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

Jennifer James, Childrens Hospital of Philadelphia
David Munson, Childrens Hospital of Philadelphia
Sara B. DeMauro, Childrens Hospital of Philadelphia
John C. Langer, RTI International
April Dworetz, Emory University
Girija Natarajan, Wayne State University
Margarita Bidegain, Duke University
Christine A. Fortney, Nationwide Childrens Hospital
Ruth Seabrook, Nationwide Childrens Hospital
Betty R. Vohr, Brown University

Only first 10 authors above; see publication for full author list.

Journal Title: Journal of Pediatrics
Volume: Volume 190
Publisher: Elsevier: 12 months | 2017-11-01, Pages 118+-
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1016/j.jpeds.2017.05.056
Permanent URL: https://pid.emory.edu/ark:/25593/tjxgn

Final published version: http://dx.doi.org/10.1016/j.jpeds.2017.05.056

Copyright information:
© 2017 Elsevier Inc.
This is an Open Access work distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Accessed August 3, 2019 9:01 PM EDT
Outcomes of Preterm Infants following Discussions about Withdrawal or Withholding of Life Support

Jennifer James, MD1, David Munson, MD1, Sara B. DeMauro, MD, MSCE1, John C. Langer, MS2, April R. Dworetz, MD3, Girija Natarajan, MD4, Margarita Bidegain, MD5, Christine A. Fortney, PhD, RN6, Ruth Seabrook, MD6, Betty R. Vohr, MD7, Jon E. Tyson, MD, MPH8, Edward F. Bell, MD9, Brenda B. Poinderex, MD, MS10, Seetha Shankaran, MD4, Rosemary D. Higgins, MD11, Abhik Das, PhD12, Barbara J. Stoll, MD2, and Haresh Kirpalani, MB, MSc1 on behalf of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network*

1Department of Pediatrics, The Children’s Hospital of Philadelphia and The University of Pennsylvania, Philadelphia, PA
2Social, Statistical, and Environmental Sciences Unit, RTI International, Research Triangle Park, NC
3Emory University School of Medicine, Department of Pediatrics, Children’s Healthcare of Atlanta, Atlanta, GA
4Department of Pediatrics, Wayne State University, Detroit, MI
5Department of Pediatrics, Duke University School of Medicine, Durham, NC
6Department of Pediatrics, Nationwide Children’s Hospital, Columbus, OH
7Department of Pediatrics, Women and Infants Hospital, Brown University, Providence, RI
8Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX
9Department of Pediatrics, University of Iowa, Iowa City, IA
10Perinatal Institute, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH
11Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda
12Social, Statistical, and Environmental Sciences Unit, RTI International, Rockville, MD

Abstract

Reprint requests: Jennifer James, MD, Department of Pediatrics, The Children’s Hospital of Philadelphia and The University of Pennsylvania, 3400 Spruce St, Ravdin Bldg, 8th Floor – Neonatology, Philadelphia, PA 19104., jamesjr@email.chop.edu.

*List of additional members of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network is available at www.jpeds.com (Appendix).

The authors declare no conflicts of interest.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.
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.

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. 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. A recent report noted that center rates of initiation of intensive care varies significantly at the limits of viability. It is unknown whether center differences in WWLST practices contribute to center variation in mortality.

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. 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. 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. 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 (FiO₂) 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 Coordinating Center (RTI International) using SAS v 9.3 (SAS Institute, Inc, Cary, North Carolina).

Results

Over the study period, between April 2011 and December 2013, 3434 infants from 18 centers met the study eligibility criteria. Discussions regarding WWLST were documented for 529 (15.4%) (Figure 1). The majority (406 of 529 or 76.7%) of infants who had a documented discussion subsequently had WWLST. Of these, only 5 (1.2%) survived to discharge (Table I; available at www.jpeds.com). Of the 123 infants (23.3%) in whom discussion was not followed by WWLST, 58 (47.2%) survived to discharge (“Survivors With Discussion”). Of the 2905 (84.6%) infants without a documented discussion, 2758 of 2905 (94.9%) survived to discharge, and these infants served as the comparison group for the
“Survivors With Discussion.” In addition, there were 14 infants who had WWLST without a documented discussion, one of whom survived to discharge (Figure 1; Table I).

Among all infants included in this report, in-hospital mortality was 17.8%. Mortality ranged from 6.4% to 27.1% across the 18 centers. Rates varied by GA: 8.5%–61.1% at 22–24 weeks GA, 5.6%–25.0% at 25–26 weeks GA, and 0%–17.6% at 27–28 weeks GA (Figure 2; available at www.jpeds.com). WWLST discussions were more frequent at earlier GAs, with the following distribution: 27.0% at 22–24 weeks GA, 11.3% at 25–26 weeks GA, and 5.6% at 27–28 weeks GA. When examined by center, the rates of discussion varied (range 6.4%–29.9%), as did rates of WWLST (range 5.2%–20.7%) (Figure 3; available at www.jpeds.com).

Center differences were most notable for the most immature infants. Among infants 22–24 weeks of GA, rates of discussion ranged between 12.8% and 66.7%; this declined to rates of 0%–15.4% for 27–28 weeks of GA. Correspondingly, rates of WWLST ranged from 6.4% to 55.6% for 22–24 weeks of GA, diminishing to 0%–15.4% for 27–28 weeks of GA. The majority of infants who died during their hospitalization had a discussion regarding WWLST, regardless of center (center range 56.1%–100%). Most inpatient deaths occurred following WWLST (overall 67.6%, center range 44.9%–100%). One center reported that 100% of mortalities occurred after WWLST and that all of these patients had a documented discussion prior to WWLST. Among infants 22–24 weeks of GA, 79.5% (center range 60%–100%) of mortalities occurred after a WWLST discussion.

The characteristics of infants with a documented discussion about WWLST compared with infants without discussion are summarized in Table II. The characteristics associated with discussion about WWLST in the multivariable regression model are depicted in Figure 4. Factors significantly associated with a discussion were male sex, white race, GA ≤24 weeks, SGA, congenital syndromes or malformations, early-onset sepsis, proven NEC, brain injury, and pulmonary hemorrhage. Any surgery was inversely associated with a discussion about WWLST. Center was highly significant in this model (P < .0001).

The characteristics significantly associated with actual WWLST after the discussion are depicted in Figure 5 (available at www.jpeds.com). Characteristics inversely associated with WWLST following discussion were delivery room epinephrine, steroids for BPD, and surgery while those associated were maternal age >25 years, proven NEC, and proportion of days on a ventilator. (Figure 5). Center was not statistically significant in this model (P < .095).

Of the 123 infants (3.6% of the total cohort) who prompted a discussion of WWLST but did not undergo WWLST, 58 (47%) survived and are designated as “Survivors With Discussion” (Figure 1). Hospital discharge outcomes in “Survivors With Discussion,” compared with outcomes of infants who did not prompt a WWLST discussion, are shown in Table III. Infants who did not have WWLST after a discussion had significantly higher rates of mortality and morbidities at the time of discharge. Five infants with a discussion and ensuing WWLST survived. Of these, 3 had medication only withdrawn and 2 had intubation/
ventilation withdrawn. Three of these 5 were discharged home by 120 days and 2 were
discharged after 120 days (Table I).

Of the 58 infants with a WWLST discussion who survived to discharge, 46 were eligible for
standard NRN follow-up (<26 weeks GA). Four (9%) of the 46 infants died after discharge,
and 18-to 26-month outcome data are available for 39 of the 42 survivors (93%). Infants
termed “Survivors With Discussion” had significantly higher rates of NDI than infants who
never had a discussion (Table III). Four infants were categorized as unimpaired (Table III).
Rates of rehospitalization and medical technology dependence were also higher in the
“Survivors With Discussion” group than in survivors without discussion. Postdischarge
mortality rates were significantly higher in the “Survivors With Discussion” group (6.9%)
than infants without a discussion (1.1%). In regards to early childhood outcomes of the 6
infants who had WWLST and survived to discharge, 3 were profoundly impaired, 1 was
mildly impaired, 1 was unimpaired, and the last was discharged home with palliative care
and is presumed to be deceased (Table I).

Discussion

This study describes recent WWLST discussion practices for extremely preterm infants (22
to <29 weeks) who survived beyond 12 hours of age in 18 large academic centers in the US.
Although most deaths among the eligible cohort were preceded by discussions about
WWLST, the occurrence of documented discussions about WWLST varied greatly across
these centers.

Variation was most pronounced at the lowest GAs. A recent large, multicenter retrospective
analysis of treatment and outcomes for extremely preterm infants conducted in the NRN
showed significant center variation in the initiation of treatment for extremely preterm
infants (22–24 weeks) in the delivery room. Because only infants who survived beyond 12
hours of life were included in our report, the variation described in this study is not directly
explained by selection of infants for delivery room intervention. However, variation in
WWLST after 12 hours of life is likely to be partly related to whether the smallest, sickest,
and most immature infants are resuscitated in the delivery room. Our data are consistent with
observations from European and Canadian descriptions of site variation in WWLST
practices.

Reasons for the marked intercenter variability in rates of WWLST discussion are not clear.
Physicians at different centers may have varying levels of comfort with end-of-life decisions,
personal beliefs, palliative care training, institutional support, and availability of a pediatric
palliative care team. There might also be center differences in aggressiveness of obstetric
care, center-specific outcomes with neonatal intensive care, and parental or physician views
about outcomes that may be considered worse than death that factor into whether a WWLST
discussion takes place. It is also possible that the operating definition of a WWLST and
documentation practices may differ by institution. One center had documented discussions
preceding every death. It is possible that in this center, discussions take place toward the end
of life, when a critically ill infant is dying despite all aggressive interventions and is
extubated for comfort. Conversely, at institutions where more discussions take place relative
to the number of deaths, care-teams may work with parents and palliative care teams to consider WWLST much sooner, considering quality of life issues and a high risk of poor outcome. Further studies are needed to better understand the reasons care teams do and do not approach families for discussion of potential WWLST.

Our data confirm that physicians and/or parents initiated discussions about WWLST when infants had factors known to be associated with severe disability or death. Sociodemographic factors such as maternal age and maternal education were not significantly different between infants who had a discussion and those who did not; however, white families were more likely than black or Hispanic families to be approached for a discussion. The reason for this difference is unclear but may represent center differences in patient demographics or differences in provider communication at the end of life. There is evidence that physicians perceive differences in ethnicity as a barrier to conducting effective end-of-life conversation with patients and their families.12

When examining raw data, ensuing WWLST after a discussion varied by center but it was not significant in the adjusted model. In contrast, center was significantly associated with a discussion of WWLST in the adjusted model of this outcome. This suggests that the significant factors in the model of WWLST impacted a postdiscussion decision on WWLST more strongly than center. By regression analysis, ensuing WWLST was associated with several factors, but notably these factors were different than those associated with having a discussion. Proportion of days spent on a ventilator is likely a surrogate for severity of lung disease, and both lung disease and NEC are diseases that portend high mortality or long-term morbidities.13–15 In contrast, other factors were associated with a significantly lower likelihood of withdrawal: delivery room epinephrine, steroids for chronic lung disease, and any surgery. We speculate that parents in these situations favored intervention and were unlikely to support limiting or withdrawing treatment. In our cohort of patients with a discussion, younger GA or severe brain injury was not associated with higher likelihood of WWLST. This is in contrast to Brecht et al,16 who found that 41 of 70 (59%) premature infants with severe intraventricular hemorrhage or periventricular leukomalacia had a treatment limitation discussion, followed by death in all but 2 infants.

Some studies note that neonatologists and neonatal nurses have only modest success in predicting which infants undergoing mechanical ventilation are unlikely to survive to discharge but suggest that clinician’s intuitions of death combined with other objective clinical data are fairly predictive of poor neurodevelopmental outcome.17,18 Our study confirm these findings. If we think of a documented discussion in our study as a marker for a physician’s intuition or prediction of death or significant morbidity, then physicians are only right about survival to discharge a little over one-half the time. However, they do seem to accurately identify infants at risk for significant morbidity and poor neurodevelopmental outcome. “Survivors With Discussion” had a high late in-hospital mortality rate (44 of 103 or 43%) or were still hospitalized at 120 days of life (86 of 103 or 83%). They also had significantly higher rates of several serious neonatal morbidities and a higher post-discharge mortality rate when compared with infants without a discussion.
Very little information is available on infants who survive despite discussions on WWLST. Aladangady et al.\(^4\) reported that 44% of babies who had a discussion about WWLST survived following a decision to continue life-sustaining treatment. However, postdischarge follow-up information is not available for these infants. In a prior abstract, survivors had a substantially better outcome than predicted: of 13 infants who had a discussion about WWLST and opted to continue intensive care treatment, 3 had normal development at 18–24 months, 4 had mild disability, and 6 had severe disability.\(^{19}\) On the other hand, other studies have found that infants with multiple morbidities have a poor neurodevelopmental prognosis and high rates of medical morbidities at 18- to 22-month follow-up.\(^{13, 14}\) Similarly, outcomes of our “Survivors With Discussion” group suggest a significant association with neurodevelopmental impairment. The higher re-hospitalization rate and dependence on medical technology likely reflect the greater burden of medical morbidity among these children.

This is the largest study to date that examines the common clinical issue of end of life practices in a large group of extremely premature infants and examined early childhood outcomes of survivors after WWLST discussions. Other strengths of this study are the prospectively collected data and the multicenter perspective. We acknowledge the limitations of the study, including uncertainty about what proportion of all WWLST discussions were documented and the full context and content of the discussions. The database does not specify the timing of discussion, who initiated it, the patient’s clinical circumstances at the time of discussion, which morbidities were diagnosed in relation to timing of discussion and WWLST, the content of the discussions, or how many discussions were held for each patient. The scope of these discussions ranges broadly, and several potential topics might be discussed with families, such as concern about the patient’s imminent death, decisions not to escalate treatment, discontinuing a treatment the patient is already receiving, or the decision to perform a compassionate extubation. It is possible that the infants for whom discussion was followed by WWLST may have had a different type of discussion than the infants where discussion was not followed by WWLST. Finally, the database is limited by the documentation in the patient’s chart, and it is not known how well physicians document such discussions. A prospective study including more detailed questions about the timing and content of WWLST discussions would be able to overcome some of the limitations of the current study.

The results of our study showed wide center variation across the NRN in rates of discussions about WWLST among very low GA infants who survived beyond 12 hours of age. This variation was most prominent at lowest GAs. The group of infants who survived despite WWLST discussions had significantly higher morbidities than peers without a discussion, both in-hospital and at the time of follow-up. Thus, clinicians appear to accurately target infants at high risk for adverse outcomes for discussions about WWLST.

**Acknowledgments**

Funded by the National Institutes of Health (2UG1HD068244), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Center for Research Resources, and the National Center for Advancing Translational Sciences.
Glossary

- **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

References


*J Pediatr. Author manuscript; available in PMC 2018 November 01.*


Appendix

The following investigators are additional members of the National Institute of Child Health and Human Development Neonatal Research Network, National Institutes of Health, Bethesda, MD:

NRN Steering Committee Chair: Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine, Chicago, Illinois.

Alpert Medical School of Brown University and Women and Infants Hospital of Rhode Island, Providence, Rhode Island (U10 HD27904) – Abbot R. Laptook, MD; Angelita M. Hensman, MS, RNC-NIC; Elisa Vieira, RN, BSN; Emiliee Little, RN, BSN; Robert Burke, MD; Melinda Caskey, MD; Katharine Johnson, MD; Barbara Alksninis, PNP; Mary Lenore Keszler, MD; Andrea M. Knoll; Theresa M. Leach, MEd, CAES; Elisabeth C. McGowan, MD; Victoria E. Watson, MS, CAS; Suzy Ventura.

Case Western Reserve University, Rainbow Babies and Children’s Hospital, Cleveland, Ohio (U10 HD21364, M01 RR80) – Michele C. Walsh, MD, MS; Avroy A. Fanaroff, MD; Anna Marie Hibbs, MD; Nancy S. Newman, BA, RN; Allison H. Payne, MD, MS; Deanne E. Wilson-Costello, MD; Bonnie S. Siner, RN; Monika Bhol, MD; Gulgun Yalcinkaya, MD; Harriet G. Friedman, MA.

Children’s Mercy Hospital, University of Missouri Kansas City School of Medicine, Kansas City, Missouri (U10 HD68284) – William E. Truog, MD; Eugenia K. Pallotto, MD, MSCE; Howard W. Kilbride MD; Cheri Gauldin, RN, BS, CCRC; Anne Holmes, RN, MSN, MBA-HCM, CCRC; Kathy Johnson RN, CCRC; Allison Knutson, BSN, RNC-NIC.

Cincinnati Children’s Hospital Medical Center, University Hospital, and Good Samaritan Hospital, Cincinnati, Ohio (U10 HD27853, M01 RR8084) – Kurt Schibler, MD; Barbara
Alexander, RN; Cathy Grisby, BSN, CCRC; Teresa L. Gratton, PA; Jean J. Steichen, MD; Estelle E. Fischer, MHSA, MBA; Lenora Jackson, CRC; Kristin Kirker, CRC; Greg Muthig, BS; Stacey Tepe, BS; Kimberly Yolton, PhD.

Duke University School of Medicine, University Hospital, University of North Carolina, and Duke Regional Hospital, Durham, North Carolina (U10 HD40492, UL1 TR1117, M01 RR30, UL1 TR1111) – Ronald N. Goldberg, MD; C. Michael Cotten, MD, MHS; Ricki F. Goldstein, MD; William F. Malcolm, MD; Patricia L. Ashley, MD, PHD; Kimberley A. Fisher, PhD, FNP-BC, IBCLC; Joanne Finkle, RN, JD; Kathryn E. Gustafson, PhD; Matthew M. Laughon, MD, MPH; Carl L. Bose, MD; Janice Bernhardt, MS, RN; Gennie Bose, RN; Janice Wereszczak CPNP-AC/PC.

Emory University, Children’s Healthcare of Atlanta, Grady Memorial Hospital, and Emory University Hospital Midtown, Atlanta, Georgia (U10 HD27851, M01 RR39) – David P. Carlton, MD; Ellen C. Hale, RN, BS, CCRC; Ira Adams-Chapman, MD; Yvonne Loggins, RN.

Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland – Stephanie Wilson Archer, MA.

Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services, Indianapolis, Indiana (U10 HD27856, M01 RR750) – Gregory M. Sokol, MD; Brenda B. Poindexter, MD, MS; LuAnn Papile, MD; Leslie Dawn Wilson, BSN, CCRC; Dianne E. Herron, RN, CCRC; Susan Gunn, NNP, CCRC; Lucy Smiley CCRC; Abbey C. Hines, PsyD.

Nationwide Children’s Hospital and the Ohio State University Medical Center, Columbus, Ohio (U10 HD68278) – Leif D. Nelin, MD; Sudarshan R. Jadcherla, MD; Pablo J. Sánchez, MD; Patricia Luzader, RN; Gail E. Besner; Nehal A. Parikh, MD.

RTI International, Research Triangle Park, North Carolina (U10 HD36790) – Dennis Wallace, PhD; Marie G. Gantz, PhD; Jamie E. Newman, PhD, MPH; Jeanette O’Donnell Auman, BS; Margaret Crawford, BS; Carolyn M. Petrie Huitema, MS; Kristin M. Zaterka-Baxter, RN, BSN.

Stanford University and Lucile Packard Children’s Hospital, Palo Alto, California (U10 HD27880, UL1 TR93) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS, CCRC; Susan R. Hintz, MD, MS Epi; Melinda S. Proud, RCP; Barbara Bentley, PsychD, MSED; Maria Elena DeAnda, PhD; Anne M. DeBattista, RN, PNP, PhD; Beth Earhart, PhD; Lynne C. Huffman, MD; Casey E. Krueger, PhD; Hali E. Weiss, MD.

University of Alabama at Birmingham Health System and Children’s Hospital of Alabama, Birmingham, Alabama (U10 HD34216, M01 RR32) – Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Myriam Peralta-Carcelen, MD, MPH; Monica V. Collins, RN, BSN MaEd; Shirley S. Cosby, RN, BSN; Fred J. Biasini, PhD; Kristen C. Johnston, MSN, CRNP; Cryshelle S. Patterson, PhD; Vivien A. Phillips, RN, BSN; Sally Whitley, MA, OTR-L, FAOTA.
University of California-Los Angeles, Mattel Children’s Hospital, Santa Monica Hospital, Los Robles Hospital and Medical Center, and Olive View Medical Center, Los Angeles, California (U10 HD68270) – Uday Devaskar, MD; Meena Garg, MD; Isabell B. Purdy, PhD, CPNP; Teresa Chanlaw, MPH; Rachel Geller, RN, BSN.

University of Iowa and Mercy Medical Center, Iowa City, Iowa (U10 HD53109, M01 RR59) – Dan L. Ellsbury, MD; Tarah T. Colaizy, MD, MPH; Jane E. Brumbaugh, MD; John A. Widness, MD; Karen J. Johnson, RN, BSN; Jacky R. Walker, RN; Donia B. Campbell, RNC-NIC; Diane L. Eastman, RN, CPNP, MA.

University of New Mexico Health Sciences Center, Albuquerque, New Mexico (U10 HD53089, UL1 TR41) – Kristi L. Watterberg, MD; Jean R. Lowe, PhD; Janell F. Fuller, MD; Robin K. Ohls, MD; Conra Backstrom Lacy, RN; Andrea F. Duncan, MD.

University of Pennsylvania, Hospital of the University of Pennsylvania, Pennsylvania Hospital, and Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania (U10 HD68244) – Barbara Schmidt, MD, MSc; Aasma S. Chaudhary, BS, RRT; Soraya Abbasi, MD; Toni Mancini, RN, BSN, CCRC; Judy C. Bernbaum, MD; Marsha Gerdes, PhD; Hallam Hurt, MD.

University of Rochester Medical Center, Golisano Children’s Hospital, Rochester, New York, and the University of Buffalo Women’s and Children’s Hospital of Buffalo, Buffalo, New York (U10 HD68263, UL1 TR42) – Carl T. D’Angio, MD; Ronnie Guilmet, MD, PhD; Satyan Lakshminrusimha, MD; Anne Marie Reynolds, MD, MPH; Rosemary L. Jensen; Joan Merzbach, LMSW; Gary J. Myers, MD; Ashley Williams, MSED; Kelley Yost, PhD; William Zorn, PhD; Karen Wynn, RN; Deanna Maffett, RN; Diane Prinzing; Julianne Hunn, BS; Stephanie Guilford, BS; Farooq Osman, MD; Mary Rowan, RN; Michael G. Sacilowski, BS; Holly I.M. Wadkins, MA; Melissa Bowman, MSN.

University of Texas Health Science Center at Houston Medical School, Children’s Memorial Hermann Hospital, Houston, Texas – Kathleen A. Kennedy, MD, MPH; Julie Arldt-McAlister, RN, BSN; Katrina Burson, RN, BSN; Andrea Freeman Duncan, MD; Carmen Garcia, RN, CCRP; Beverly Foley Harris, RN, BSN; Janice John, CPNP; Patrick M. Jones, MD; Layne M. Lillie, RN, BSN; Karen Martin, RN; Sara C. Martin, RN; Georgia E. McDavid, RN; Shawna Rodgers, RN; Saba Siddiki, MD; Daniel Sperry, RN; Patti L. Pierce Tate, RCP; Sharon L. Wright, MT (ASCP).

University of Texas Southwestern Medical Center, Parkland Health and Hospital System, and Children’s Medical Center Dallas, Dallas, Texas (U10 HD40689, M01 RR633) – Myra Wyckoff, MD; Pablo J. Sánchez, MD; Luc P. Brion, MD; Diana M. Vasil, RNC-NIC; Lijun Chen, PhD, RN; Roy J. Heyne, MD; Sally S. Adams, MS, RN, CPNP; Linda A. Madden, RN, BSN, CPNP; Elizabeth Heyne, PsyD PA-C; Alicia Guzman, Lizette E. Torres, RN; Catherine Twell Boatman, MS, CIMI.

Wayne State University, Hutzel Women’s Hospital and Children’s Hospital of Michigan, Detroit, Michigan (U10 HD21385) – Athina Pappas, MD; Rebecca Bara, RN, BSN; Laura...
A. Goldston, MA; John Barks MD, Mary Christensen RT, Stephanie Wiggins MS, Diane White RT.
Figure 1.
Flow diagram for all eligible infants up until time of discharge. References to discussions and WWLST here refer to documented discussions and documented WWLST. For the 397 infants who died before 12 hours, the majority (61.2%) did not have any intensive care initiated.
Figure 2.
Variation in mortality by GA at each center. The x-axis shows 18 centers labeled A–R. The y-axis shows mortality rate as a percentage. Centers ranged from 9% to 60% mortality at 22–24 weeks, from 3% to 21% mortality at 25–26 weeks, and from 0%–14% mortality at 27–28 weeks gestation.
Figure 3.
Rates of discussion and WWLST for each center. The x-axis shows 18 centers labeled A–R. The y-axis represents rates as percentage of total infants. Rates of discussion varied (range 6.4%–29.9%), as did rates of ensuing WWLST (range 5.2%–20.7%).
Figure 4.
The y-axis displays aORs of factors assessed by logistic regression, for discussion about WWLST. The OR is represented by the mean and the 95% CI. Factors with statistically significantly increased OR are above the line and exclude 1 (dotted line). These include male sex (95% CI 1.11–1.68), white race (95% CI 1.16–2.47), GA ≤ 24 weeks (95% CI 3.14–4.86), SGA (95% CI 1.97–3.33), congenital syndromes or malformations (95% CI 1.73–4.17), early-onset sepsis (95% CI 1.57–4.78), proven NEC (95% CI 2.12–3.90), brain injury (95% CI 2.14–3.37), and pulmonary hemorrhage (95% CI 1.55–2.99). In contrast, values below the line and excluding 1 are factors with a significantly lower OR. Only 1 factor analyzed is in this range, and this is any surgery (95% CI 0.51–0.83). Additional factors included in the logistic regression model that were not significant and are not shown are maternal age >25 years (OR 0.98, 95% CI 0.78–1.22); maternal education ≥ college (OR 0.95, 95% CI 0.71–1.26); and delivery room epinephrine (OR 1.52, 95% CI 0.97–2.40).
Figure 5.
The y-axis displays aORs of factors assessed by logistic regression, for WWLST. The OR is represented by the mean and the 95% CI. Factors with statistically significantly increased OR are above the line and exclude 1 (dotted line). These include maternal age >25 years (range 95% CI 1.02–2.75), proven NEC (95% CI 2.11–9.80), and proportional of days on a ventilator (95% CI 1.10–1.52). In contrast, values below the line and excluding 1 are factors with a significantly lower OR. These include delivery room epinephrine (95% CI 0.14–0.90), steroids for BPD (95% CI 0.26–0.84), and surgery (95% CI 0.19–0.62). Additional factors included in the logistic regression model that were not significant and are not shown are maternal education ≥college (OR 1.52 95% CI 0.75–3.07); GA ≤24 weeks (OR 1.04, 95% CI 0.63–1.74); SGA (OR 1.21, 95% CI 0.67–2.18); syndrome or malformations (OR 1.06, 95% CI 0.45–2.52); early onset sepsis (OR 1.4, 95% CI 0.4–4.6); late onset sepsis (OR 0.79, 95% CI 0.46–1.32); brain injury (OR 0.95, 95% CI 0.59–1.54); pulmonary hemorrhage (OR 0.87, 95% CI 0.45–1.70); and maximum fraction of inspired oxygen (FiO2) (OR 1.02, 95% CI 0.79–1.31).
Table I

Infants who survived to discharge following WWLST*

<table>
<thead>
<tr>
<th>Demographics</th>
<th>In-hospital outcomes</th>
<th>Treatment withdrawn</th>
<th>Age at discharge (d)</th>
<th>Follow-up outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td>GA</td>
<td>Sex</td>
<td>Moderately/severely BPD, brain injury, ROP</td>
<td>Medication</td>
</tr>
<tr>
<td>Infant 1</td>
<td>940</td>
<td>26</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td>Infant 2</td>
<td>770</td>
<td>25</td>
<td>F</td>
<td>Moderately/severely BPD, GI perforation, ROP</td>
</tr>
<tr>
<td>Infant 3</td>
<td>936</td>
<td>27</td>
<td>M</td>
<td>Syndrome/malformation (CHARGE syndrome, Dandy-Walker, congenital cardiac disease)</td>
</tr>
<tr>
<td>Infant 4</td>
<td>710</td>
<td>25</td>
<td>F</td>
<td>Brain injury, moderately/severely BPD, late-onset sepsis, ROP, major surgery</td>
</tr>
<tr>
<td>Infant 5</td>
<td>795</td>
<td>26</td>
<td>F</td>
<td>Moderately/severely BPD, late-onset sepsis, ROP</td>
</tr>
<tr>
<td>Infant 6</td>
<td>500</td>
<td>23</td>
<td>M</td>
<td>Brain injury, moderately/severely BPD, ROP, major surgery</td>
</tr>
</tbody>
</table>

*CHARGE, Coloboma of the eye, Heart defects, Atresia choanae, Retardation of growth, Genital abnormalities, and Ear abnormalities; F, female; GI, gastrointestinal; M, male; ROP, retinopathy of prematurity.

5 infants had documented discussion before WWLST and 1 did not have documented discussion.
Table II
Characteristics and morbidities of patients with a documented discussion of WWLST

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Discussion (N = 529)</th>
<th>No discussion (N = 2905)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean birth weight (g)</td>
<td>654.2 g</td>
<td>767.6</td>
</tr>
<tr>
<td>GA (wk)</td>
<td>24.5</td>
<td>25.6</td>
</tr>
<tr>
<td>22–24</td>
<td>53.9%</td>
<td>24.8%</td>
</tr>
<tr>
<td>24–26</td>
<td>35.7%</td>
<td>44.4%</td>
</tr>
<tr>
<td>26–28</td>
<td>11.7%</td>
<td>30.8%</td>
</tr>
<tr>
<td>SGA</td>
<td>22.8%</td>
<td>15.3%</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>57.3%</td>
<td>47.5%</td>
</tr>
<tr>
<td>Female</td>
<td>42.7%</td>
<td>52.5%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>39.9%</td>
<td>41.6%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>12.1%</td>
<td>12.1%</td>
</tr>
<tr>
<td>White</td>
<td>41.8%</td>
<td>40.9%</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>6.2%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Multiple birth</td>
<td>25.7%</td>
<td>27.0%</td>
</tr>
<tr>
<td>Maternal age &gt;25 y</td>
<td>58.8%</td>
<td>61.7%</td>
</tr>
<tr>
<td>Maternal education – college degree</td>
<td>17.8%</td>
<td>19.7%</td>
</tr>
<tr>
<td>Morbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delivery room epinephrine ‡</td>
<td>6.0%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Congenital malformation or syndrome ‡</td>
<td>7.8%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Seizures</td>
<td>5.3%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Brain injury (ICH Grade 3 or 4, PVL, or ventriculomegaly) ‡</td>
<td>40.8%</td>
<td>17.2%</td>
</tr>
<tr>
<td>Max FIO₂ requirement (mean) ‡</td>
<td>0.91</td>
<td>0.67</td>
</tr>
<tr>
<td>Pulmonary hemorrhage</td>
<td>14.9%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Proportion of time (d) on ventilator (mean) ‡</td>
<td>0.82</td>
<td>0.25</td>
</tr>
<tr>
<td>Any surgery ‡</td>
<td>25.0%</td>
<td>18.8%</td>
</tr>
<tr>
<td>GI perforation ‡</td>
<td>7.2%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Proven NEC ‡</td>
<td>19.1%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Early sepsis ‡</td>
<td>4.7%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Late sepsis ‡</td>
<td>30.9%</td>
<td>23.1%</td>
</tr>
<tr>
<td>Severe BPD ‡</td>
<td>19.9%</td>
<td>45.6%</td>
</tr>
<tr>
<td>ROP ‡</td>
<td>21.0%</td>
<td>59.4%</td>
</tr>
<tr>
<td>Death ‡</td>
<td>88.1%</td>
<td>5.0%</td>
</tr>
</tbody>
</table>
\( \text{FiO}_2 \); fraction of inspired oxygen; GI, gastrointestinal; ICH, intracranial hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

* Unadjusted \( p \) value is <.0001.

† Unadjusted \( p \) value is <.01.
### Table III

Survivors with discussion: in-hospital and postdischarge outcomes and morbidities

<table>
<thead>
<tr>
<th>In-hospital morbidities</th>
<th>Survivors with discussion N = 58</th>
<th>Survivors without discussion N = 2758</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids for BPD</td>
<td>36.6%</td>
<td>18.8%</td>
<td>.0001</td>
</tr>
<tr>
<td>Severe BPD</td>
<td>82.8%</td>
<td>47.6%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>GI surgery resulting in short gut</td>
<td>5.2%</td>
<td>1.1%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Other major surgery</td>
<td>41.4%</td>
<td>19.0%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ROP</td>
<td>89.7%</td>
<td>62.1%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Brain injury</td>
<td>48.3%</td>
<td>17.1%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Discharged on oxygen</td>
<td>61.2%</td>
<td>35.9%</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Early childhood outcomes and morbidities</th>
<th>Survivors with discussion N = 39</th>
<th>Survivors without discussion N = 1642</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayley III composite scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive score &lt;70</td>
<td>48.6%</td>
<td>10.5%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Language score &lt;70</td>
<td>50.0%</td>
<td>19.7%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Motor score &lt;70</td>
<td>50.0%</td>
<td>13.2%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cerebral palsy–moderate/severe</td>
<td>28.2%</td>
<td>6.9%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Moderate to severe neurodevelopmental impairment†</td>
<td>51.3%</td>
<td>14.9%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Unimpaired‡</td>
<td>10.3%</td>
<td>33.6%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Severe impairment§</td>
<td>48.7%</td>
<td>11.2%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Any rehospitalization</td>
<td>66.7%</td>
<td>49.1%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Mean number of rehospitalizations</td>
<td>3.06</td>
<td>2.29</td>
<td>.165</td>
</tr>
<tr>
<td>Use of home oxygen</td>
<td>15.4%</td>
<td>6.7%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Ventilator/CPAP</td>
<td>10.3%</td>
<td>2.3%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>10.3%</td>
<td>3.4%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Gastrostomy tube</td>
<td>23.1%</td>
<td>10.9%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Independent in feeding</td>
<td>66.7%</td>
<td>81.3%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Use of assistive motor devices</td>
<td>30.8%</td>
<td>11.8%</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

*CPAP, continuous positive airway pressure.

All P values are unadjusted.

†Moderate to severe cerebral palsy: Corresponds to gross motor function classification of 2 or 3 (moderate) and 4 or 5 (severe).

‡Moderate to severe neurodevelopmental impairment: Bayley III cognitive <70 (2 SD below mean), gross motor function level 2 or greater, cerebral palsy, moderate or severe, blind with no useful vision in both eyes, and hearing impaired with hearing aid requirement in both ears.

§Unimpaired: No Bayley score <85, gross motor function level = 1 (normal), no cerebral palsy, no vision impairment, no hearing impairment (with or without amplification).

§Severe Impairment: Bayley III cognitive <70 (2SD below the mean or untestable), severe to profound CP, GMFCS ➔, bilateral blindness, or bilateral hearing impairment ± amplification.

J Pediatr. Author manuscript; available in PMC 2018 November 01.