Maternal age	30 [25, 32]	27 [21, 32]	0.287
Maternal race (n, %)			0.078
White	158 (67.5)	44 (59.46)	
Black	37 (15.8)	15 (20.27)	
Other	29 (12.4)	15 (20.27)	
Unknown	10 (4.3)	0 (0)	
Hispanic ethnicity	32 (13.68)	15 (20.27)	0.194
Delivery type			0.856
Caesarean	163 (69.66)	55 (74.32)	
Operative, vaginal	23 (9.83)	7 (9.46)	
Vaginal	45 (19.23)	12 (16.22)	
Unknown	3 (1.28)	0 (0)	
Apgar scores at 10 min	3 [1, 4]	2 [0, 4]	0.113
Presenting pH	6.9 [6.7, 7.1]	6.9 [6.8, 7]	0.962
Presenting base deficit	20.4 [12,26.8]	18 [15,29]	0.967
Perinatal sentinel event			
Nuchal cord	28 (11.97)	7 (9.46)	0.676
Cord prolapse	6 (2.56)	4 (5.41)	0.260
Uterine rupture	19 (8.12)	7 (9.46)	0.810
Placental abruption	36 (15.38)	11 (14.86)	1.000
Fetal distress	43 (18.38)	16 (21.62)	0.611
CPR outside DR (n, %)	22 (9.4)	7 (9.5)	1.000
ECMO (n, %)	20 (8.6)	9 (12.2)	0.365
iNO (n, %)	86 (36.8)	30 (40.5)	0.584
Maternal insurance (n, %)			**0.0000**
Public	92 (39.32)	54 (72.97)	
Private	112 (47.86)	14 (18.92)	
Combined	5 (2.14)	5 (6.76)	
Uninsured/self-pay	15 (6.41)	0 (0)	
Median annual household income	$41733 [34223, 54028]	$36804.5 [29192, 45146.5]	**0.006**
Center volume (n, %)			1.000
Low	163 (69.66)	52 (70.27)	
High	71 (30.34)	22 (29.73)	
Geographical distribution - regions			
West	62 (26.5)	21 (28.38)	0.765
South	82 (35.04)	15 (20.27)	**0.021**
Midwest	64 (27.35)	28 (37.84)	0.109
Northeast	26 (11.11)	10 (13.51)	0.541

P value derived from chi-square test and Wilcoxon-rank sum test as appropriate.

Multivariable logistic regression analyses were conducted to evaluate the medical and sociodemographic predictors of WLS (Table 3). Covariates included maternal race, insurance type, geographic region, aEEG/EEG background at 24 hours, and seizures during TH. The interaction between socioeconomic variables was not found to be significant, so was not included in the model. Private insurance was associated with WLST whereas birth in the Midwest and Northeast regions referent to the South tended to be less associated with WLS even after adjusting for disease severity. Maternal race, aEEG/EEG background at 24 hours and seizures were not associated with WLS.

Discussion

Nearly 90% of deaths in infants with perinatal HIE admitted to regional NICUs were preceded by WLS, with brain injury coded as the cause of death in more than 75% of cases. As expected, infants who died after WLS had evidence of more severe brain injury by EEG and MRI than those who survived with severe short-term outcomes. However, evidence of severe brain injury on imaging and/or EEG was neither universally sought nor found prior to WLS, suggesting that these tests are not essential to the shared clinician-family decisions regarding WLST. Sociodemographic factors including public insurance, and geographic region were also significantly associated with WLS. As HIE is the fifth commonest cause of death in children under the age of five years, these data are important for clinicians to understand the frequency of WLS in HIE and to recognize the role of non-clinical factors in end-of-life decision making.[16]

The mortality and WLS rates in the current study are broadly consistent with previous studies. In the pre-TH era, 24 (26.7%) infants with severe encephalopathy died in the neonatal period and intensive care was withdrawn in 13 (54%) infants.[17] In the randomized controlled trials of TH, 50% to 90% of deaths in the TH group followed WLS, with poor neurological outcome or asphyxial brain injury accounting for 70% to 75% of WLST.[11,18,19] In the NICHD randomized controlled trial of longer and/or

TABLE 2. Comparison of Neurodiagnostic Studies between WLST Versus Survived Severe Groups

Neurodiagnostic Characteristic	WLST (n = 234)	Survived Severe (n = 74)	*P*
EEG seizures during cooling	43 (18.4)	21 (28.4)	0.017
aEEG at 6 hrs	n = 85 (36.3%)	n = 27 (36.5%)	0.0138
Normal	0 (0)	0 (0)	
Moderately abnormal	13 (15.3%)	5 (18.5%)	
Severely abnormal	60 (70.6%)	14 (51.9%)	
Unknown	12 (14.1%)	8 (29.6%)	
aEEG/EEG within 24 hrs	n = 175 (74.8%)	n = 62 (83.8%)	0.046
Normal	1 (0.6%)	0 (0)	
Moderately abnormal	40 (22.9%)	18 (29%)	
Severely abnormal	112 (64%)	29 (46.8%)	
Unknown	22 (12.6%)	15 (24.2%)	
Status epilepticus at 24 hrs n (%)	13 (7.4%)	1 (1.6%)	0.122
MRI findings	n = 101 (43.2%)	n = 72 (97.3%)	0.034
Normal	2 (2%)	8 (11.1%)	
Global injury	17 (16.8%)	6 (8.3%)	
Deep gray matter	19 (18.8%)	27 (37.5%)	
Other	63 (62.4%)	31 (43.1%)	

P value from chi-square test and Wilcoxon-rank sum test.

deeper TH in HIE, rates of WLS ranged from 75% to 90% in the four study groups, with 49% of all deaths documented to be caused by asphyxial brain injury.[4]

The median age at death following WLS was four days. In the CoolCap trial and the randomized trial in China, 75% and 60% respectively of deaths in the TH groups were within a week.[20,21] The timing of WLS decision-making in HIE is a balance between greater prognostic certainty after completion of TH and a perception of "urgency" to an early "window" of time when mechanical ventilation may be required for diminished respiratory efforts.[13,22–26]

While it is acknowledged that some infants in the WLS group may have been withdrawn for other medical reasons, almost 90% had severe HIE and the majority had brain injury as the documented cause of death, suggesting that the decision for WLS was primarily driven by the anticipated poor neurological outcome. Similar findings have been noted in smaller previous studies. One previous study from South Australia in 145 neonates with severe brain injury (including severe HIE or intraventricular hemorrhage) reported that 73% of deaths following treatment limitation occurred in physiologically stable infants.[15] In NICUs across Canada, 66 of 76 (86.8%) of term infants with HIE underwent WLS; 57% due to anticipated poor quality of life, 20% each for inevitable death and prevention of prolonged suffering when death was likely.[7] In another single center study of 31 infants with HIE treated with TH who died at a median of three days, 90% were severely encephalopathic on examination and 87% had severely abnormal EEG findings.[27] All 13 infants who had MRI had evidence of moderate-severe brain injury; six had near-total brain injury. At the time of death, 90% were physiologically stable; 81% who underwent WLS did so for quality of life considerations.

We also noted a nonuniform reliance on EEG and MRI for deciding about WLS; only a subset of infants underwent the tests and the results were not universally consistent with devastating brain injury. A survey of practices among Australian neonatologists showed that when considering WLS, 62% (58/94) of respondents would arrange an MRI scan before making that decision; MRI was available in the same hospital facility for 74% of respondents.[28] It has been recently suggested that while MR biomarkers should not be used in isolation, they may be useful in combination with clinical and electrophysiological evidence to identify infants with a high degree of certainty of very severe impairment.[29] The 43% rate of MRI in our study is somewhat surprising given that MRI services are widely available at most regional NICUs and suggests that other factors may be drivers of WLS decisions in some instances. These data are in line with previous single center rate of 42% for MRI prior to WLS, although all infants in this report underwent EEG.[27] We

TABLE 3. Multivariable Logistic Regression Analysis on the Association with WLST

Parameter	β Estimate	Standard Error	Wald 95% CI		*P* value
Maternal race					
White	−0.427	0.507	−1.420	0.566	0.399
Others	−0.075	0.717	−1.329	1.480	0.916
Private insurance	1.932	0.452	1.047	2.818	<0.0001
Seizures at 24 hrs	−0.389	0.382	−1.138	0.359	0.308
EEG background at 24 hrs					
Moderately abnormal	19.923	-	-	-	0.100
Normal	−0.622	0.396	−1.399	0.154	0.116
Region:					
West	−0.733	0.490	−1.711	0.245	0.142
Northeast	−1.147	0.610	−2.343	0.049	0.060
MidWest	−0.872	0.483	−1.819	0.076	0.071

Reference categories were Black race, severely abnormal EEG at 24 hours and South region.

speculate that the reasons for the low rate of MRI could be related to the early timing for WLS, the severity of illness which may preclude safe transport for MRI, and the reliance on other prognostic indicators (e.g., clinical exam and/or EEG) to counsel families about WLS.

Sociodemographic factors associated with WLS in HIE have not been previously explored, except for one study that reported intercenter variation (5% to 100%) in rates of WLS discussions.[7] While we did not have data on WLS discussions, we did observe variation with regard to the proportion of deaths occurring after WLS (ranging from 3% to 35% across centers). However, given sample size limitations (i.e., wide range in number of cases by site which can effect mortality estimation by site), we used the approach of evaluating differences by geographical cluster in our adjusted analyses. There was a tendency for geographic differences in WLS practices, which may reflect racial, cultural or religious differences across regions or differences in center specific approaches (e.g., availability and involvement of palliative care teams). In our study, racial differences did not remain significant after adjusting for HIE severity. In a large multicenter study of Pediatric ICUs in the United States, government insurance (odds ratio [OR] 1.58; 95% confidence interval [CI] 1.12 to 2.22) and Black non-Hispanic race (odds ratio [OR] 0.42; confidence interval [CI] 0.26 to 0.67) were independently associated with discussions of limitation or withdrawal of life support.[30] Only 15% of the patients undergoing WLS were less than a month of age and 47% (versus 66% in our study) were White. In contrast, in our disparate population focusing on actual WLST rather than discussions, we found that private insurance was associated with WLS after controlling for HIE severity.

Our study has several strengths. First, it includes a large recent cohort of infants diagnosed with HIE using standard definitions across multiple regional NICUs in the United States, who underwent TH. Data abstraction was consistent across centers using trained data abstractors. The detailed available data provide insights into "real world" practice variations that drive end-of-life decisions. We restricted our study to deaths following WLS and to a reasonable comparison group of infants with severe HIE needing tube feedings at discharge, presumed to have had a high risk of death or disability.

We also acknowledge the limitations of our study. Infants who are hospitalized in NICUs participating in CHND were referred to these institutions; thus, both the bias of referral and unmeasured outcomes of those who were never referred limit the generalizability of the study. We did not have available details of specific withheld or withdrawn therapies, number, and content of discussions with the families, physician sociodemographic characteristics or center specific algorithms for WLS (e.g., the involvement of palliative care teams). While our comparison group was carefully selected to include infants at high risk for death or disability in whom a discussion about the prognosis was likely held, we do not know for certain whether options for WLS were offered to the family. Likewise, the survived severe group may have included infants who survived after some aspects of medical care were withdrawn. The survived severe group did have fewer severe abnormalities in aEEG, EEG and MRI compared to the WLS group. While the American Academy of Pediatrics guidelines recommends explicit documentation of WLS orders, a lack of clarity and consistency in the documentation in charts has been previously noted.[31,32] In fact, 3% of infants in the WLS group underwent resuscitation prior to death and 40% did not have a "DNR" order in place, findings that may suggest inconsistency in documentation or that WLS decisions were made and executed acutely during periods of clinical decompensation. As MRI results were abstracted from clinical reports, assessment of brain injury by MRI was limited by the lack of (1) consistent timing, (2) standardized scoring system, and (3) central reader. We did not have data on MR spectroscopy, shown to be an accurate predictor of neurodevelopmental outcome in HIE.[33] Similarly, we did not have data on EEG findings after 24 hours or other later neurodiagnostic studies.

Integrated neurocritical care with multidisciplinary input, neurodiagnostic studies and an open honest discussion with families about predictive uncertainty are critical to achieve a shared value-based decision making process regarding WLS for each individual infant.[24] Our data provide novel insights into factors associated with the ethically and contextually complex decision for WLS in infants with HIE undergoing TH and underscore that nonmedical factors may impact such decision-making.

Appendix: Participants of the Children's Hospitals Neonatal Consortium

The data summarized in this article were collected from all participating institutions of the Children's Hospitals Neonatal Consortium. Here we list the members of the Consortium and site sponsors for the Children's. Hospitals Neonatal Database: Jeanette Asselin, David Durand, Francine Dykes, Jacquelyn Evans (Chair), Karna Murthy, Michael Padula, Eugenia Pallotto, Kristina Reber and Billie Lou Short are members of the Children's Hospitals Neonatal Consortium, Inc.

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