Original Investigation

Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012

Barbara J. Stoll, MD; Nellie I. Hansen, MPH; Edward F. Bell, MD; Michele C. Walsh, MD, MS; Waldemar A. Carlo, MD; Seetha Shankaran, MD; Abbot R. Laptook, MD; Pablo J. Sánchez, MD; Krisa P. Van Meurs, MD; Myra Wyckoff, MD; Abhik Das, PhD; Ellen C. Hale, RN, BS, CCRC; M. Bethany Ball, BS, CCRC; Nancy S. Newman, BA, RN; Kurt Schibler, MD; Brenda B. Poindexter, MD, MS; Kathleen A. Kennedy, MD, MPH; C. Michael Cotten, MD, MHS; Kristi L. Watterberg, MD; Carl T. D'Angio, MD; Sara B. DeMauro, MD, MSCE; William E. Truog, MD; Uday Devaskar, MD; Rosemary D. Higgins, MD; for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

IMPORTANCE Extremely preterm infants contribute disproportionately to neonatal morbidity and mortality.

OBJECTIVE To review 20-year trends in maternal/neonatal care, complications, and mortality among extremely preterm infants born at Neonatal Research Network centers.

DESIGN, SETTING, PARTICIPANTS Prospective registry of 34 636 infants, 22 to 28 weeks' gestation, birth weight of 401 to 1500 g, and born at 26 network centers between 1993 and 2012.

EXPOSURES Extremely preterm birth.

MAIN OUTCOMES AND MEASURES Maternal/neonatal care, morbidities, and survival. Major morbidities, reported for infants who survived more than 12 hours, were severe necrotizing enterocolitis, infection, bronchopulmonary dysplasia, severe intracranial hemorrhage, cystic periventricular leukomalacia, and/or severe retinopathy of prematurity. Regression models assessed yearly changes and were adjusted for study center, race/ethnicity, gestational age, birth weight for gestational age, and sex.

RESULTS Use of antenatal corticosteroids increased from 1993 to 2012 (24% [348 of 1431 infants]) to 87% (1674 of 1919 infants]; $P < .001$), as did cesarean delivery (44% [625 of 1431 births] to 64% [1227 of 1921]; $P < .001$). Delivery room intubation decreased from 80% (1144 of 1433 infants) in 1993 to 65% (1253 of 1922) in 2012 ($P < .001$). After increasing in the 1990s, postnatal steroid use declined to 8% (141 of 1757 infants) in 2004 ($P < .001$), with no significant change thereafter. Although most infants were ventilated, continuous positive airway pressure without ventilation increased from 7% (120 of 1666 infants) in 2002 to 11% (190 of 1756 infants) in 2012 ($P < .001$). Despite no improvement from 1993 to 2004, rates of late-onset sepsis declined between 2005 and 2012 for infants of each gestational age (median, 26 weeks [37% {109 of 296} to 27% {85 of 320}]; adjusted relative risk [RR], 0.93 [95% CI, 0.92-0.94]). Rates of other morbidities declined, but bronchopulmonary dysplasia increased between 2009 and 2012 for infants at 26 to 27 weeks' gestation (26 weeks, 50% [130 of 258] to 55% [164 of 297]; $P < .001$). Survival increased between 2009 and 2012 for infants at 23 weeks' gestation (27% [41 of 152] to 33% [50 of 150]; adjusted RR, 1.09 [95% CI, 1.05-1.14]) and 24 weeks (63% [156 of 248] to 65% [174 of 269]; adjusted RR, 1.05 [95% CI, 1.03-1.07]), with smaller relative increases for infants at 25 and 27 weeks' gestation, and no change for infants at 22, 26, and 28 weeks' gestation. Survival without major morbidity increased approximately 2% per year for infants at 25 to 28 weeks' gestation, with no change for infants at 22 to 24 weeks' gestation.

CONCLUSIONS AND RELEVANCE Among extremely preterm infants born at US academic centers over the last 20 years, changes in maternal and infant care practices and modest reductions in several morbidities were observed, although bronchopulmonary dysplasia increased. Survival increased most markedly for infants born at 23 and 24 weeks' gestation and survival without major morbidity increased for infants aged 25 to 28 weeks. These findings may be valuable in counseling families and developing novel interventions.

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network members are listed at the end of this article.

Corresponding Author: Barbara J. Stoll, MD, Department of Pediatrics, Emory University School of Medicine, 1760 Haygood Dr, Ste W400, Atlanta, GA 30322 (bstoll@emory.edu).

Advances in medicine over the past 2 decades have changed care for mothers in preterm labor and for extremely preterm infants. Slow but steady improvements in outcomes have been reported, with substantial differences across centers.[1-7] Nonetheless, extremely preterm infants continue to contribute disproportionately to the burden of neonatal morbidity, mortality, and long-term neurodevelopmental disability.[8,9] Evaluation of current in-hospital morbidity and mortality data among extremely preterm infants is important in counseling families and considering novel interventions to improve outcome.

Since 1987, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) has monitored outcomes and trends in antenatal and postnatal care, morbidities, and mortality among extremely preterm infants born at academic centers of the NRN.[10] The last overview evaluated data from 2003 through 2007.[2] Because there have been considerable changes in obstetric and neonatal care since the early 1990s, this study comprehensively reviews interventions and outcomes of infants at 22 to 28 weeks' gestation born at NRN hospitals between 1993 and 2012.

Methods

This study evaluated infants born at NRN hospitals between 1993 and 2012, with gestational age of 22 weeks 0 days through 28 weeks 6 days and birth weight of 401 to 1500 g. NRN centers are selected by peer review and represent academic institutions with large obstetric and neonatal services, expertise in caring for high-risk mothers and extremely preterm infants, and experience in multicenter clinical research. Study sites are distributed throughout the United States. All delivery hospitals at NRN sites are included in the registry and represent almost 5% of all extremely preterm births in the United States.

From 1993-2007, all very-low-birth weight infants (401-1500 g) born at or admitted to study centers within 14 days of birth were included in the registry. Eligibility criteria changed in 2008 to include inborn infants with a birth weight of 401 to 1000 g or gestational age 22 to 28 weeks. Our study population of infants at 22 to 28 weeks' gestation was restricted to inborn infants with a birth weight of 401 to 1500 g to maintain consistency over the entire study period.

Data were collected prospectively with maternal pregnancy and delivery information collected soon after birth, and infant data collected until death, hospital discharge/transfer, or 120 days of age. Infants who died in the first 12 hours of life were included in analyses of overall mortality but were excluded from analyses focused on morbidities and respiratory support because these outcomes were not collected for infants who died within 12 hours. Morbidities diagnosed during the initial hospital stay[1,2,10-15] were recorded for infants who survived more than 12 hours. Definitions were used consistently over the study period. Detailed respiratory support data were collected beginning 2002.

This study was approved by the institutional review board at each site, with waiver of consent granted at most study sites and written or oral parental consent required by 3 sites.

Outcomes

We focused on changes over time in maternal and neonatal care practices and neonatal morbidity and mortality. Changes in maternal/neonatal characteristics, including maternal age, race/ethnicity (based on chart abstraction using categories specified in the study manual of operations), prenatal care, insulin-dependent diabetes, hypertension, multiple birth, birth defects, infant gestational age, birth weight, and small size for gestational age were examined to assess changes over time that might influence outcomes. Care practices reported were chosen because they have been associated with neonatal outcomes and included antenatal steroids, antenatal antibiotics, cesarean delivery, delivery room resuscitation, surfactant therapy, postnatal steroids, and respiratory support. Morbidities included necrotizing enterocolitis (NEC) (stage 2-3)[16,17]; early-onset sepsis (≤72 hours) and late-onset sepsis (>72 hours) (defined by cultures positive for bacteria or fungi and antibiotic therapy ≥5 days or intent to treat but death <5 days)[18,19]; intracranial hemorrhage (ICH); cystic periventricular leukomalacia (PVL); retinopathy of prematurity (ROP) among infants hospitalized at 28 days; and bronchopulmonary dysplasia (BPD) (defined as oxygen use at 36 weeks' postmenstrual age or at discharge/transfer if before 36 weeks in infants who survived to 36 weeks). ICH was determined by the most severe cranial sonogram prior to hospital discharge, transfer, or death. A grade 3/4 ICH was considered severe.[20] Survival to discharge and survival without major morbidity (NEC, severe ICH, PVL, early- or late-onset sepsis or meningitis, BPD, or ROP ≥stage 3) were studied.

Statistical Analysis

Descriptive statistics are shown in 4 discrete 5-year periods (1993-1997, 1998-2002, 2003-2007, 2008-2012) and for the first and last years of the study (1993, 2012), and yearly changes are shown in figures. Analyses examined yearly changes over time, with birth year treated as a continuous variable. Changes in maternal/neonatal characteristics were assessed using linear or logistic models. Linear trends in outcomes were assessed using Poisson regression models with robust variance estimators[21] to estimate relative risks (RRs) and 95% CIs for the change per year while adjusting for covariates. Models included covariates for birth year, study center, maternal race/ethnicity, infant gestational age, small size for gestational age, and sex, with exceptions noted in table footnotes. *P* values for tests of trends were determined by Score, or Wald χ^2, or *F* tests. Analyses were based on infants with nonmissing values of covariates and outcomes. Less than 1% of observations were missing values of covariates or outcomes except that approximately 5% of infants could not be evaluated for major morbidity and 4% of infants surviving to 36 weeks' postmenstrual age were not evaluated for BPD. Missing values were not imputed with the exception of missing ethnicity for white race (0.4%) and black race (2%), which was considered to be non-Hispanic.

Graphs of the percent of infants with each outcome by birth year were examined to suggest the modeling strategy with respect to year. Each graph included a local regression (LOESS) curve that was fit using the data proportions and a smoothing parameter (0.3 or 0.4) for assessment of trend. Trends generally consistent over the period were assessed by including year in the models as a single continuous variable. For trends that varied over the period, linear splines with knot points (changes in trend) suggested by the graph were used to assess variation. Where one RR was reported for an outcome, the change per year was estimated for 1993-2012. Where more than one RR was reported, the change per year was estimated for the periods shown to capture variation in trend over time. Yearly trends in outcomes were assessed overall and for infants of each gestational age through use of interaction terms between each level of gestational age and year effects. For outcomes with nonsignificant year-gestational age interactions, adjusted RRs from main effects models are reported. For outcomes with significant year-gestational age interactions, adjusted RRs from models that included the interaction are reported for infants of each gestational age, with graphs shown by gestational age in supplemental figures.

The primary analyses used data from all centers. Analyses were repeated using data from the centers in the NRN all 20 years. Except as noted, results were similar to those from the primary analyses and are not reported. A 2-sided *P* value of less than .05 was considered significant. Analyses were completed using SAS statistical software version 9.3 (SAS Institute).

Results

During 1993-2012, 34 636 infants at 22 to 28 weeks' gestation and 401 to 1500 g birth weight were born at 26 NRN centers. Eight centers participated all 20 years (18 236 infants, 53%), 5 for 14 to 19 years (26%), 1 for 12 years (4%), 7 for 6 to 9 years (14%), 1 for 4 years (2%), and 4 for 2 years (2%). Maternal age increased from a mean (SD) of 25.7 (6.5) years in 1993 to 27.8 (6.3) years in 2012, $P < .001$ (**Table 1**). Race/ethnicity changed, with smaller percentages of non-Hispanic black mothers (55% in 1993 to 39% in 2012) and higher percentages of non-Hispanic white and Hispanic mothers (31% to 42% and 12% to 14%, respectively, $P < .001$). Maternal hypertension increased from 12% in 1993 to 27% in 2012 ($P < .001$) and maternal insulin-dependent diabetes from 2% to 5% ($P < .001$).

A major birth defect was reported for 1292 infants (3.7%) and the proportion did not change significantly between 1993 and 2012, $P = .25$. The percent of infants from a multiple birth increased from 18% in 1993 to 27% in 1998 ($P < .001$), with no further increase noted. Study participants were 52% male, with similar proportions in each year.

Care Practices

Use of antenatal corticosteroids increased from 1993 to 1996 (24% [348 of 1431 infants] to 74% [1049 of 1413 infants]; $P < .001$) (**Figure 1**). The change varied significantly by gestational age, with larger relative increases each year among mothers of lower gestational aged infants (22 weeks; 3% [2 of 79] to 24% [17 of 70]; adjusted RR for change per year, 1.81 [95% CI, 1.38-2.38]) vs 28 weeks' gestation (30% [93 of 310] to 85% [252 of 295]; adjusted RR, 1.30 [95% CI, 1.26-1.35]) (eFigure 1 in the Supplement). After 1996, use increased more slowly; by 2012, 87% of mothers (1674 of 1919) received at least 1 dose of corticosteroids (eTable 1 in the Supplement). Antenatal antibiotic use increased during the early 1990s from 44% (631 of 1431) in 1993 to 76% (1310 of 1729) in 1997 ($P < .001$) (Figure 1 and eTable 1 in the Supplement). After 1997, antenatal antibiotic use decreased to 63% (1191 of 1889) in 2006 ($P < .001$), but rose to 73% (1401 of 1916) in 2012 ($P < .001$). In the 8 centers in the NRN all 20 years, no increase was noted after 2006.

Cesarean deliveries increased most markedly from 1993 to 2005 (44% [625 of 1431] to 62% [1247 of 2024]; $P < .001$) (Figure 1). The increase differed by gestational age, with larger relative yearly increases among infants of lower gestational age (eFigure 2 and eTable 1 in the Supplement). Cesarean deliveries continued to increase slightly after 2005 for infants born at 26 and 27 weeks.

Delivery room tracheal intubation, resuscitation drugs, and chest compression decreased over time, while surfactant use increased (Figure 1 and eTable 1 in the Supplement). In 1993, 80% of infants (1144 of 1433) were intubated in the delivery room, compared with 65% (1253 of 1922) in 2012; decreases differed by gestational age (eFigure 3 in the Supplement). Surfactant was given to 60% of infants (861 of 1433) in 1993, compared with 78% (1501 of 1913) in 2003, with increases in all gestational ages, except infants born at 22 weeks (eFigure 4 in the Supplement). After 2003, surfactant use decreased slightly among infants born at 27 to 28 weeks.

Among infants who survived more than 12 hours, postnatal corticosteroid use increased significantly in the early 1990s from 29% (356 of 1240) in 1993 to 41% (508 of 1230) in 1996 (adjusted RR, 1.18 [95% CI, 1.14-1.21]; $P < .001$) (Figure 1). Postnatal steroid use decreased to a low of 8% (141 of 1757) in 2004 ($P < .001$) with no significant change thereafter.

Respiratory Support (2002-2012)

Most infants who survived more than 12 hours were mechanically ventilated (**Table 2**). In 2002, 90% of infants (1497 of 1666) received conventional ventilation. Conventional ventilation decreased to 82% (1442 of 1756) in 2012; changes per year varied by gestational age (eTable 2 in the Supplement). High-frequency ventilation increased from 30% (504 of 1666) in 2002 to 41% (646 of 1569) in 2007 (adjusted RR, 1.03 [95% CI, 1.01-1.04]; $P < .001$), with no significant change between 2008 and 2012. The percent never ventilated decreased for infants born at 22 to 23 weeks, but increased for infants born at 24 weeks and at 26 to 28 weeks (26 weeks, 6% [20 of 328 infants] in 2002 to 9% [29 of 326 infants] in 2012; adjusted RR, 1.06 [95% CI, 1.02-1.10]; $P = .002$; 28 weeks, 21% [81 of 380 infants] in 2002 to 30% [128 of 423 infants] in 2012; adjusted RR, 1.05 [95% CI, 1.03-1.07]; $P < .001$) (eTable 2 in the Supplement). Nasal

Table 1. Maternal and Infant Characteristics for Infants Born at Low Gestational Ages in Neonatal Research Network Centers[a]

	Total (n = 34 636)	1993 (n = 1433)	2012 (n = 1922)	1993-1997 (n = 7027)	1998-2002 (n = 9132)	2003-2007 (n = 9600)	2008-2012 (n = 8877)	*P* Value for Linear Trend[b]
Maternal Characteristics[c]								
Age, mean (SD), y	27.0 (6.6)	25.7 (6.5)	27.8 (6.3)	26.3 (6.7)	26.8 (6.7)	27.2 (6.6)	27.5 (6.4)	<.001
Race/ethnicity								
Black, non-Hispanic	14 472 (42)	781 (55)	751 (39)	3450 (49)	3908 (43)	3745 (39)	3369 (38)	<.001
White, non-Hispanic	13 124 (38)	451 (31)	796 (42)	2483 (35)	3491 (38)	3557 (37)	3593 (41)	
Hispanic	5563 (16)	174 (12)	262 (14)	903 (13)	1425 (16)	1825 (19)	1410 (16)	
Other	1377 (4)	26 (2)	101 (5)	179 (3)	280 (3)	450 (5)	468 (5)	
≥1 Prenatal visit	32 235 (93)	1233 (87)	1835 (97)	6296 (90)	8498 (93)	8997 (94)	8444 (96)	<.001
Insulin-dependent diabetes	1317 (4)	28 (2)	96 (5)	136 (2)	302 (3)	436 (5)	443 (5)	<.001
Hypertension								
All infants	6991 (20)	172 (12)	508 (27)	1067 (15)	1607 (18)	2121 (22)	2196 (25)	<.001
By gestational age, wk								
22	94 (6)	2 (3)	6 (8)	13 (4)	19 (4)	34 (8)	28 (8)	
23	242 (8)	2 (2)	25 (17)	21 (3)	49 (6)	84 (10)	88 (11)	
24	596 (13)	10 (6)	49 (18)	67 (8)	122 (10)	198 (14)	209 (17)	
25	1014 (19)	23 (10)	86 (28)	139 (13)	241 (17)	304 (20)	330 (24)	
26	1289 (22)	30 (12)	93 (28)	206 (17)	297 (19)	392 (25)	394 (26)	
27	1684 (25)	49 (17)	116 (33)	282 (21)	374 (22)	498 (27)	530 (31)	
28	2072 (28)	56 (18)	133 (32)	339 (22)	505 (26)	611 (30)	617 (33)	
Infant Characteristics								
Multiple birth	8448 (24)	265 (18)	521 (27)	1466 (21)	2265 (25)	2406 (25)	2311 (26)	<.001
Birth weight, mean (SD), g	840 (241)	857 (245)	847 (241)	847 (244)	837 (240)	836 (241)	843 (238)	.01
Male	18 104 (52)	748 (52)	980 (51)	3657 (52)	4743 (52)	5104 (53)	4600 (52)	.82
Major birth defect	1292 (4)	50 (3)	87 (5)	342 (5)	283 (3)	336 (4)	331 (4)	.25
Gestational age, mean (SD)[d]	25.7 (1.8)	25.8 (1.8)	25.8 (1.8)	25.7 (1.8)	25.7 (1.8)	25.7 (1.8)	25.8 (1.8)	.11
By gestational age, wk								
22	1550 (4)	79 (6)	75 (4)	358 (5)	437 (5)	421 (4)	334 (4)	
23	3133 (9)	122 (9)	150 (8)	660 (9)	821 (9)	873 (9)	779 (9)	
24	4762 (14)	163 (11)	269 (14)	871 (12)	1273 (14)	1377 (14)	1241 (14)	
25	5361 (15)	225 (16)	308 (16)	1070 (15)	1397 (15)	1503 (16)	1391 (16)	
26	5829 (17)	250 (17)	333 (17)	1194 (17)	1542 (17)	1580 (16)	1513 (17)	
27	6627 (19)	283 (20)	357 (19)	1337 (19)	1720 (19)	1837 (19)	1733 (20)	
28	7374 (21)	311 (22)	430 (22)	1537 (22)	1942 (21)	2009 (21)	1886 (21)	
Small for gestational age, all infants[e]	2497 (7)	90 (6)	135 (7)	445 (6)	674 (7)	722 (8)	656 (7)	.01
By gestational age, wk								
22	0	0	0	0	0	0	0	
23	95 (3)	2 (2)	9 (6)	15 (2)	23 (3)	32 (4)	25 (3)	
24	275 (6)	5 (3)	14 (5)	36 (4)	72 (6)	86 (6)	81 (7)	
25	401 (7)	15 (7)	23 (8)	68 (6)	109 (8)	116 (8)	108 (8)	
26	492 (8)	21 (8)	34 (10)	93 (8)	140 (9)	130 (8)	129 (9)	
27	554 (8)	20 (7)	25 (7)	102 (8)	137 (8)	178 (10)	137 (8)	
28	680 (9)	27 (9)	30 (7)	131 (9)	193 (10)	180 (9)	176 (9)	

[a] Data shown as No. (%) unless otherwise indicated. All infants were born at 22 to 28 weeks' gestation between January 1, 1993, through December 31, 2012.

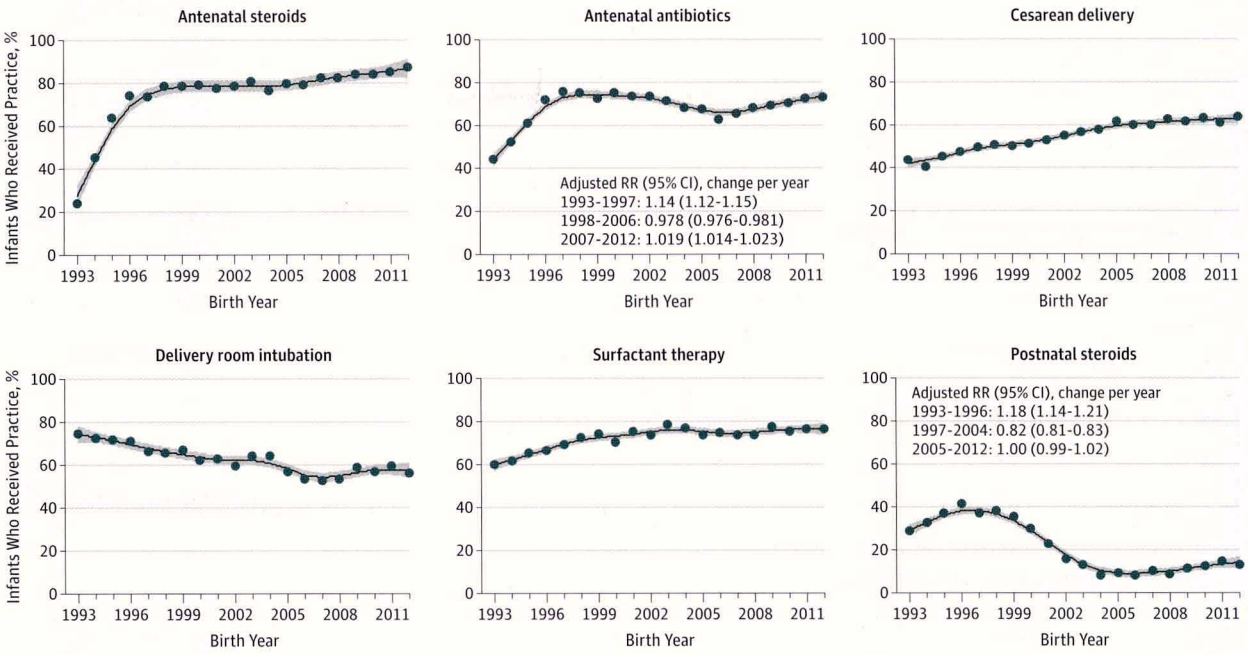
[b] The *P* value for linear trend was for 1993-2012. Determined using the *F* or Wald χ^2 test from linear or logistic regression models, adjusting for study center, maternal race/ethnicity, infant gestational age, small size for gestational age, and sex except as noted. For assessing yearly change in maternal race/ethnicity, models included study center, infant gestational age, small size for gestational age, sex, and year; for yearly change in gestational age, they included study center, maternal race/ethnicity, infant sex, and year; for yearly change in birth weight and small size for gestational age, they included study center, maternal race/ethnicity, infant gestational age, sex, and year. Maternal hypertension, infant gestational age and small for gestational age are shown by gestational age for descriptive purposes only; tests of linear trend were not conducted separately by gestational age.

[c] Missing information: mother's age (6 infants), prenatal care (71 infants), maternal diabetes (66 infants), maternal hypertension (70 infants), maternal race/ethnicity (100 infants), sex (6 infants), and small size for gestational age (6 infants). Infants with black or white maternal race and missing ethnicity were classified as non-Hispanic (2% of black infants, 0.4% of white infants). Maternal hypertension was collected as hypertension/pre-eclampsia/eclampsia prior to 2006; but as hypertension only afterwards.

[d] Hierarchy for assessing gestational age: (1) by obstetrical measures based on last menstrual period, obstetrical parameters, and/or prenatal ultrasound (per the maternal chart); or (2) by neonatologist's estimate based on physical criteria, neurologic examination, combined physical and gestational age examination (Ballard or Dubowitz), or examination of the lens.

[e] Small for gestational age was defined as birth weight lower than the 10th percentile for age and sex based on Alexander percentiles.[9]

Figure 1. Care Practices for Infants Born at Gestational Ages 22 through 28 Weeks



Circles indicate the percent of infants born each year who received the practice, the smoothed curve shows the trend, and shading indicates the 95% CI for the curve. Shading is not visible where CIs are close to values on the curve. Percentages are among all infants except those for postnatal steroids (which include only infants who survived >12 hours; this outcome was not collected for infants who died ≤12 hours of age). Adjusted relative risks (RRs) are based on infants of all gestational ages and are shown for outcomes for which the year-gestational age interaction was not significant. When the year-gestational age interaction was significant, graphs and RRs are shown for each gestational age in eFigures 1-4 in the Supplement. RRs for the change per year were adjusted for study center, maternal race/ethnicity, infant gestational age, small size for gestational age, and sex. Total number of infants (mean [range] per year): 34 576 (1728 [1214-2022]) for antenatal steroids; 34 531 (1726 [1210-2020]) for antenatal antibiotics; 34 611 (1730 [1213-2024]) for cesarean delivery; 34 611 (1730 [1214-2024]) for intubation; 34 599 (1729 [1214-2023]) for surfactant; and 30 645 (1532 [1036-1802]) for postnatal steroids.

Table 2. Respiratory Support for Infants Born at Gestational Ages 22 to 28 Weeks in NRN Centers Who Survived More Than 12 Hours After Birth[a]

	No. (%) (N=18 246)			
	2002 (n = 1666)	2012 (n = 1756)	2003-2007 (n = 8546)	2008-2012 (n = 8034)
Never used conventional or high-frequency ventilation[b]	167 (10)	255 (15)	886 (10)	1047 (13)
Any high-frequency ventilation[b]	504 (30)	632 (36)	3123 (37)	3070 (38)
Any conventional ventilation[b]	1497 (90)	1442 (82)	7446 (87)	6653 (83)
Any nasal SIMV[b]	239 (14)	657 (37)	1510 (18)	2592 (32)
Any CPAP therapy[b]	1314 (79)	1357 (77)	6680 (78)	6227 (78)
Nasal SIMV, highest[b,c]	13 (<1)	45 (3)	89 (1)	178 (2)
CPAP, highest[b,d]	120 (7)	190 (11)	663 (8)	746 (9)

Abbreviations: CPAP, continuous positive airway pressure; NRN, Neonatal Research Network; SIMV, synchronized intermittent mandatory ventilation.

[a] All infants were born at gestational ages 22 to 28 weeks between January 1, 1993, and December 31, 2012. Respiratory support outcomes were examined for infants born between 2002 and 2012 due to changes in data collection. Analyses were repeated in the subset of 11 centers in the NRN all years 2002-2012 (n = 12 879).

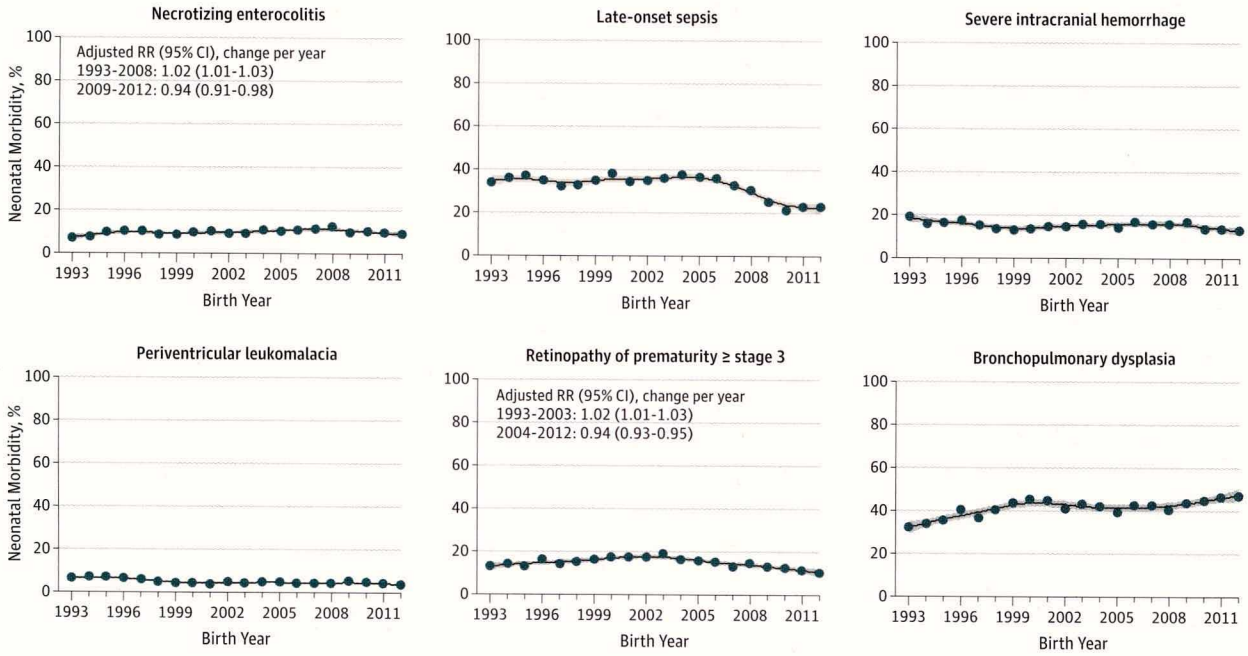
[b] Information was missing as follows: never used conventional or high-frequency ventilation, 6 infants; high-frequency ventilation, 9 infants; conventional ventilation, 6 infants; any nasal SIMV, 11 infants; any CPAP, 13 infants; nasal SIMV highest, 6 infants; CPAP highest, 6 infants.

[c] Highest level of support was defined for nasal SIMV as never used conventional or high-frequency ventilation but used nasal SIMV.

[d] Highest level of support was defined for CPAP as never used conventional or high-frequency ventilation or nasal SIMV but received CPAP therapy.

synchronized intermittent mandatory ventilation (SIMV) increased from 14% (239 of 1666 infants) in 2002 to 37% (657 of 1755 infants) in 2012 ($P < .001$) (Table 2). Nasal SIMV was the highest level of support for fewer than 1% of infants (13 of 1666) in 2002 but increased to 3% (45 of 1756 infants) in 2012 ($P < .001$). Use of continuous positive airway pressure (CPAP) without ventilation increased from 7% of infants (120 of 1666) in 2002 to 11% of infants (190 of 1756) in 2012 (adjusted

Figure 2. Neonatal Morbidities for Infants Born at Gestational Ages 22 Through 28 Weeks



Circles show the percent of infants born each year diagnosed with the morbidity and the smoothed curve shows the trend. Shading to indicate the 95% CI for each curve is not visible where CIs are close to values on the curve. Percentages shown in graphs are among infants of all gestational ages who survived more than 12 hours with additional restrictions as noted in the text and eTable 3 in the Supplement. Relative risks (RRs) are based on infants of all gestational ages and are shown for outcomes for which the year-gestational age interaction was not significant. When the year-gestational age interaction was significant, graphs and RRs are shown for each gestational age for late-onset sepsis, severe intracranial hemorrhage, periventricular leukomalacia, and bronchopulmonary dysplasia in eFigures 5-8 in the Supplement. RRs for the change per year were adjusted for study center, maternal race/ethnicity, infant gestational age, small size for gestational age, and sex. Total number of infants (mean [range] per year): 30 790 (1539 [1035-1809]) for necrotizing enterocolitis; 29 252 (1462 [980-1702]) for late-onset sepsis; 29 883 (1494 [1016-1741]) for severe intracranial hemorrhage (ICH); 28 498 (1424 [769-1744]) for periventricular leukomalacia (PVL); 24 951 (1247 [808-1509]) for retinopathy of prematurity (ROP) of stage 3 or greater; and 25 000 (1250 [746-1534]) for bronchopulmonary dysplasia (BPD).

RR, 1.05 [95% CI, 1.03-1.07]; $P < .001$) (eTable 2 in the Supplement). Few infants born before 25 weeks received nasal SIMV or CPAP without first receiving mechanical ventilation.

Morbidities

Overall, 2% (689 of 30 789) of infants had early-onset sepsis, with no significant change over the entire study period (eTable 3 in the Supplement). In 1993, 7% (89 of 1240) of infants were diagnosed with NEC, increasing to 13% (187 of 1496) in 2008 ($P < .001$) before declining to 9% (161 of 1756) by 2012 ($P < .01$) (**Figure 2**). Among infants surviving more than 3 days, 32% (9482 of 29 252) were diagnosed with late-onset sepsis, with the percent increasing with decreasing gestational age (28 weeks, 20% [1396 of 7149]; 22 weeks, 61% [122 of 200]). From 1993 to 2004, the percent of infants with late-onset sepsis remained stable or increased slightly depending on gestational age (Figure 2 and eTable 3 in the Supplement). From 2005 to 2012, the rate of late-onset sepsis decreased for infants of each gestational age (eg, 24 weeks, 54% [143 of 264] to 40% [89 of 225]; adjusted RR, 0.94 [95% CI, 0.93-0.95]; 26 weeks, 37% [109 of 296] to 27% [85 of 320]; adjusted RR, 0.93 [95% CI, 0.92-0.94]); 28 weeks, 20% [84 of 415] to 8% [34 of 418]; adjusted RR, 0.91 [95% CI, 0.90-0.92]) (eFigure 5 in the Supplement).

The percent of infants with severe ICH decreased from 1993 to 2012 (Figure 2 and eTable 3 in the Supplement). The reduction was significant for infants born at 26 weeks (19% [44 of 235] to 11% [35 of 321]; $P = .03$), 27 weeks (15% [40 of 261] to 7% [25 of 349]; $P = .02$), and 28 weeks (11% [32 of 297] to 5% [21 of 417]; $P < .01$), but not for infants with gestational ages of 22 through 25 weeks (eFigure 6 in the Supplement). PVL decreased for infants born at gestational ages of 26 through 28 weeks (26 weeks, 8% [15 of 194]] in 1993 to 4% [13 of 322] in 2012; adjusted RR, 0.94 [95% CI, 0.92-0.96]) (eTable 3 and eFigure 7 in the Supplement).

Of the 26 749 infants still hospitalized at 28 days, 93% (24 991) had an ophthalmologic examination prior to discharge. Retinopathy of prematurity was diagnosed for 60% of infants (15 022 of 24 987) overall (15% [3720 of 24 951] with ≥stage 3), with an inverse relationship between diagnosis and gestational age (eg, 22 weeks, 89% [101 of 113] overall and 42% [47 of 113] with ≥stage 3; 28 weeks, 34% [2156 of 6289] overall and 3% [171 of 6279] with ≥stage 3). Diagnosis of ROP decreased for infants born at 25 through 28 weeks, with limited or no change for infants born at 22 through 24 weeks (eTable 3 in the Supplement). ROP of stage 3 or higher increased from 13% of infants (124 of 941) in 1993 to 19% (262 of 1385) in 2003, but decreased to 11% of infants (160 of 1509) by 2012

(adjusted RR for the change per year 2004-2012, 0.94 [95% CI, 0.93-0.95]) (Figure 2).

The diagnosis of BPD rose from 32% (295 of 911) in 1993 to 45% (547 of 1213) in 2000 (adjusted RR, 1.05 [95% CI, 1.04-1.06]), but decreased to 40% (498 of 1230) in 2008 (Figure 2). From 2009 through 2012, BPD rates increased for infants born at 26 weeks (50% [130 of 258] to 55% [164 of 297]; $P < .001$) and 27 weeks (33% [103 of 312] to 40% [134 of 339]; $P = .007$), but not for infants born at 22 through 25 weeks or at 28 weeks (eTable 3 and eFigure 8 in the Supplement). Among the 8 centers in the NRN all 20 years, BPD rates increased from 2009 through 2012 for all gestational ages except 28 weeks.

Survival

Survival increased with increasing gestational age (2012: 22 weeks, 9% [7 of 75]; 28 weeks, 94% [405 of 430]) (**Table 3**). Survival rates remained unchanged from 1993 through 2008. After 2008, trends in survival varied by gestational age (**Figure 3**). From 2009 through 2012, survival increased for infants born at 23 weeks (27% [41 of 152] to 33% [50 of 150]; adjusted RR for the change per year, 1.09 [95% CI, 1.05-1.14]; $P < .001$) and 24 weeks (63% [156 of 248] to 65% [174 of 269]; adjusted RR, 1.05 [95% CI, 1.03-1.07]; $P < .001$), with smaller relative increases for infants born at 25 weeks (79% [237 of 300] to 81% [249 of 308]; adjusted RR, 1.02 [95% CI, 1.01-1.03]) and 27 weeks (90% [311 of 345] to 94% [337 of 357]; adjusted RR, 1.01 [95% CI, 1.002-1.016]). Survival to discharge did not change significantly between 2009 and 2012 for infants born at 22, 26, and 28 weeks.

Among infants who survived to discharge, survival without major morbidity varied by gestational age (Table 3 and **Figure 4**), with no significant change in the proportion of infants born at 22 through 24 weeks who survived to discharge without major morbidity. Although 6% (99 of 1550) infants born at 22 weeks survived to discharge, only 5 survived without major morbidity. However, an increase of approximately 2% per year was seen among infants born between 25 and 28 weeks (Figure 4). By 2012, more than half of infants born at 28 weeks who survived to discharge survived without major morbidity (for 1993: 43% [88 of 207]; for 2012: 59% [230 of 387]; adjusted RR, 1.03 [95% CI, 1.02-1.03]; $P < .001$). Trends in survival and survival without major morbidity were similar in the 8 centers in the NRN all 20 years (eTable 4 in the Supplement).

Survivors remained in hospital an average of 93 days (median [interquartile range], 85 days [66-109 days]), with median hospitalization varying with gestational age from 140 days for those born at 22 weeks to 63 days for infants born at 28 weeks. Median postmenstrual age at discharge decreased from 42 weeks for surviving infants born at 22 weeks gestational age to 37 weeks for those born at 28 weeks ($P < .001$).

Discussion

This study of extremely preterm infants born at NRN centers is the first comprehensive review to our knowledge to evaluate how care practices, major morbidities, and mortality have evolved over a 20-year period. The study provides a global overview and level of detail not presented in earlier studies. Findings demonstrate that progress is being made and outcomes of the most immature infants are improving.

We demonstrated a significant increase in survival to discharge for infants born at 23, 24, 25, and 27 weeks, with the largest gains for those born at 23 and 24 weeks. Although methods differed, these findings are consistent with a recent study from the NRN on causes and timing of death among extremely preterm infants.[22] In addition to increasing survival, an important goal of obstetrical and neonatal care is to reduce morbidities and improve neonatal outcome. Perhaps the most important new finding is a significant increase in survival without major neonatal morbidity for infants born at 25 through 28 weeks. Although overall survival increased for infants aged 23 and 24 weeks, few infants younger than 25 weeks' gestational age survived without major neonatal morbidity, underscoring the continued need for interventions to improve outcomes for the most immature infants.

At very early gestational ages, the decision to provide active obstetrical management and neonatal intensive care is complex and requires a team approach with discussions between the obstetrical and neonatal teams and the family.[23-25] All infants in this study were delivered in academic centers with availability of tertiary maternal fetal medicine and comprehensive neonatal care. Changes in race/ethnicity likely reflect changes in the centers in the NRN over time and changes in populations served. Approximately one-fourth of infants were from multiple births, with a significant increase over the study period, consistent with national trends and increased use of fertility treatments.[26]

An important finding is the increased adherence to care practices that have been associated with improved neonatal outcomes. Antenatal corticosteroid use is one of the most effective interventions.[27-31] The 1995 National Institutes of Health consensus statement on antenatal corticosteroids led to widespread use. Recent studies have documented benefits to infants as young as 22 to 23 weeks. Among patients in this study, antenatal steroid administration increased from only 24% in 1993 to 87% in 2012. We also found a changing pattern of antenatal antibiotic use and a significant increase in cesarean deliveries between 1993 and 2005, with increases noted for infants of each gestational age. Increased obstetrical interventions among the most immature infants, 22 through 24 weeks' gestation, suggests increased willingness to provide active management of pregnancies near the limit of viability.

Strategies to reduce lung injury, including less aggressive ventilation, are increasingly embraced. In this cohort, changes in respiratory care were documented with decreased intubation in the delivery room but increased surfactant use, suggesting an increase in selective use of surfactant.[32] Avoidance of intubation in the delivery room might lead to increased surfactant use if early CPAP is insufficient to prevent alveolar collapse in some infants. There were modest increases in the percent of infants aged 24 through 28 weeks who were never ventilated. High-frequency ventilation increased for infants at each gestational age, mainly between 2002 and 2007, and less-invasive methods of ventilation (nasal SIMV, CPAP as highest

Table 3. Survival to Discharge for Infants Born at Gestational Ages 22 Through 28 Weeks in NRN Centers[a]

	Study Year, No. of Infants/Total No. (%)					
	1993	2012	1993-1997	1998-2002	2003-2007	2008-2012
All infants (N = 34 636)	1433	1922	7027	9132	9600	8877
Died	426/1433 (30)	409/1922 (21)	1992/7027 (28)	2489/9132 (27)	2725/9600 (28)	2131/8877 (24)
Died within 12 h	193/1433 (13)	166/1922 (9)	909/7027 (13)	1025/9132 (11)	1054/9600 (11)	843/8877 (9)
Survived to Discharge Among All Infants						
All infants	1007/1433 (70)	1513/1922 (79)	5035/7027 (72)	6643/9132 (73)	6875/9600 (72)	6746/8877 (76)
By gestational age, wk						
22	5/79 (6)	7/75 (9)	25/358 (7)	27/437 (6)	25/421 (6)	22/334 (7)
23	34/122 (28)	50/150 (33)	184/660 (28)	215/821 (26)	226/873 (26)	252/779 (32)
24	85/163 (52)	174/269 (65)	465/871 (53)	715/1273 (56)	752/1377 (55)	774/1241 (62)
25	153/225 (68)	249/308 (81)	784/1070 (73)	1065/1397 (76)	1081/1503 (72)	1077/1391 (77)
26	208/250 (83)	291/333 (87)	980/1194 (82)	1317/1542 (85)	1322/1580 (84)	1281/1513 (85)
27	238/283 (84)	337/357 (94)	1183/1337 (88)	1536/1720 (89)	1615/1837 (88)	1568/1733 (90)
28	284/311 (91)	405/430 (94)	1414/1537 (92)	1768/1942 (91)	1854/2009 (92)	1772/1886 (94)
Survived to Discharge Without Major Morbidity Among All Infants[b]						
All infants evaluated[c]	256/1256 (20)	559/1895 (29)	1096/6100 (18)	2119/8869 (24)	2318/9368 (25)	2493/8723 (29)
By gestational age, wk						
22	0/79	0/75	2/355 (<1)	3/437 (<1)	0/421	0/334
23	2/120 (2)	1/150 (<1)	12/650 (2)	9/820 (1)	16/871 (2)	13/779 (2)
24	12/160 (8)	15/268 (6)	60/850 (7)	77/1269 (6)	65/1377 (5)	87/1238 (7)
25	33/208 (16)	61/306 (20)	128/1001 (13)	198/1384 (14)	212/1493 (14)	237/1383 (17)
26	52/213 (24)	85/331 (26)	199/1028 (19)	371/1516 (24)	433/1555 (28)	413/1505 (27)
27	69/242 (29)	167/353 (47)	305/1090 (28)	628/1650 (38)	669/1785 (37)	735/1693 (43)
28	88/234 (38)	230/412 (56)	390/1126 (35)	833/1793 (46)	923/1866 (49)	1008/1791 (56)
Survived to Discharge Without Major Morbidity Among Infants Who Survived to Discharge						
All survivors to discharge (n = 25 299)	1007	1513	5035	6643	6875	6746
All survivors evaluated[d]	256/830 (31)	559/1486 (38)	1096/4108 (27)	2119/6380 (33)	2318/6643 (35)	2493/6592 (38)
By gestational age, wk						
22	0/5	0/7	2/22 (9)	3/27 (11)	0/25	0/22
23	2/32 (6)	1/50 (2)	12/174 (7)	9/214 (4)	16/224 (7)	13/252 (5)
24	12/82 (15)	15/173 (9)	60/444 (14)	77/711 (11)	65/752 (9)	87/771 (11)
25	33/136 (24)	61/247 (25)	128/715 (18)	198/1052 (19)	212/1071 (20)	237/1069 (22)
26	52/171 (30)	85/289 (29)	199/814 (24)	371/1291 (29)	433/1297 (33)	413/1273 (32)
27	69/197 (35)	167/333 (50)	305/936 (33)	628/1466 (43)	669/1563 (43)	735/1528 (48)
28	88/207 (43)	230/387 (59)	390/1003 (39)	833/1619 (51)	923/1711 (54)	1008/1677 (60)

Abbreviations: BPD, bronchopulmonary dysplasia; ICH, intracranial hemorrhage; NRN, Neonatal Research Network; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

[a] All infants were born between January 1, 1993, and December 31, 2012.

[b] Major morbidity was defined as 1 or more of necrotizing enterocolitis, infections (early-onset sepsis, late-onset sepsis, or meningitis), BPD, severe ICH, PVL, and ROP of stage 3 or greater.

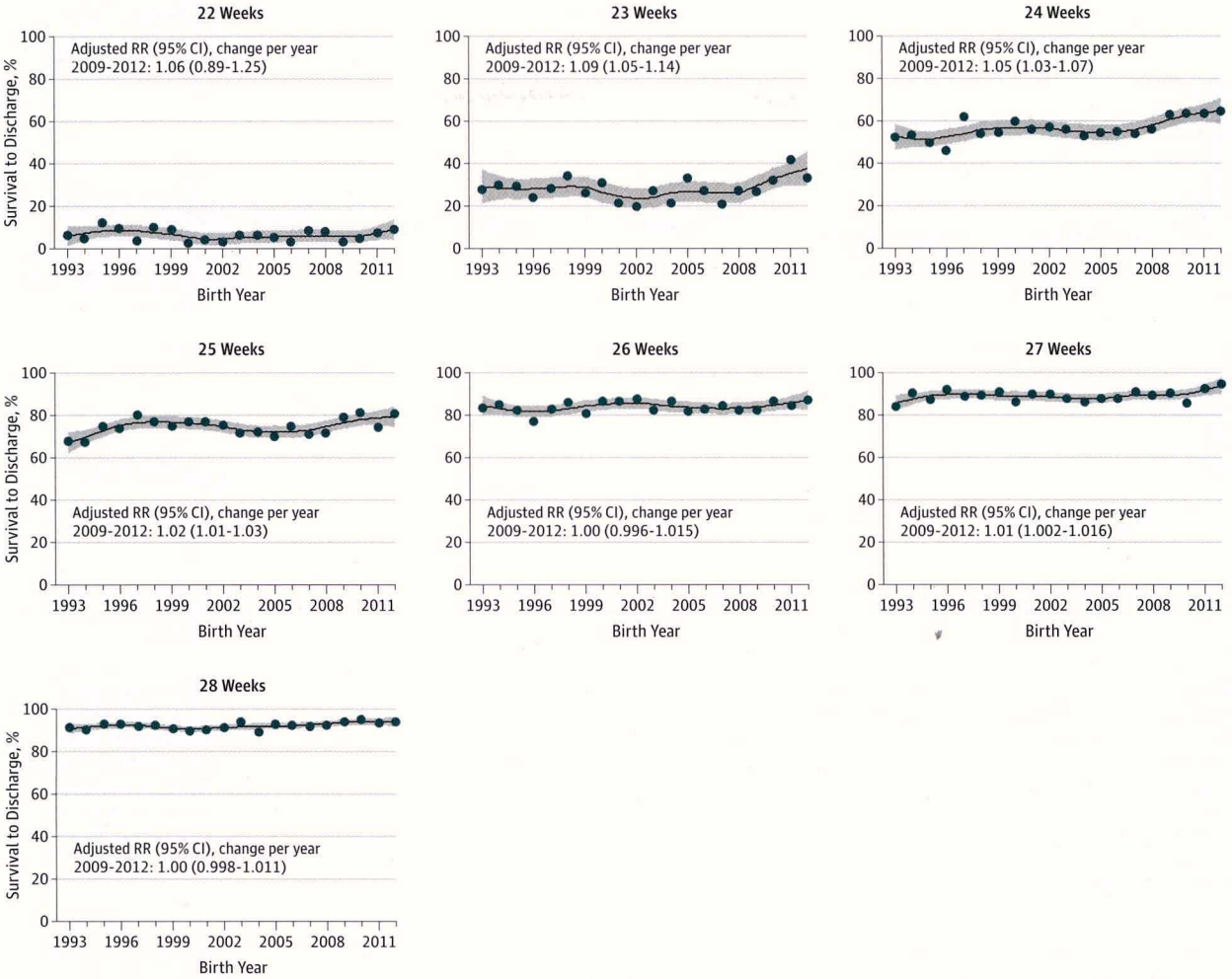
[c] Of the 34 636 infants in the cohort, 1576 (4.6%) could not be evaluated for survival without major morbidity because of missing information for 1 or more morbidities. More than half of those missing information were infants born between 1993 and 1997. During this period, data for BPD and PVL were most frequently missing; PVL was missing when a cranial sonogram was not performed at 2 weeks or later. Between 1998 and 2012, data for ROP was most frequently missing because no examination was completed prior to discharge. Values are among the 33 060 infants who could be evaluated, including infants who died within 12 hours of life.

[d] Values indicate the 23 723 of 25 299 infants who survived to discharge, excluding 1576 infants who survived but could not be evaluated for major morbidity due to missing information.

level of support) increased overall. These trends are consistent with changes in care reported by other multicenter networks.[4,7,33]

Despite increased use of maternal antibiotics over the years, rates of early-onset sepsis did not change significantly. Earlier NRN studies among extremely preterm infants reported a substantial reduction in early-onset Group B streptococcal sepsis with a concomitant increase in early-onset *Escherichia coli* sepsis.[18,34] By contrast, we documented a substantial reduction in late-onset sepsis from 2005 to 2012 for infants of each gestational age. Although we did not collect information about infection control practices, the reduction in late-onset sepsis likely reflects increased attention to improved hand hygiene, skin care, human milk feeding, uniform practices for catheter insertion and care (central line bundles), and attention to discontinuing invasive devices when

Figure 3. Infant Survival to Discharge By Birth Year and Gestational Age



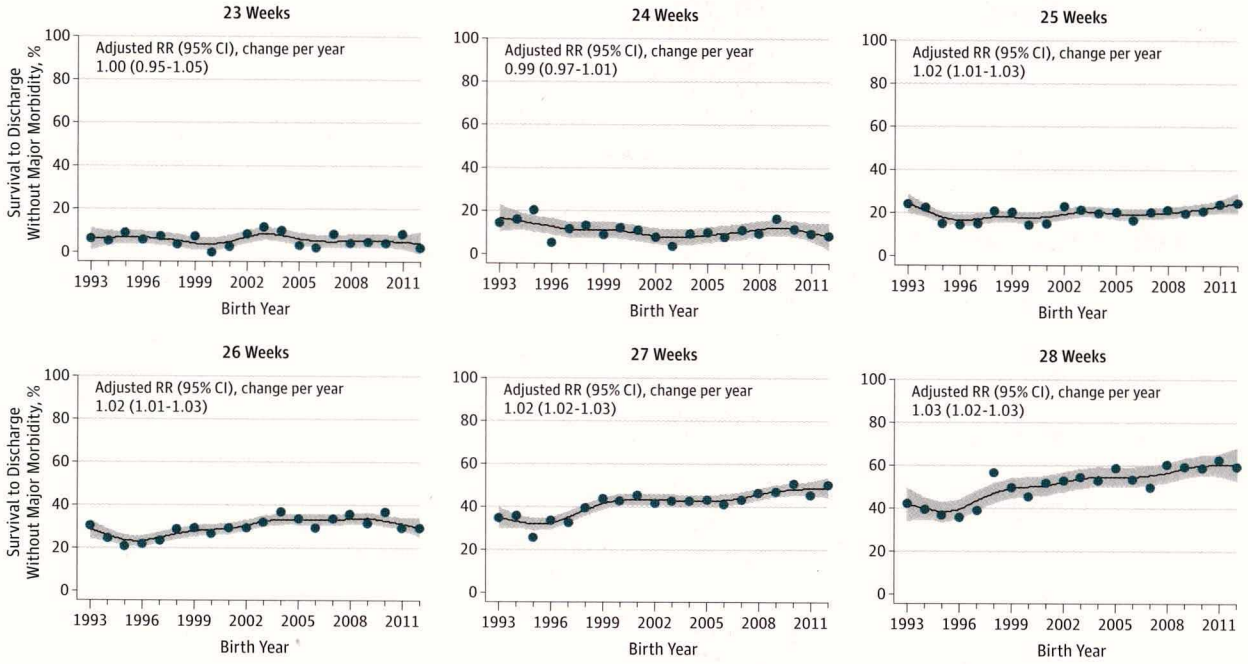
Circles show the percent of infants born each year who survived to discharge, a smoothed curve shows the trend, and shading indicates a 95% CI for the curve. Shading is not visible where CIs are close to values on the curve. Percentages are among all infants, including those who died at 12 hours of age or less. Relative risks (RRs) for the change per year were adjusted for study center, maternal race/ethnicity, infant gestational age, small size for gestational age, and sex. Survival trends did not vary significantly by gestational age from 1993-2008 (year-gestational age interaction, $P = .46$), with no significant change in survival ($P = .90$), but varied by gestational age from 2009-2012 (year-gestational age interaction, $P < .001$). Therefore, RRs are shown for 2009 through 2012 only. Total number of infants (mean [range] per year): 1550 (77 [48-96]) for 22 weeks; 3133 (156 [122-189]) for 23 weeks; 4762 (238 [151-334]) for 24 weeks; 5361 (268 [170-339]) for 25 weeks; 5829 (291 [182-361]) for 26 weeks; 6627 (331 [204-399]) for 27 weeks; and 7374 (368 [275-430]) for 28 weeks.

not needed.[35-38] Given earlier studies linking infection to increased risk of impairment, decreased rates of late-onset sepsis may contribute to improved long-term outcomes for extremely preterm infants.[39] Rates of ROP decreased for infants born at 25 through 28 weeks and may be related to changes in oxygen use in the delivery room and oxygen saturation targets or to improved adherence to oxygen targets at NRN hospitals during and after the SUPPORT trial (2005-2009).[40]

Among infants who survived to 36 weeks' postmenstrual age, BPD rates increased from 2009 through 2012 for infants born at 26 and 27 weeks, with significant increases for infants 22 through 27 weeks born in the 8 centers in the NRN all 20 years. This may partly be explained by increased active resuscitation, intensive care, and increased survival, especially for the most immature infants. The effect of decreased intubation/ventilation and decreased postnatal corticosteroid use in our population is unclear, although recent meta-analyses suggest that increased early CPAP with reduced intubation/ventilation has a modest effect in reducing BPD,[41] while decreased use of postnatal steroids increases BPD risk.[42]

Strengths of this study are the large number of infants and rigorous prospective data collection. However, the study has several limitations. The NRN cohort is hospital-based rather than population-based. Although large, our cohort is not representative of the entire US preterm population, but rather, a selected preterm population from academic centers. Although infants who died within 12 hours were included in the analyses of survival, we collected limited information on these infants and thus could not include

Figure 4. Infant Survival to Discharge Without Major Morbidity by Birth Year and Gestational Age



Major morbidity was defined as one or more of necrotizing enterocolitis, infections (early-onset sepsis, late-onset sepsis, or meningitis), bronchopulmonary dysplasia (BPD), severe intracranial hemorrhage (ICH), periventricular leukomalacia (PVL), and retinopathy of prematurity (ROP) of stage 3 or greater. Circles show the percent of infants who survived without major morbidity each year, the smoothed curve shows the trend, and shading indicates a 95% CI for the curve. Percentages are among infants who survived to discharge, excluding those not adequately evaluated for major morbidity. Infants born at gestational age 22 weeks are not shown because only 99 of 1550 survived to discharge and only 5 survived without major morbidity. Relative risks (RRs) for the change per year were adjusted for study center, maternal race/ethnicity, infant gestational age, small size for gestational age, and sex. Trends varied by gestational age (year-gestational age interaction, $P = .01$). Total number of infants [mean (range) per year]: 877 (43 [33-69]) for 23 weeks; 2706 (135 [75-183]) for 24 weeks; 4007 (200 [119-249]) for 25 weeks; 4900 (245 [155-313]) for 26 weeks; 5902 (295 [184-350]) for 27 weeks; and 6808 (340 [256-405]) for 28 weeks.

them in analyses of morbidities. Although the registry's manual of operations provides detailed definitions, we were unable to evaluate potential diagnostic variabilities across sites (eg, differences in reading cranial ultrasounds or interpreting ophthalmologic examinations). We presented epidemiologic associations and changes over time, but registry data and the cohort design do not provide definitive reasons for the changes observed.

Although the NRN conducts developmental follow-up on a subset of infants included in the registry, follow-up data are not included in this study. We reported only modest declines in severe ICH and PVL, early markers of brain injury. Given the long-term goal of intact survival and a healthy neurodevelopmental trajectory, it is critical to develop neuroprotective and neuropromoting "brain care bundles," similar to infection-reduction approaches. Attention to optimal nutrition, limitation of invasive procedures, pain management, infection-control practices, and reduction of other inflammatory conditions may also promote healthy neurodevelopment.

Despite improvements in survival, medical science may have reached the limits of what current technologies can provide. Ongoing studies are addressing whether sequencing the genome can provide useful information beyond current newborn screening to accelerate diagnoses and improve care. Other novel areas that warrant further study include advanced brain imaging to better understand injury, repair, and growth; minimally invasive delivery of aerosolized surfactant; tissue-engineering and regenerative medicine; and selected growth factors and cellular therapies.

Although survival of extremely preterm infants has increased over the past 2 decades, including survival without major morbidity, the individual and societal burden of preterm birth remains substantial,[43] with approximately 450 000 neonates born prematurely in the United States each year.[44] To truly affect newborn outcomes, a comprehensive and sustained effort to reduce the high rates of preterm birth is necessary.

Conclusions

Among extremely preterm infants born at US academic centers over the last 20 years, changes in maternal and infant care practices and modest reductions in several morbidities were observed, although BPD increased. Survival increased most markedly among infants born at 23 and 24 weeks' gestation and survival without major morbidity increased for infants born at 25 through 28 weeks' gestation. These findings are valuable in counseling families and developing novel interventions.

ARTICLE INFORMATION

Author Affiliations: Department of Pediatrics, Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, Georgia (Stoll, Hale); Social, Statistical, and Environmental Sciences Unit, RTI International, Research Triangle Park, North Carolina (Hansen); Department of Pediatrics, University of Iowa, Iowa City (Bell); Department of Pediatrics, Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland, Ohio (Walsh, Newman); Division of Neonatology, University of Alabama at Birmingham (Carlo); Department of Pediatrics, Wayne State University, Detroit, Michigan (Shankaran); Department of Pediatrics, Women and Infants Hospital, Brown University, Providence, Rhode Island (Laptook); Center for Perinatal Research, Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University, Columbus (Sánchez); Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, California (Van Meurs, Ball); Lucile Packard Children's Hospital, Palo Alto, California (Van Meurs, Ball); Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas (Wyckoff); Social, Statistical, and Environmental Sciences Unit, RTI International, Rockville, Maryland (Das); Perinatal Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio (Schibler); Department of Pediatrics, Indiana University School of Medicine, Indianapolis (Poindexter); Department of Pediatrics, University of Texas Medical School at Houston (Kennedy); Department of Pediatrics, Duke University, Durham, North Carolina (Cotten); University of New Mexico Health Sciences Center, Albuquerque (Watterberg); University of Rochester School of Medicine and Dentistry, Rochester, New York (D'Angio); Department of Pediatrics, University of Pennsylvania, Philadelphia (DeMauro); Department of Pediatrics, Children's Mercy Hospital, Kansas City, Missouri (Truog); Department of Pediatrics, University of California, Los Angeles (Devaskar); *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland (Higgins).

Author Contributions: Dr Das had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Stoll, Poindexter, Devaskar, Higgins.
Acquisition, analysis, or interpretation of data: Stoll, Hansen, Bell, Walsh, Carlo, Shankaran, Laptook, Sanchez, Van Meurs, Wyckoff, Das, Hale, Ball, Newman, Schibler, Poindexter, Kennedy, Cotten, Watterberg, D'Angio, DeMauro, Truog, Higgins.
Drafting of the manuscript: Stoll, Hansen, Laptook, Van Meurs, Wyckoff.
Critical revision of the manuscript for important intellectual content: Bell, Walsh, Carlo, Shankaran, Sanchez, Van Meurs, Wyckoff, Das, Hale, Ball, Newman, Schibler, Poindexter, Kennedy, Cotten, Watterberg, D'Angio, DeMauro, Truog, Devaskar, Higgins.
Statistical analysis: Stoll, Hansen, Das.
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Study supervision: Stoll, Shankaran, Wyckoff, Das, Schibler, Kennedy, Higgins.

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Group Information: Dr Stoll, principal investigator (PI), Emory University; oversaw enrollment (2146 infants in this study). Dr Bell, PI, University of Iowa; oversaw enrollment at the site (546 infants). Dr Walsh, PI, Case Western Reserve University; oversaw enrollment (1857 infants). Dr Carlo, PI, University of Alabama at Birmingham; oversaw enrollment (2632 infants). Dr Shankaran, PI, Wayne State University; oversaw enrollment (2317 infants). Dr Laptook, PI, Brown University; oversaw enrollment (2221 infants). Dr Sánchez, PI, Nationwide Children's Hospital; oversaw enrollment (206 infants). Dr Van Meurs, PI, Stanford University; oversaw enrollment (1400 infants). Dr Wyckoff, PI. University of Texas Southwestern Medical Center; oversaw enrollment (2141 infants). Dr Das, PI, Neonatal Research Network (NRN) Data Coordinating Center. Ms Hale, research coordinator, Emory University; enrolled 2146 infants. Ms Ball, research coordinator, Stanford University; enrolled 1400 infants. Ms Newman, research coordinator, Case Western Reserve University; enrolled 1857 infants. Dr Schibler, PI, University of Cincinnati; oversaw enrollment (3496 infants). Dr Poindexter, PI, Indiana University; oversaw enrollment (2658 infants). Dr Kennedy, PI, University of Texas Medical School at Houston; oversaw enrollment (2038 infants). Dr Cotton, PI, Duke University; oversaw enrollment (1288 infants). Dr Watterberg, PI, University of New Mexico; oversaw enrollment (871 infants). Dr D'Angio, PI, University of Rochester; oversaw enrollment (666 infants). Dr DeMauro, site investigator, University of Pennsylvania; oversaw enrollment (218 infants). Dr Truog, PI, Children's Mercy Hospital; oversaw enrollment (83 infants). Dr Devaskar, PI, University of California—Los Angeles; oversaw enrollment (47 infants). Dr Higgins, program scientist for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) NRN; helped develop the protocol, oversaw compliance, and assisted with data edits from the sites. Members of the Generic Database Subcommittee include Drs Stoll (chair), Bell, Walsh (vice chair) Carlo, Shankaran, Laptook, Sánchez, Wyckoff, Das, and Higgins; and Mss Hale, Ball, and Newman.

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Teresa Chanlaw, MPH; Rachel Geller, RN, BSN. University of California—San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461): Neil D. Finer, MD; Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Wade Rich, BSHS, RRT; Kathy Arnell, RNC; Clarence Demetrio, RN; Christopher Henderson, AS, CRTT. University of Iowa and Mercy Medical Center (U10 HD53109, M01 RR59, UL1 TR442): Tarah T. Colaizy, MD, MPH; John A. Widness, MD; Dan L. Ellsbury, MD; Karen J. Johnson, RN, BSN; Donia B. Campbell, RNC-NIC. University of Miami, Holtz Children's Hospital (U10 HD21397, M01 RR16587): Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN. University of New Mexico Health Sciences Center (U10 HD53089, U10 HD27881, M01 RR997, UL1 TR41): Robin K. Ohls, MD; Conra Backstrom Lacy, RN. University of Pennsylvania, Hospital of the University of Pennsylvania, Pennsylvania Hospital, and Children's Hospital of Philadelphia (U10 HD68244): Barbara Schmidt, MD, MSc; Haresh Kirpalani, MB, MSc; Aasma S. Chaudhary, BS, RRT; Toni Mancini, RN, BSN, CCRC; Dara M. Cucinotta, RN. University of Rochester Medical Center, Golisano Children's Hospital, and the University of Buffalo Women's and Children's Hospital of Buffalo (U10 HD68263, U10 HD40521, M01 RR44, UL1 TR42): Dale L. Phelps, MD; Ronnie Guillet, MD, PhD; Satyan Lakshminrusimha, MD; Linda J. Reubens, RN, CCRC; Holly I.M. Wadkins; Michael G. Sacilowski, BS; Erica Burnell, RN; Ashley Williams, MSEd. University of Tennessee Health Science Center (U10 HD21415): Sheldon B. Korones, MD; Tina Hudson, RN, BSN. University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633): Luc P. Brion, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Diana M. Vasil, RNC-NIC; Alicia Guzman; Gaynelle Hensley, RN; Melissa H. Leps, RN; Nancy A. Miller, 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): Jon E. Tyson, MD, MPH; Georgia E. McDavid, RN; Esther G. Akpa, RN, BSN; Beverly Foley Harris, RN, BSN; Claudia I. Franco, RNC, MSN; Anna E. Lis, RN, BSN; Sara C. Martin, RN, BSN; Patricia Ann Orekoya, RN, BSN; 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, UL1 TR105): Roger G. Faix, MD; Bradley A. Yoder, MD; Karen A. Osborne, RN, BSN, CCRC; Jennifer J. Jensen, RN, BSN; Cynthia Spencer, RNC; Kimberlee Weaver-Lewis, RN, BSN. Wake Forest Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122): T. Michael O'Shea, MD, MPH; Robert G. Dillard, MD; Nancy J. Peters, RN, CCRP. Wayne State University, University of Michigan, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385): Beena G. Sood, MD, MS; Athina Pappas, MD; John Barks, MD; Rebecca Bara, RN, BSN; Maria Batts, RRT; Elizabeth Billian, RN, MBA; Shelley Hendel, AD; Kimberly Hayes-Hart, RN, MSN, NNP-BC; Mary E. Johnson, RN, BSN; Geraldine Muran, RN, BSN; Carolyn Rosman, RN; Kara Sawaya, RN, BSN; Laura Sumner, RN, BSN; Mary Christensen, RT; Stephanie A. Wiggins, MS. Yale University, Yale-New Haven Children's Hospital (U10 HD27871, M01 RR6022, UL1 TR142): Richard A. Ehrenkranz, MD; Monica Konstantino, RN, BSN; Matthew Bizzarro, MD; Patricia Gettner, RN; JoAnn Poulsen, RN; Janet Taft, RN, BSN; Joanne Williams, RN, BSN.

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