Outcomes of Preterm Infants following Discussions about Withdrawal or Withholding of Life Support

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Objectives To describe the frequency of postnatal discussions about withdrawal or withholding of life-sustaining therapy (WWLST), ensuing WWLST, and outcomes of infants surviving such discussions. We hypothesized that such survivors have poor outcomes.

Study design This retrospective review included registry data from 18 centers of the National Institute of Child Health and Human Development Neonatal Research Network. Infants born at 22-28 weeks of gestation who survived >12 hours during 2011-2013 were included. Regression analysis identified maternal and infant factors associated with WWLST discussions and factors predicting ensuing WWLST. In-hospital and 18- to 26-month outcomes were evaluated.

Results WWLST discussions occurred in 529 (15.4%) of 3434 infants. These were more frequent at 22-24 weeks (27.0%) compared with 27-28 weeks of gestation (5.6%). Factors associated with WWLST discussion were male sex, gestational age (GA) of ≤24 weeks, birth weight small for GA, congenital malformations or syndromes, early onset sepsis, severe brain injury, and necrotizing enterocolitis. Rates of WWLST discussion varied by center (6.4%-29.9%) as did WWLST (5.2%-20.7%). Ensuing WWLST occurred in 406 patients; of these, 5 survived to discharge. Of the 123 infants for whom intensive care was continued, 58 (47%) survived to discharge. Survival after WWLST discussion was associated with higher rates of neonatal morbidities and neurodevelopmental impairment compared with babies for whom WWLST discussions did not occur. Significant predictors of ensuing WWLST were maternal age >25 years, necrotizing enterocolitis, and days on a ventilator.

Conclusions Wide center variations in WWLST discussions occur, especially at ≤24 weeks GA. Outcomes of infants surviving after WWLST discussions are poor. *(J Pediatr 2017;■■:■■-■■).*

Trial registration ClinicalTrials.gov: NCT00063063.

A significant percentage of deaths in neonatal intensive care units (NICUs) occur after life-sustaining treatment is withheld or withdrawn.[1-4] Physicians and families often discuss withdrawal or withholding of life-sustaining therapy (WWLST) when facing a high likelihood of death, an unacceptable level of suffering, or a poor long-term prognosis. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN), a consortium of academic centers across the US, maintains a data registry for premature infants born at 22-28 weeks of gestation and/or with extremely low birth weight (401-1000 g). Previous NRN publications have noted significant, unexplained variation in mortality rates for extremely premature infants across centers, with in-hospital mortality rates of 5%-59% for gestational ages (GAs) of 22-26 weeks.[5,6] A recent report noted that center rates of initiation of intensive care varies significantly at the limits of viability.[6] It is unknown whether center differences in WWLST practices contribute to center variation in mortality.

BPD	Bronchopulmonary dysplasia
GA	Gestational age
ND	Neurodevelopmental impairment
NEC	Necrotizing enterocolitis
NRN	Neonatal Research Network
SGA	Small for GA
WWLST	Withdrawal or withholding of life-sustaining therapy

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A recent prospective Canadian study concluded that neonatologists mainly offer WWLST for the purpose of avoiding pain and suffering when death is imminent or to avoid survival with a poor quality of life.[7] A multicenter study in the United Kingdom evaluated short-term outcomes of treatment limitation discussions for neonates and found that a significant portion of families chose to continue full intensive care after such discussions.[4] How often neonatologists and parents in the US initiate WWLST discussions, what patient characteristics prompt such discussions, and how these discussions result in redirection of care, is unknown. When families wish to pursue aggressive treatment despite receiving counseling about WWLST, the number and outcomes of survivors are unknown. The purpose of this study was to examine the frequency and center variation of documented discussions on WWLST and to determine how often discussions were followed by WWLST. An additional aim was to describe characteristics of infants undergoing discussions and WWLST and the outcomes up to 18-26 months of infants who survive following such a discussion. We hypothesized that survivors after WWLST discussions have high rates of morbidity, late mortality, and neurodevelopmental impairment.

Methods

The study was a retrospective review of registry data that were prospectively collected from medical records from the NICHD NRN (n = 18 centers) (ClinicalTrials.gov: NCT00063063). Institutional Review Boards at all centers approved data collection by trained research personnel during the patients' birth hospitalization. The NRN uses a predefined protocol that systematically collects in-hospital data on infants born at 22-28 weeks of gestation or with extremely low birth weight (401-1000 g) and follow-up data on all infants born before 26 weeks of gestation and admitted to a participating NRN neonatal intensive care unit (NICU). This study included all in-born infants who survived beyond 12 hours of life to focus the analysis on infants for whom intensive care had been initiated. GA was determined by the best obstetric estimate, where available, otherwise by neonatal examination. Maternal and infant demographics, pregnancy and delivery information, and morbidity and mortality data were collected from birth until death, hospital discharge, or transfer to a non-NRN hospital.

Palliative care decision-making data were assessed using the following questions from the database: At any time after birth was there documentation of discussion with parents to limit, withdraw, or not escalate care? Was an order written to limit treatment at any time? Were the following treatments withdrawn at any time with the intent to limit care: intubation/ventilation, nutrition/hydration, or medication? These questions were assessed at 36 weeks postmenstrual age, death, discharge, or transfer. The data collected regarding WWLST discussions do not specify the content of the discussion, the specific reasons the discussion was initiated, at which point during the hospitalization the discussion occurred, or the number of discussions that occurred.

Severe brain injury was defined as intraparenchymal hemorrhage, intracranial hemorrhage with persistent ventricular enlargement, or cystic periventricular leukomalacia on cranial ultrasound in the first 28 days. Retinopathy of prematurity refers to any severity of retinopathy of prematurity. Necrotizing enterocolitis (NEC) was defined as stage II or III, based on the modified Bell staging criteria.[8] Infants were classified with malformations or syndromes if they were diagnosed with any major malformations, chromosomal abnormalities, or other syndromes with multiorgan involvement at any point during the hospitalization.

Moderate to severe neurodevelopmental impairment (NDI) was defined as neurologic impairment – moderate to severe cerebral palsy; developmental delay – cognitive or motor score <70 on the Bayley Scales of Infant Development-III; visual impairment – limited with correction or blindness in 1 or both eyes; or hearing impairment – permanent hearing loss that does not permit child to understand verbal directions and communicate. NDI was present when 1 or more of the components of the composite outcome were known to be present, or absent if no component was present.[9]

Statistical Analyses

Maternal and infant demographics, infant morbidities and mortality from birth to discharge, death, or transfer to a non-NRN hospital were linked to documented discussions and WWLST. Rates of discussion about WWLST were compared with rates of actual WWLST, by center, and GA. Multiple logistic regression analysis was used to examine the relationship between factors associated with the discussion and those associated with subsequent WWLST after a discussion. Logistic regression models were created for predictor variables associated with discussion when applicable early in the hospital course (<28 days) including center, sex, race, maternal age, maternal education, GA, birth weight small for GA (SGA),[10] congenital syndromes or malformations, delivery room epinephrine, surgery, proven NEC, early onset sepsis, severe brain injury, and pulmonary hemorrhage. The multiple logistic regression model of ensuing postdiscussion WWLST adjusted for the same factors, but also included diagnoses with potential late impact: steroids for bronchopulmonary dysplasia (BPD), late onset sepsis, proportion of days hospitalized on high-frequency or conventional ventilation, and the maximum fraction of inspired oxygen (FiO_2) requirement. Birth weight was not included in the adjusted models due to its correlation with other covariates, such as GA and SGA. All data was available for modeling except for 7 of 3434 infants who were, thus, excluded from the model of a discussion of WWLST and 1 of 529 infants who were excluded from the model of WWLST after discussion.

Follow-up data of the survivors group were analyzed using unadjusted tests for rates of medical morbidities and neurodevelopmental outcomes. Because of the relatively small number of infants who survived to the follow-up assessment, descriptive data are presented and adjusted modeling was not performed. Unadjusted *P* values have been provided for reference. Data analysis was performed at the NRN Data

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