Individual and Center-Level Factors Affecting Mortality Among Extremely Low Birth Weight Infants

AUTHORS: Brandon W. Alleman, BS, BA,^a Edward F. Bell, MD,^a Lei Li, PhD,^b John M. Dagle, MD, PhD,^a P. Brian Smith, MD, MPH, MHS,^c Namasivayam Ambalavanan, MD,^d Matthew M. Laughon, MD, MPH,^e Barbara J. Stoll, MD,^f Ronald N. Goldberg, MD,^g Waldemar A. Carlo, MD,^d Jeffrey C. Murray, MD,^a C. Michael Cotten, MD, MHS,^c Seetha Shankaran, MD,^g Michele C. Walsh, MD,^h Abbot R. Laptook, MD,ⁱ Dan L. Ellsbury, MD,^j Ellen C. Hale, RN, BS, CCRC,^f Nancy S. Newman, RN,^h Dennis D. Wallace, PhD,^b Abhik Das, PhD,^k and Rosemary D. Higgins, MD,^l for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

^aDepartment of Pediatrics, University of Iowa, Iowa City, Iowa;

^bStatistics and Epidemiology Unit, RTI International, Research Triangle Park, North Carolina; ^cDepartment of Pediatrics, Duke University, Durham, North Carolina; ^dDepartment of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama;

^eDepartment of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; ^fDepartment of Pediatrics, Emory University School of Medicine, and Children's Healthcare of Atlanta, Atlanta, Georgia; ^gDepartment of Pediatrics, Wayne State University, Detroit, Michigan; ^hDepartment of Pediatrics, Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland, Ohio; ⁱDepartment of Pediatrics, Women and Infants Hospital, Brown University, Providence, Rhode Island; ^jCenter for Research, Education, and Quality, Pediatrix Medical Group, Sunrise, Florida; ^kStatistics and Epidemiology Unit, RTI International, Rockville, Maryland; and ^lEunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland

KEY WORDS

mortality rates, outcome, NICU, preterm infants, extremely preterm infants

ABBREVIATIONS

CI—confidence interval

CPAP—continuous positive airway pressure

ELBW—extremely low birth weight

GA—gestational age

NRN—National Institute of Child Health and Human Development Neonatal Research Network

OR—odds ratio

Mr Alleman participated in the conception and design of the study including the analysis plan and in the interpretation of the data and wrote the first and subsequent drafts of the manuscript and helped to revise it critically for important intellectual content; Dr Bell conceived and helped to design the study including the analysis plan, participated in the interpretation of the data, and revised the manuscript critically for important intellectual content; Dr Li helped to design the analysis plan and was responsible for the data management and analysis, performed the analysis with guidance from Mr Alleman and Dr Bell and with advice from Drs Das and Wallace, and helped to revise the manuscript critically for important intellectual content;

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WHAT'S KNOWN ON THIS SUBJECT: Significant variation in the mortality of preterm infants has been observed among NICUs. Factors explaining this variation have been difficult to identify.

WHAT THIS STUDY ADDS: Sizable center differences in mortality exist, even among similarly sized NICUs in academic centers. Patient characteristics and center treatment rates explain some of the center effect, especially for the youngest infants, but a significant portion of these differences remains unexplained.

abstract

OBJECTIVE: To examine factors affecting center differences in mortality for extremely low birth weight (ELBW) infants.

METHODS: We analyzed data for 5418 ELBW infants born at 16 Neonatal Research Network centers during 2006–2009. The primary outcomes of early mortality (≤ 12 hours after birth) and in-hospital mortality were assessed by using multilevel hierarchical models. Models were developed to investigate associations of center rates of selected interventions with mortality while adjusting for patient-level risk factors. These analyses were performed for all gestational ages (GAs) and separately for GAs < 25 weeks and ≥ 25 weeks.

RESULTS: Early and in-hospital mortality rates among centers were 5% to 36% and 11% to 53% for all GAs, 13% to 73% and 28% to 90% for GAs < 25 weeks, and 1% to 11% and 7% to 26% for GAs ≥ 25 weeks, respectively. Center intervention rates significantly predicted both early and in-hospital mortality for infants < 25 weeks. For infants ≥ 25 weeks, intervention rates did not predict mortality. The variance in mortality among centers was significant for all GAs and outcomes. Center use of interventions and patient risk factors explained some but not all of the center variation in mortality rates.

CONCLUSIONS: Center intervention rates explain a portion of the center variation in mortality, especially for infants born at < 25 weeks' GA. This finding suggests that deaths may be prevented by standardizing care for very early GA infants. However, differences in patient characteristics and center intervention rates do not account for all of the observed variability in mortality; and for infants with GA ≥ 25 weeks these differences account for only a small part of the variation in mortality. *Pediatrics* 2013;132:e175–e184

Both patient factors (eg, gestational age [GA]) and preventive or therapeutic interventions (eg, antenatal corticosteroids) are known to affect the mortality risk of very preterm infants.¹ The hospital in which care is provided also affects mortality risk. Variability in mortality rate by center has been observed in several populations and networks.^{2–7} Two factors may contribute to these center differences: (1) the inherent risk of the patient population served by a center and (2) the patient care delivered at the center. Existing models to predict neonatal mortality at birth are based on individual patient characteristics surrounding birth.^{1,8–11} These models are useful in providing outcome benchmarks and have been modified as clinical care has improved. They do not, however, adequately address the center effect on outcome. Variation in the patient populations accounts for some but not all of the differences in mortality among centers.^{12,13} Examining the effect of center on the mortality of extremely low birth weight (ELBW; ≤ 1000 g) infants may yield insights into ways to improve neonatal care.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN), a consortium of university-affiliated NICUs, has maintained a data registry of extremely premature infants using standard data collection and follow-up assessment methods since 1986. This data set allows examination of the variation in neonatal practice and outcomes among academic medical centers. It provides an opportunity to examine possible explanations for the center effect on mortality while controlling for infant and maternal characteristics. In this study, we estimated the variability of ELBW mortality among NRN centers. We assessed the effect of the rates at which centers use certain interventions on this variability in mortality, while adjusting for the effects of

patient risk factors known to influence mortality.

METHODS

Eligible infants from all NRN centers were identified, and patient risk factors and center intervention rates were extracted from records of neonatal and maternal characteristics and interventions available in the NRN registry. These variables were used to build models designed to predict mortality outcomes. Early mortality (≤ 12 hours) and in-hospital mortality were analyzed separately, first for all infants and then for 2 subgroups of infants, those with GA < 25 weeks and those with GA ≥ 25 weeks.

Data Source

Infants born at NRN centers in 2006–2009 with birth weight of 401 to 1000 g and GA of 22 (0/7) through 28 (6/7) weeks were included. Infants with syndromes or major malformations were excluded. The final data set consisted of 5418 infants from 16 centers. NRN membership did not change during the period of study, 2006–2009.

The NRN ELBW patient registry was approved by the institutional review board at each participating site. Trained research personnel collected maternal, pregnancy, delivery, and infant data as well as morbidity and intervention data from birth until hospital discharge, death, or 120 days of age if still hospitalized. Hospital death after 120 days or survival to discharge was obtained for infants who were hospitalized for longer periods. Definitions for maternal and infant characteristics and interventions were predetermined and described in the manual of operations. GA was determined as the best obstetric estimate on the basis of the mother's last menstrual period and fetal ultrasonography. Patient risk factors and interventions were obtained from individual patient records. Center intervention rates were calculated from the patient data within a given center.

Outcomes

The 2 main outcomes examined in this study were mortality in the first 12 hours after birth (early mortality) and mortality before discharge (in-hospital mortality). These outcomes were not mutually exclusive, because in-hospital mortality included those infants who died early. Deaths that occurred in the delivery room were included in these mortality outcomes. These outcomes were additionally examined in 2 subgroups of patients, those with GA < 25 weeks and those with GA ≥ 25 weeks. The rationale behind testing in these subgroups was that centers or individual physicians within centers may have different policies regarding the resuscitation of infants born at < 25 weeks. We assumed that infants born at ≥ 25 weeks' GA were likely to receive aggressive obstetric and neonatal care, whereas infants born before 25 weeks might have had less aggressive care before and after birth.¹⁴

Patient Risk Factors

Patient risk factors used in this study included mother's educational level (less than versus high school diploma or higher), private health insurance coverage, prenatal care utilization, gender of the infant, race, ethnicity, birth weight, gestational age, 5-minute Apgar score (< 5 vs ≥ 5), and multiple birth (versus single birth). Individual birth weights and gestational ages were expressed as differences from local NICU means.

Center Intervention Rates

Interventions available in the NRN registry that may be related to mortality were included in the analysis. These variables were as follows: provision of antenatal corticosteroids, mode of delivery, support given to the infant at delivery (continuous positive airway pressure [CPAP], tracheal intubation, epinephrine), NICU admission, prophylactic

indomethacin, early antibiotics (started in the first 72 hours and given for ≥ 5 days), respiratory support in the NICU (supplemental oxygen, CPAP or assisted ventilation, surfactant, inhaled nitric oxide), postnatal corticosteroids, and any human milk feeding. Center rates of specific interventions (ie, percentage of mothers or infants receiving an intervention) were calculated by aggregating individual patient data for eligible infants over the period of the years 2006–2009 at each center.

Statistical Analysis

Multilevel hierarchical models were used to evaluate center differences in mortality and to evaluate 2 major sources of variation that might explain differences in mortality among centers: patient risk factors and center intervention rates. The assessment of center intervention rates by the presence or absence of patient-level risk factors in a hierarchical model was conducted by using 4 models (Table 1). The derivation and underlying assumptions of the models are described in Appendix 1.

Each model yields an estimated parameter that measures the average center mortality (in log odds terms) and the mortality variance, an estimate of the magnitude of variation or dispersion in center mortality. An estimated mortality variance significantly greater than zero indicates variation in mortality among centers that is unlikely to have occurred by chance alone. A decrease in the variance estimates from models with, to those without, center intervention rates indicates the degree to which these interventions explain the center difference in mortality. By using principal components analysis, all center

intervention rates were assigned appropriate weights and combined into a single center intervention score for inclusion in the final models. Principal components analysis allowed this to be accomplished despite the collinearity (ie, high correlation between independent variables) among intervention rates. A technical description of the principal components analysis is provided in Appendix 2 and Appendix Table. The clinical implications of these models, ie, their ability to explain center variation in mortality rate, are described below.

Model 1: Intercept Only

This baseline reference model includes center mortality data and is used to assess the level of and variation in overall center mortality but does not include patient risk factors or the intervention score.

Model 2: Center Intervention Rates

This model extends Model 1 by adding the center intervention score as a predictor of mortality to assess the extent to which variation of center mortality can be explained by center intervention rates. Compared with Model 1, the decrease in the estimated mortality variance provides a measure of overall center mortality that can be explained by intervention rates, without correcting for patient population.

Model 3: Patient-Level Risk Factors

This model includes only infant and maternal characteristics. It is used to assess the magnitude of center variation in mortality while controlling for infant and maternal characteristics. Models 3 and 4 can be compared directly only with each other and not with Model 1 or 2.

Model 4: Patient Risk Factors and Center Intervention Rates

This model extends Model 3 by adding the center intervention score as a predictor

of center mortality and includes covariates of the infant and maternal characteristics. This model is used to assess the effect of the intervention rates on center mortality after controlling for patient-level risk factors. A decrease in the mortality variance provides a measure of the center variation in mortality explained by center intervention rates after controlling for patient risk factors. These models were derived for all infants and for the subgroups with GAs < 25 weeks and ≥ 25 weeks. All modeling analyses were performed by using the *Xtmelogit* command in Stata 12 (StataCorp, College Station, TX).

RESULTS

Wide ranges in intervention rates and mortality were observed among NRN centers for infants of all GAs as well as for those with GAs < 25 weeks and ≥ 25 weeks (Table 2, Fig 1). The ranges of the intervention rates for infants with GA < 25 weeks were typically wider than those for infants with GA ≥ 25 weeks.

Our major estimation results from the multilevel models are summarized in the following paragraphs (Table 3).

Infants of All GAs: Early Mortality

Model 2 indicates the intervention score had a significant association with center mortality (odds ratio [OR]: 0.79; 95% confidence interval [CI]: 0.74–0.84) and reduced the center mortality variance from 0.38 to 0.07. After controlling for patient risk factors in Models 3 and 4, the association of the intervention score remained significant (OR: 0.76; 95% CI: 0.67–0.86) and the mortality variance was reduced by from 0.64 to 0.27.

Infants of All GAs: In-Hospital Mortality

Before controlling for individual risk factors, the intervention score significantly reduced the odds of the overall

TABLE 1 Components of Multilevel Hierarchical Models

Patient-Level Factors	Center Intervention Rates	
	No	Yes
No	Model 1	Model 2
Yes	Model 3	Model 4

TABLE 2 Medians and Ranges of Center Intervention Rates and Outcomes: 2006–2009

	Percentage of Infants in Centers					
	All Infants (N = 152–588)		<25 Weeks' GA (n = 32–205)		≥25 Weeks' GA (n = 120–392)	
	Median	Range	Median	Range	Median	Range
Intervention						
Antenatal corticosteroids	82	35–93	58	21–81	92	47–99
Vaginal vertex delivery	30	22–41	46	31–61	21	16–26
Cesarean delivery	63	45–76	36	10–63	77	68–83
Tracheal intubation	63	41–82	63	24–94	62	37–88
CPAP	29	4–53	9	0–31	39	6–65
NICU admission	86	74–98	65	45–95	99	95–100
Epinephrine	4	1–12	5	0–14	3	1–11
Respiratory support excluding high-frequency ventilation	80	61–91	54	23–87	95	83–98
Supplemental oxygen	82	61–95	61	26–89	95	87–98
High-frequency ventilation	38	23–76	44	20–84	33	15–79
Surfactant	70	50–88	61	25–92	77	65–91
Nitric oxide	5	1–22	6	0–44	6	1–20
Postnatal corticosteroids	10	1–29	11	0–50	8	1–23
Prophylactic indomethacin	12	0–80	13	0–75	11	0–94
Early antibiotics	39	23–92	37	16–84	41	22–94
Human milk feeding	64	50–95	41	13–81	81	59–98
Outcome						
Early mortality (≤12 hours)	18	5–36	42	13–73	3	1–11
In-hospital mortality	34	11–53	63	28–90	16	7–26

The range in the number of infants per center (*n*) is shown for each GA category.

center in-hospital mortality (OR: 0.87; 95% CI: 0.83–0.90) and reduced its variance from 0.16 to 0.03. After controlling for patient characteristics, the effect of the intervention score also remained significant (OR: 0.84; 95% CI: 0.77–0.91) and reduced the variance of the center mortality rate from 0.31 to 0.14.

Infants With GA <25 Weeks: Early Mortality

The intervention score was significantly related to mortality (OR: 0.76; 95% CI: 0.72–0.79) and accounted for all variation in mortality among centers as evidenced by the variance estimate of 0 for Model 2. After accounting for patient risk factors, the intervention score was still significant (OR: 0.67; 95% CI: 0.61–0.74) and reduced the mortality variance from 1.08 to 0.08.

Infants With GA <25 Weeks: In-Hospital Mortality

Before correcting for patient characteristics, the intervention score was

significantly related to odds of mortality (OR: 0.83; 95% CI: 0.78–0.88) and reduced the mortality variance from 0.35 to 0.05. After controlling for individual risk factors, the intervention score remained significant (OR: 0.79; 95% CI: 0.71–0.87) and reduced the mortality variance from 0.62 to 0.20 among centers.

Infants With GA ≥25 Weeks: Early Mortality

The association of the intervention score with early mortality was significant for infants with GA ≥25 weeks but had a wider CI than that among all infants or the <25-week subgroup (OR: 0.84; 95% CI: 0.73–0.96). Including the intervention score reduced the center mortality variance from 0.21 to 0.11. After controlling for patient risk factors, the association of the intervention score became borderline significant (OR: 0.86; 95% CI: 0.73–1.01) and reduced the variance of the center mortality rate from 0.25 to 0.17.

Infants With GA ≥25 Weeks: In-Hospital Mortality

The association of the intervention score was not statistically significant either before or after accounting for patient risk factors.

The mortality variance estimates from all models, in all subgroups of each outcome, after accounting for patient risk factors were significantly greater than zero. Thus, center variation in early and in-hospital mortality exists even after controlling for intervention rates and patient risk factors.

DISCUSSION

Our study yields a number of interesting points for consideration. First, it reveals that in the NRN, there was significant variation among centers in ELBW mortality. This result was true for both early and in-hospital mortality for each GA subset; it is shown in the observed center death rates and also by the significant center mortality variance estimates from Model 1, which did not include center interventions or patient risk factors, for each outcome and subgroup. Second, our modeling results cast doubt on the commonly held concept that variation in outcomes is due largely to differences in patient population. The center mortality variance estimates after correcting for patient risk factors (Model 3) were still significant for all outcomes and subgroups. Finally, center intervention rates predicted mortality outcomes and reduced differences in the outcomes among the centers. In deriving the intervention scores, interventions not generally given in the first 12 hours of life were excluded for the early mortality outcome. As indicated by the weighting factors used in the principal components analysis (Appendix 2), the intervention scores were primarily composed of the averages of the center intervention rates of NICU admission, respiratory support, supplemental oxygen, surfactant, and, for infants of <25 weeks' GA, antenatal

FIGURE 1

Mortality rates by center. A, Results for infants of all GAs (22 [0/7] through 28 [6/7] weeks). B, Results for infants with GA of 22 [0/7] through 24 [6/7] weeks. C, Results for infants with GA of 25 [0/7] through 28 [6/7] weeks. Closed circles represent in-hospital mortality and open circles early (≤ 12 hours) mortality. The size of the circles represents the number of infants treated at a given center over the study period. The centers are ordered by in-hospital mortality for each graph individually, which means that a center may not have the same number in each panel.

corticosteroids, cesarean delivery, and tracheal intubation. The intervention scores showed significantly positive association with both early and in-hospital mortality in the all-GA population and in the <25 -week GA subgroup, but they showed only a trend toward significance in the ≥ 25 -week GA subgroup. In addition, the center mortality variance was greatly reduced when the intervention score was included in the models. These intervention

scores reduced the mortality variance estimates substantially for both early and in-hospital mortality for the all-GA group, and in the <25 -week GA subgroup the reductions were even greater. This finding was true even after correction for patient risk factors. Therefore, a substantial number of additional infants would be predicted to survive both past 12 hours and until discharge should the utilization of the examined interventions be increased for infants at

the earliest gestational ages (<25 weeks). One potential explanation for the finding that increased intervention is especially beneficial for infants with GA <25 weeks concerns the wider range of the centers' use of supportive therapies in the intrapartum period and the first hours of life. In particular, there was large practice variation among centers in the use of antenatal corticosteroids, cesarean delivery, respiratory support, and NICU admission for these most premature infants. Our derived intervention score more effectively represents the specific intervention therapies examined among infants with GA <25 weeks than among infants with GA ≥ 25 weeks. More research is needed to identify and determine other factors associated with mortality among infants with GA ≥ 25 weeks.

This study's strengths include the use of high-quality data from the centers of the NRN collected by trained research staff applying standardized methods. The use of prospectively collected data has presumably limited the probability of selection bias and misclassification of covariates and outcomes. The use of the hierarchical modeling method allowed us to separate the effects of patient- and center-level variables and to assess the impacts of center-level variables both on mortality and on its variability among centers. Limitations of the study include the relatively small number of centers. Also, capturing all variability in care is unlikely given the limited number of elements in the NRN database, even after correcting for patient-level differences. Thus, some interventions or approaches not available in the NRN database may affect center mortality rates. This observational study reveals an association between interventions and survival, but intervention trials are required to demonstrate a true causal link between specific interventions and patient survival. Finally, our study was not able to examine variability in physician-level

TABLE 3 Estimation Results from Multilevel Models

	Model 1	Model 2	Model 3	Model 4
All GAs: early mortality				
Variance in mortality	0.38 (0.18–0.83)	0.07 (0.03–0.19)	0.64 (0.29–1.42)	0.27 (0.11–0.64)
OR of intervention		0.79 (0.74–0.84)		0.76 (0.67–0.86)
All GAs: in-hospital mortality				
Variance in mortality	0.16 (0.07–0.37)	0.03 (0.01–0.09)	0.31 (0.14–0.67)	0.14 (0.06–0.32)
OR of intervention		0.87 (0.83–0.90)		0.84 (0.77–0.92)
GA <25 weeks: early mortality				
Variance in mortality	0.50 (0.23–1.10)	0 ^a	1.08 (0.49–2.40)	0.08 (0.02–0.38)
OR of intervention		0.76 (0.72–0.79)		0.67 (0.61–0.74)
GA <25 weeks: in-hospital mortality				
Variance in mortality	0.35 (0.14–0.85)	0.05 (0.01–0.19)	0.62 (0.27–1.46)	0.20 (0.08–0.52)
OR of intervention		0.83 (0.78–0.88)		0.79 (0.71–0.87)
GA ≥25 weeks: early mortality				
Variance in mortality	0.21 (0.06–0.71)	0.11 (0.02–0.52)	0.25 (0.07–0.92)	0.17 (0.04–0.74)
OR of intervention		0.84 (0.73–0.96)		0.86 (0.73–1.01)
GA ≥25 weeks: in-hospital mortality				
Variance in mortality	0.09 (0.03–0.25)	0.07 (0.03–0.21)	0.14 (0.05–0.37)	0.13 (0.05–0.35)
OR of intervention		0.92 (0.84–1.01)		0.94 (0.84–1.05)

Variance in center mortality (log odds of mortality) and ORs for intervention scores of center intervention rates are shown (95% CI in parentheses).

^a Not statistically significant.

care within centers or the quality with which interventions were implemented, which are additional possible contributors to variation in outcome.

Our results show that even though aggressive intervention with more infants would increase survival, the use of the interventions we studied does not fully explain the center variation in mortality, which implies that there are unaccounted-for variables that affect the center differences in mortality. Previous studies have postulated what these factors may be. Horbar et al¹² found that patient volume and the presence of a residency program were not predictive of outcomes. Rogowski et al¹³ found that the percentage of Medicaid beneficiaries, type of hospital ownership, and presence of a teaching hospital were not significant predictors of outcomes. These investigators also found that very low volume centers had worse outcomes and that the outcome was related to the level of NICU. These findings do not explain the variation in mortality among NRN centers, which are all high-volume, high-level centers.

Our results suggest that decisions of whether to resuscitate very preterm infants affect mortality and are detect-

able at the center level. This observation raises ethical issues. However, creating clear policies on the appropriateness of resuscitating ELBW infants is extremely difficult,^{15,16} and a thorough examination of this topic is beyond the scope of this study. This report simply highlights that increased survival is possible, and the authors believe that decision makers (parents and physicians) should be aware of this fact. More aggressive intervention of these neonates would increase their likelihood of survival. The current study does not address the impact of more aggressive intervention on the likelihood of “intact” survival, ie, survival without major neurodevelopmental impairment, but this association has been shown in this network.¹⁷ More active intervention of extremely preterm infants may benefit not only these infants but also more mature infants; centers in which intensive care is more frequently provided to extremely preterm infants have been shown to have better outcomes, too, for preterm infants of later gestation.¹⁸

Neonatal care has been advanced by the development and testing of beneficial therapies.¹⁹ It is important to note that the magnitude of the center effect on ELBW mortality is larger than the inter-

vention effects of even the most potent therapies, such as antenatal corticosteroids and surfactant replacement therapy. This fact underscores the importance of stratification by center in all multicenter clinical trials in neonatology. The findings of our study support a role for comprehensive, well-designed, quality-improvement trials focusing on the care of very early GA infants.

CONCLUSIONS

There are large differences among centers in the mortality rate of extremely preterm infants. Patient characteristics do not adequately account for this variability. Center use of certain interventions predicts survival for the lowest GA infants, but it explains little of the observed variability in in-hospital mortality for infants born at ≥25 weeks. Some as-yet-unmeasured characteristics of the centers account for the remainder of the observed variability. The variation in mortality among centers may be reduced through standardization of care for very early GA infants. However, other center differences may explain the residual differences in mortality.

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The following investigators, in addition to those listed as authors, participated in this study:

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

Alpert Medical School of Brown University and Women and Infants Hospital of Rhode Island (U10 HD27904): William Oh, MD; Angelita M. Hensman, RN, BSN; Dawn Andrews, RN MS; Kristen Angela, RN.

Case Western Reserve University, Rainbow Babies and Children's Hospital (U10 HD21364, M01 RR80): Avroy A. Fanaroff, MD; Bonnie S. Siner, RN.

Cincinnati Children's Hospital Medical Center, University Hospital, and Good Samaritan Hospital (U10 HD27853, M01 RR8084): Kurt Schibler, MD; Edward F. Donovan, MD; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN, CCRC; Holly L. Mincey, RN, BSN; Jody Hessling, RN; Lenora Jackson.

Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30): Kathy J. Auten, MSHS; Kimberley A. Fisher, PhD, FNP-BC, IBCLC; Katherine A. Foy, RN.

Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory University Hospital Midtown (U10 HD27851, M01 RR39): David P. Carlton, MD; Ann M. Blackwelder, RNC, BS, MS.

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

Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, M01 RR750): Brenda B. Poindexter, MD, MS; Dianne E. Herron, RN; Leslie Dawn Wilson, BSN, CCRC.

RTI International (U10 HD36790): W. Kenneth Poole, PhD; Jeanette O'Donnell Auman, BS; Margaret Cunningham, BS; Carolyn M. Petrie Huitema, MS; James W. Pickett II, BS; Scott E. Schaefer, MS; Kristin M. Zaterka-Baxter, RN, BSN.

Stanford University, Dominican Hospital, El Camino Hospital, and Lucile Packard Children's Hospital (U10 HD27880, M01

RR70): Krisa P. Van Meurs, MD; David K. Stevenson, MD; Marian M. Adams, MD; M. Bethany Ball, BS, CCRC; Melinda S. Proud, RCP; Andrew W. Palmquist, RN, BSN.

Tufts Medical Center (U10 HD53119, M01 RR54): Ivan D. Frantz III, MD; Brenda L. MacKinnon, RNC; Ellen Nylen, RN, BSN.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32): Monica V. Collins, RN, BSN, MaEd; Shirley S. Cosby, RN, BSN.

University of California—San Diego Medical Center and Sharp Mary Birch Hospital for Women and Newborns (U10 HD40461): Neil N. Finer, MD; Maynard R. Rasmussen MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Renee Bridge, RN; Clarence Demetrio, RN; Wade Rich, BSHS, RRT.

University of Iowa Children's Hospital (U10 HD53109, M01 RR59): John A. Widness, MD; Karen J. Johnson, RN, BSN; Nancy J. Krutzfeld, RN, MA.

University of Miami Holtz Children's Hospital (U10 HD21397): Shahnaz Duara, MD; Ruth Everett-Thomas, RN, MSN.

University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997): Kristi L. Watterberg, MD; Lu-Ann Papile, MD; Robin K. Ohls, MD; Conra Backstrom Lacy, RN; Rebecca Montman, BSN; Carol Hartenberger, BSN, MPH.

University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44): Dale L. Phelps, MD; Linda J. Reubens, RN, CCRC; Erica Burnell, RN; Cassandra Horiham, MS; Rosemary Jensen.

University of Texas Southwestern Medical Center at Dallas, Parkland Health and Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633): Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Luc P. Brion, MD; Alicia

Guzman; Gaynelle Hensley, RN; Melissa H. Leps, RN; Diana M. Vasil, RNC-NIC; Nancy A. Miller, RN; Lizette E. Torres, RN. University of Texas Health Science Center at Houston Medical School, Children's Memorial Hermann Hospital, and Lyndon Baines Johnson General Hospital/Harris County Hospital District (U10 HD21373): Kathleen A. Kennedy, MD, MPH; Jon E. Tyson, MD, MPH; Beverly Foley Harris, RN, BSN; Anna E. Lis, RN, BSN; Sarah Martin, RN, BSN; Georgia E. McDavid, RN; Patti L. Pierce Tate, RCP; Maegan C. Simmons, RN.

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64): Roger G. Faix, MD; Bradley A. Yoder, MD; Karen A. Osborne, RN, BSN, CCRC; Karie Bird, RN; Jill Burnett, RNC; Cynthia Spencer, RNC; Kimberlee Weaver-Lewis, RN, BSN; Karen Zanetti, RN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122): T. Michael O'Shea, MD, MPH; Nancy J. Peters, RN, CCRP.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385): Rebecca Bara, RN, BSN; Mary E. Johnson, RN, BSN; Elizabeth Billian, RN, MBA.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, M01 RR125): Richard A. Ehrenkranz, MD; Harris Jacobs, MD; Patricia Cervone, RN; Monica Konstantino, RN, BSN; JoAnn Poulsen, RN; Janet Taft, RN, BSN.

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Address correspondence to Edward F. Bell, MD, Department of Pediatrics, University of Iowa, 200 Hawkins Dr, Iowa City, IA 52242. E-mail: edward-bell@uiowa.edu
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APPENDIX 1: SPECIFICATIONS OF MULTILEVEL HIERARCHICAL MODELS

Denote the outcome variable by an indicator y_{ij} , such that patient i in center j will die ($y_{ij} = 1$) or survive ($y_{ij} = 0$). Let a_j be a random variable and u_j be a normally distributed random-error term with a mean of 0 and an SD of σ for center j . Let PC_j be the principal components score from the center intervention rates with coefficients γ_1 and $x_{1ij} \dots x_{9ij}$ representing the 9 patient and maternal characteristics with corresponding coefficients ($\beta_1 \dots \beta_9$). The 4 model forms used for the probability of death, $P(y_{ij} = 1)$, are as follows.

Model 1

Patient-Level Model

$$\log\left(\frac{P(y_{ij} = 1)}{P(y_{ij} = 0)}\right) = \alpha_j$$

Center-Level Model

$$\alpha_j = \gamma_0 + \mu_j$$

Model 2

Patient-Level Model

$$\log\left(\frac{P(y_{ij}=1)}{P(y_{ij}=0)}\right) = \alpha_j$$

Center-Level Model

$$\alpha_j = \gamma_0 + \gamma_1 PC_j + \mu_j$$

Model 3

Patient-Level Model

$$\log\left(\frac{P(y_{ij} = 1)}{P(y_{ij} = 0)}\right) = \alpha_j + \beta_1 x_{1ij} + \dots + \beta_9 x_{9ij}$$

Center-Level Model

$$\alpha_j = \gamma_0 + \mu_j$$

Model 4

Patient-Level Model

$$\log\left(\frac{P(y_{ij} = 1)}{P(y_{ij} = 0)}\right) = \alpha_j + \beta_1 x_{1ij} + \dots + \beta_9 x_{9ij}$$

Center-Level Model

$$\alpha_j = \gamma_0 + \gamma_1 PC_j + \mu_j$$

On the basis of the above models, the average center mortality rate and its range within 2 SDs (presented in Tables 2 and 3) can be computed as

$$\frac{e^{\gamma_0}}{1 + e^{\gamma_0}}$$

and the range as

$$\frac{e^{\gamma_0 \pm 2\sigma}}{1 + e^{\gamma_0 \pm 2\sigma}}$$

APPENDIX 2: COMPOSITION OF FIRST PRINCIPAL COMPONENTS OF CENTER INTERVENTION RATES

Principal components analysis is a method to reduce the number of variables under consideration. We have included as many as 15 types of interventions in this study. It is unrealistic to include all of these interventions simultaneously in the multilevel models, but we can try to derive an index from these intervention rates and use it as a predictor. The principal components generated from the intervention rates are such indices in the form of linear combinations of the intervention rates and can best represent the variation of these intervention rates among centers. A brief description of the method follows.

Let X represent a matrix in which each column contains the intervention rates for a center and β represent a standardized vector of the weighting factors in the linear combination of the intervention rates such that $\beta'\beta = 1$. For simplicity of notation, the intervention

rates are deducted by their means so that they have a mean of 0. Then, linear combinations of the intervention rates can be represented for all centers as $\beta'X$.

A variance estimate of linear combination of the intervention rates will be as follows:

$$(\beta'X)(\beta'X)'/(n-1) = \beta'(XX'/(n-1))\beta'$$

Note that $XX'/(n-1)$ is a variance estimate of the intervention rates and often denoted by Σ . Principal components analysis produces a set of uncorrelated linear combinations whose variances, added together, are identical to that in Σ . Usually, they are ordered by their variances, and the proportion of variance to total variance indicates their relative importance. The first principal component that has the maximum variance is often of particular interest. Those principal components with a small variance may be ignored.

The proportion of variance and the weighting factor β for the first principal component of the intervention rates for predicting early mortality and in-hospital mortality are shown below. It can be seen that the proportion of variance is higher for the intervention rates for early mortality and much higher among infants with GA <25 weeks. Also, these principal components are essentially an average of all center rates except for CPAP and epinephrine. The weighting factors for the center rates are nearly equal, but those for CPAP and epinephrine are close to zero. Similarly, the principal components score for in-hospital mortality is an average of all center rates except for CPAP, epinephrine, and prophylactic indomethacin.

APPENDIX TABLE Proportion of Variance and Weighting Factors (β) for the First Principal Component of the Intervention Rates for Predicting Early Mortality and In-Hospital Mortality

	Early Mortality			In-Hospital Mortality		
	All Infants	GA <25 Weeks	GA $\geq$ 25 Weeks	All Infants	GA <25 Weeks	GA $\geq$ 25 Weeks
Variance accounted for by first principal component, %	53.2	69.8	31.2	44.7	60.5	25.1
Principal component (weighting factors)						
Antenatal corticosteroids	0.34	0.33	−0.01	0.31	0.30	0.07
Cesarean delivery	0.36	0.33	−0.24	0.33	0.30	−0.09
Tracheal intubation	0.29	0.35	0.40	0.26	0.32	0.35
CPAP	−0.05	0.10	−0.16	0.00	0.12	0.01
NICU admission	0.38	0.34	0.32	0.33	0.30	0.16
Epinephrine	0.00	0.09	−0.30	0.02	0.09	−0.09
Respiratory support excluding high-frequency ventilation	0.34	0.31	0.34	0.30	0.28	0.12
Supplemental oxygen	0.39	0.35	0.44	0.36	0.31	0.36
High-frequency ventilation	0.23	0.28	0.13	0.24	0.26	0.35
Surfactant	0.38	0.36	0.46	0.34	0.32	0.42
Early antibiotics	0.25	0.32	0.15	0.27	0.30	0.34
Postnatal corticosteroids	NA	NA	NA	0.23	0.20	0.30
Prophylactic indomethacin	NA	NA	NA	−0.02	0.08	−0.21
Nitric oxide	NA	NA	NA	0.15	0.17	0.30
Human milk feeding	NA	NA	NA	0.28	0.31	0.22

NA, not applicable.