ORIGINAL ARTICLE

Changes in mortality and morbidities among infants born at less than 25 weeks during the post-surfactant era

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Objectives: To compare mortality and death or major morbidity (DOMM) among infants <25 weeks estimated gestational age (EGA) born during two post-surfactant era time periods.

Study design and patients: Comparative cohort study of very low birthweight (501–1500 g) infants <25 weeks EGA in the NICHD Neonatal Research Network born during two post-surfactant era time periods (group I, 1991–1994, n = 1408; group II, 1995–1998, n = 1348). Perinatal and neonatal factors were compared, and group related mortality and DOMM risk were evaluated.

Results: Mortality was higher for group I (63.1% v 56.7%; p = 0.0006). Antenatal steroids (ANS) and antenatal antibiotics (AABX), surfactant (p<0.0001), and bronchopulmonary dysplasia (p = 0.0008) were more prevalent in group II. In a regression model that controlled for basic and delivery factors only, mortality risk was greater for group I than for group II (odds ratio (OR) 1.4, 95% confidence interval (CI) 1.2 to 1.7); the addition of AABX and surfactant, or ANS (OR 0.97, 95% CI 0.79 to 1.2) to the model appeared to account for this difference. There was no difference in DOMM (86.8% v 88.4%; p = 0.2), but risk was lower for group I in regression models that included ANS (OR 0.70, 95% CI 0.52 to 0.94).

Conclusion: Survival to discharge was more likely during the more recent period because of group differences in ANS, AABX, and surfactant. However, this treatment shift may reflect an overall more aggressive management approach. More consistent application of treatment has led to improving survival of <25 week EGA infants during the post-surfactant era, but possibly at the cost of greater risk of major in-hospital morbidities.

Advances in perinatal and neonatal care, particularly use of antenatal steroids and surfactant, contributed to improved survival among very low birthweight infants from the 1980s to the early 1990s.[1–5] The National Institute of Child Health and Human Development (NICHD) Neonatal Research Network reported further decreases in mortality from 1991 to 1996, but increased major morbidity, particularly bronchopulmonary dysplasia (BPD), among the smallest survivors.[1] Other investigators have reported relatively unchanging mortality among infants with birth weight less than 800 g and estimated gestational age (EGA) <26 weeks over the past several years,[6] suggesting that opportunities for improved survival in this population may be exhausted with current technologies and management approaches.

Although studies have often reported outcomes in terms of birth weight, many clinicians rely on gestational age when considering viability and counselling families. Obstetrical estimates of gestational age predict survival at least as well as, if not better than, birth weight.[7 8] Unfortunately, available outcome data vary for infants at the cusp of viability.[9–13] Yet, enormous and arguably disproportionate resources are expended in the rescue and care of these extremely preterm infants.[14 15]

The degree to which continued improvement in mortality and morbidity can be achieved for infants less than 25 weeks EGA during the post-surfactant era is not well described. We therefore undertook a comparative cohort study of infants <25 weeks EGA in the NICHD Neonatal Research Network, examining mortality and death or major morbidity (DOMM) during two post-surfactant era time periods.

METHODS AND PATIENT POPULATION
Patient selection and definitions
This was a comparative cohort analysis of infants born in the post-surfactant era at <25 weeks EGA and birth weight 501–1500 g in the NICHD Neonatal Research Network Very

Low Birthweight Registry. Group I included infants born from 1 January 1991 through to 31 December 1994. Group II included infants born from 1 January 1995 through to 31 December 1998. Time frames were chosen to compare the earliest and subsequent post-surfactant periods; the US Food and Drug Administration approved Exosurf Neonatal (colfosceril) in 1990, and Survanta (beractant) in 1991. Twelve centres participated in prospective data collection from 1991 through 1996, and 14 centres participated from 1996 through 2001 (see the appendix). Only data from centres participating during both periods were used. The institutional review boards at each centre reviewed the data collection procedures. Infants were included in the Very Low Birthweight Registry if they were live born but died in the delivery room of a Network centre, or were admitted to a Network centre within 14 days of birth, if birth weight was 501–1500 g during 1991–1992, and 401–1500 g during 1993–1998. Because of this discrepancy, only data of infants 501–1500 g were analysed.

Research nurses collected data at each centre using definitions developed by the investigators.[16 17] Definitions were consistent throughout the entire study period. Data were collected until death, discharge, or 120 days; after 120 days, or if the patient was transferred, data were collected on death or discharge home. Antenatal antibiotics (AABX) was defined as administration of any antibiotics to the mother during the admission that resulted in delivery. Antenatal steroids (ANS) was defined as administration of any corticosteroids to accelerate fetal lung maturity. A "complete ANS course" was two doses of betamethasone 12–24 hours apart, or four doses of dexamethasone six hours apart. Gestational age in completed weeks was determined by

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Table 1 Basic information and statistical comparisons for infants of less than 25 weeks estimated gestational age in the Neonatal Research Network in group I (birth from 1 January 1991 to 31 December 1994) and group II (birth 1 January 1995 to 31 December 1998)

	Group I (n = 1408)	Group II (n = 1348)	p Value
Birth weight (g)*	645 (108)	645 (101)	NS
Male (%)	54.4	54.3	NS
Race			<0.0001
White (%)	27.5	32.6	
Black (%)	60	49.3	
Hispanic (%)	10.7	15.6	
Inborn (%)	88.9	89.1	NS
EGA†			0.0064
<22	45 (3.2)	24 (1.8)	
22	174 (12.3)	130 (9.6)	
23	473 (33.6)	453 (33.6)	
24	716 (50.9)	741 (55.0)	

*Values are mean (SD).
†EGA, estimated gestational age in weeks, with results presented as total number of patients within the group in the particular EGA category followed by % of group in parentheses.
NS, Not significant by χ^2 test; significance was assigned at p<0.05.

Table 2 Perinatal and early neonatal characteristics treatments of infants less than 25 weeks estimated gestational age in the Neonatal Research Network in group I (birth from 1 January 1991 to 31 December 1994) and group II (birth 1 January 1995 to 31 December 1998)

|	Group I (n = 1408)	Group II (n = 1348)	p Value
ANS	13.4	54.6	<0.0001
Complete ANS	7.4	31.4	<0.0001
Antenatal antibiotics	39.2	67.8	<0.0001
ROM >24 h	26.0	26.8	NS
Multiple gestation	17.1	19.4	NS
Caesarean section	19.5	26.3	<0.0001
Apgar ⩽3 at 1 min	72.7	62.5	<0.0001
Apgar ⩽3 at 5 min	39.4	35.1	0.02
Surfactant	58.2	68.6	<0.0001

ANS, Antenatal steroid treatment; ROM, rupture of membranes before delivery; Surfactant, any surfactant given at any time; NS, not significant by χ^2 test; significance was assigned at p<0.05.

best obstetric estimate using last menstrual period, standard obstetric parameters, and ultrasonography. If there was a two week range of gestational age among obstetric estimates, the lowest estimate was used. If the range was ⩾3 weeks, or if several estimates existed, the median estimate of gestational age was used. Surfactant therapy was any surfactant given at any time. For some later neonatal treatments and morbidities, data were only collected if infants survived >12 hours. Patent ductus arteriosus was defined by echocardiography or by clinical evidence. Intraventricular haemorrhage was reported according to the classification of Papile et al.[18] "Early sepsis" was culture proven septicaemia or bacteraemia at ⩽72 hours, and "late sepsis" at >72 hours. Necrotising enterocolitis was defined as Bell's classification stage II or greater. Cystic periventricular leucomalacia diagnosis was by head ultrasound performed after two weeks of life. BPD was defined as receiving supplemental oxygen at 36 weeks postmenstrual age by best obstetric estimate. Postnatal steroids was defined as any steroid given during the hospital stay for prevention or treatment of BPD. "Major morbidity" was one or more of necrotising enterocolitis, intraventricular haemorrhage grade 3 or 4, cystic periventricular leucomalacia, or BPD.

Statistical analysis
Univariate analyses were performed using χ^2 analysis and Student's t test. Multivariate analysis was by regression analysis. Regression models were developed to evaluate group related risk for the outcomes (a) mortality and (b)

DOMM, with adjustment for basic, perinatal, and early neonatal factors. For each outcome, "model I" covariates included Network centre, group, sex, multiple gestation, inborn or outborn, caesarean section, race, gestational age, and birth weight. Further regression models included AABX, ANS, and surfactant treatment added separately, and in combination, as covariates. The rationale for this approach was that, if adjusted risk for group I versus group II changed with the addition of perinatal or early neonatal treatments, the potential benefits of those treatments would be differentiated. Other later treatments were not added to the models because the focus of these analyses was on early treatments. Also, data on later factors were not collected for patients who died before 12 hours; addition of these factors would thus have selected for a later surviving subpopulation.
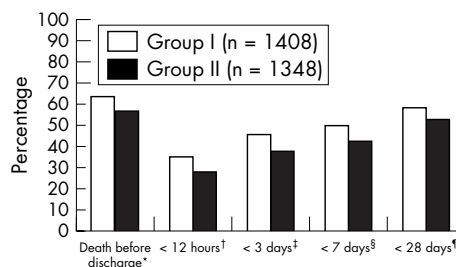
Figure 1 Percentage mortality by group and time to death. *p = 0.0006, †p<0.0001, ‡p = 0.0001, ¶p = 0.002 (χ^2 test).

Table 3 In-hospital morbidities among infants surviving >12 hours in group I (birth from 1 January 1991 to 31 December 1994) and group II (birth from 1 January 1995 to 31 December 1998)

	Group I (n = 917)	Group II (n = 974)	p Value
PDA	57.0	54.4	NS
NEC	7.3	9.9	0.049
Early sepsis	3.4	3.1	NS
Late sepsis	45.3	44.1	NS
IVH 3/4	35.5	36.0	NS
cPVL	10.5	7.5	0.0546
BPD	50.1	60.0	0.0008
PNS	41.1	57.7	<0.0001

Values are percentages. n = 917 for group I and n = 974 for group II, except for IVH (836 and 912), cPVL (598 and 707), and BPD (541 and 597).
PDA, Patent ductus arteriosus; IVH 3/4, intraventricular haemorrhage grade 3 or 4; cPVL, cystic periventricular leucomalacia; BPD, bronchopulmonary dysplasia; PNS, postnatal steroids.

Table 4 Adjusted risk of mortality in group I compared with group II using regression model I with addition of antenatal antibiotics (AABX), antenatal steroids (ANS), and surfactant, separately and in combination, as covariates

Model covariates	OR (95% CI)	p Value
Model I	1.40 (1.2 to 1.7)	<0.0001
+AABX	1.20 (1.0 to 1.5)	0.02
+Surfactant	1.30 (1.1 to 1.6)	0.003
+AABX+surfactant	1.10 (0.95 to 1.4)	0.17
+ANS	0.97 (0.79 to 1.2)	0.75
+ANS+AABX	0.92 (0.75 to 1.1)	0.43
+ANS+surfactant	0.91 (0.74 to 1.1)	0.39
+ ANS+AABX +surfactant	0.87 (0.70 to 1.1)	0.18

Group I, birth from 1 January 1991 to 31 December 1994; group II, birth from 1 January 1995 to 31 December 1998.

RESULTS

Basic, perinatal, and early neonatal descriptors

Table 1 presents basic information on the study infants. There were 1408 infants in group I and 1348 in group II. Group differences existed in racial and gestational age distribution.

Table 2 presents perinatal and early neonatal characteristics of the groups. Significantly greater proportions of group II infants were exposed to ANS and AABX, delivered by caesarean section, and treated with surfactant. Apgar score ≤3 at one minute or at five minutes was more likely in group I.

Group comparisons: mortality and DOMM

In group I, 889 infants died before discharge (63.1%) compared with 764 infants in group II (56.7%; p = 0.0006).

Figure 1 presents comparisons of group mortality by time to death. There were significant group differences at 12 hours, three days, seven days, and 28 days. However, analysis of only those infants who survived >12 hours (group I, n = 917; group II, n = 974) revealed no significant differences in percentage survival between group I and II at any time point (at three days, 83.0% *v* 86.3%, p = 0.06; at seven days, 77.6% *v* 80.1%, p = 0.21; at 28 days, 64.2% *v* 66.3%, p = 0.37; before discharge, 56.5% *v* 59.9%, p = 0.14). Analysis of percentage of total deaths attained by specific time points revealed differences between groups I and II at 12 hours (55.0% *v* 48.8%, p = 0.01) and three days (72.6% *v* 66.4%, p = 0.007), but not at time points after three days. Deaths after 28 days accounted for only 8.1% of deaths in group I, and 8.3% of deaths in group II.

In group I, 80% (36/45) of infants <22 weeks EGA died before discharge, 86.2% (150/174) of infants 22 weeks EGA, 72.3% (342/473) of infants 23 weeks EGA, and 50.4% (361/716) of infants 24 weeks EGA. In group II, 95.8% (23/24) of infants <22 weeks EGA died before discharge, 83.8% (109/

130) of infants 22 weeks EGA, 67.5% (306/453) of infants 23 weeks EGA, and 44.0% (326/741) of infants 24 weeks EGA.

The incidence of DOMM was 86.8% (1206/1389) in group I and 88.4% (1175/1329) in group II (p = 0.23).

Later morbidities among infants surviving >12 hours (table 3)

Among infants who survived for more than 12 hours (table 3), the incidence of necrotising enterocolitis, BPD, and postnatal steroid treatment was greater in group II. Patient deaths before observation of the morbidity accounted for most of the missing expected data points in late morbidities. For instance, for BPD, 99.8% of the missing expected data points were patients who died before a diagnosis could be made.

Death before discharge: logistic regression analyses (table 4)

Regression analyses were performed to determine any potential adjusted survival benefit to group membership (table 4). In model I, group I was at significantly increased risk of death before discharge (OR 1.4, 95% CI 1.2 to 1.7). However, in model I + AABX + surfactant, and in any model that included ANS, the risk of death before discharge was not different between the groups, suggesting that those treatments may in part be responsible for increased survival in group II. In the full regression model, inborn status was not an independent risk factor for death (OR 1.16, 95% CI 0.85 to 1.56).

DOMM: logistic regression analyses (table 5)

In regression model I, as well as model I + AABX, or + surfactant, or + AABX + surfactant, no group related risk of DOMM was noted (table 5). However, in all regression models that included ANS, group I was associated with a significantly lower risk of DOMM. This suggests that

Table 5 Adjusted risk of death or major morbidity in group I compared with group II using regression model I with addition of antenatal antibiotics (AABX), antenatal steroids (ANS), and surfactant, separately and in combination, as covariates

Model covariates	OR (95% CI)	p Value
Model I	0.90 (0.69 to 1.2)	0.41
+AABX	0.86 (0.66 to 1.1)	0.26
+Surfactant	0.89 (0.68 to 1.1)	0.36
+AABX+surfactant	0.85 (0.65 to 1.1)	0.22
+ANS	0.70 (0.52 to 0.94)	0.02
+ANS+AABX	0.70 (0.52 to 0.94)	0.02
+ANS+surfactant	0.69 (0.51 to 0.93)	0.01
+ANS+AABX+surfactant	0.69 (0.51 to 0.93)	0.01

Group I, birth from 1 January 1991 to 31 December 1994; group II, birth from 1 January 1995 to 31 December 1998.

treatments associated with decreased mortality in this extremely high risk population may result in survivors at higher risk of secondary morbidities. In the full regression model, inborn patients were at reduced risk of DOMM (OR 0.46, 95% CI 0.26 to 0.83).

DISCUSSION

This study evaluated survival and major in-hospital morbidities of infants <25 weeks EGA and 501–1500 g birth weight in the NICHD Neonatal Research Network during two post-surfactant time periods. Mortality was high for both groups, but higher for group I in unadjusted comparison. In regression model I, the risk of death was significantly greater for group I, but there was no significant group related risk difference in models that included AABX+surfactant, or ANS. Furthermore, although there was no unadjusted group difference in DOMM, group II was at significantly greater risk in regression models that included ANS as a covariate. These findings suggest that some treatments, particularly ANS, more often applied in the later time period, are associated with the increased survival noted among extremely premature infants in the more recent time period. However, not surprisingly, the resulting surviving population may be at higher risk for major in-hospital morbidity.

Timing of death was examined. Comparison of mortality by group and time to death (fig 1) indicated a highly significant difference between the groups at <12 hours, which persisted throughout the subsequent time points. This early advantage to survival for group II is of considerable import: when only those infants surviving >12 hours were analysed, no significant mortality differences between groups were found at subsequent time points. This finding may be in part attributable to better condition at birth, reflected by the significantly lower proportion of infants in group II with Apgar scores ≤3 at one and five minutes. This, in turn can be explained by increased use of ANS during the more recent period, a therapeutic shift possibly driven by the 1994 NIH Consensus Statement.[19] However, other intangible factors are likely to have played a role. Shankaran et al[20] showed that a lack of aggressive prenatal and neonatal intervention was associated with a significantly increased risk of death at <12 hours in infants 501–1000 g. These data support the notion that physician perception of outcome may play an important role in determining patient survival. Obstetricians, paediatricians, and neonatologists have been shown to underestimate survival and handicap-free survival,[21–23] possibly leading to alterations in physician behaviour with respect to management. In this study, a smaller proportion of infants in group I was exposed to ANS or AABX, delivered by caesarean section, or received surfactant compared with group II. In addition, the reduction of <12 hour deaths in group II accounted for the significant difference in mortality between groups. The reasons for these discrepancies are likely

to be multifactorial, but may have been influenced by a more optimistic consideration of extremely preterm infant outcomes during the more recent time period.

A significant advantage to survival for group II was shown in regression model I, but group related risk was similar in models that adjusted for AABX and surfactant, or ANS. This finding underscores differences in ANS use between the periods, and reinforces the benefit to survival with ANS.[24] However, although the group related risk for DOMM was similar in model I, group II was at higher risk if ANS treatment was added as a covariate. This suggests that the benefit to survival achieved through perinatal and early neonatal treatments may result in a more vulnerable group, at higher risk of major morbidity. Consistent with other studies,[6] the single most striking increase in morbidity between time periods was in BPD. Given previous data showing an association of morbidities such as BPD with later neurodevelopmental abnormalities,[25–29] it might be speculated that infants in group II would be at higher risk of impairment. But in-hospital morbidity may not be a strong predictor of long term outcome, which is influenced by a multitude of other circumstances.[25 26 30–32] Of note, postnatal steroid use, which has also been linked with neurological and developmental delay,[33 34] was higher in group II. It is not known whether increased postnatal steroid use in group II was indicative of a broader change in management approach, or of an overall more tenuous clinical condition observed during that period.

It has been suggested that, as improvements in perinatal and neonatal management and technology proceed, overall mortality among preterm infants will not change, but deaths will be substantially "delayed" after multiple failed interventions.[35 36] Our analysis does not support this theory. The proportion of group deaths attained by 28 days was nearly identical at about 92%, which compares well to the results of Philip.[3]

There are limitations to this analysis. Only infants of birth weight >500 g were included because data were available for this population throughout the entire study period. Also, recent studies have shown that outcomes of 401–500 g birth weight infants may be uniquely poor; approach to management could differ greatly from that of larger extremely preterm infants.[37 38] Separate analyses may thus be more appropriate for that birthweight subgroup. Data on stillbirths within participating centres and deaths at referring hospitals were not collected. It should therefore be stated that absolute survival statistics are likely to be overestimated. Group inequality in condition at birth is suggested by a higher proportion of group I infants with Apgar score ≤3 at one and five minutes; the reasons may include differences in perinatal management and EGA distribution. CRIB (clinical risk index for babies) or SNAP (score for neonatal acute physiology) data were not prospectively collected, but adjustments were made in our analyses for other variables that could contribute

to group differences in severity of illness. In addition, there might have been alternative approaches to regression model development. We evaluated AABX, ANS, and surfactant, rather than later factors, both because these early treatments were likely to have the greatest effect on neonatal outcome, and because data were collected from the time of delivery. Caesarean section might have been added as a subsequent "step" rather than in model I; however, choice of delivery mode could have been driven by factors other than physician decision. The definition of BPD may also be criticised; the pathophysiology of BPD may have changed over the years, and many criteria for BPD have been suggested.[39] Nonetheless, definitions remained consistent throughout the study periods.

In summary, this analysis of mortality and in-hospital morbidity in infants <25 weeks EGA in the NICHD Neonatal Research Network during two post-surfactant time periods shows a significantly decreased mortality during the more recent time period. Results of regression analysis suggest that treatments more often used in group II, particularly ANS, may be responsible for this improvement. It is also possible that use of such treatments merely reflects a more aggressive overall approach to management of the extremely preterm infant, and that unmeasured factors or later interventions may also help to explain improved survival. Not surprisingly, increased use of these life saving treatments and approaches in this vulnerable population may result in survivors who are at higher risk of significant in-hospital morbidities, particularly BPD. The implications of these findings for changes in neurodevelopmental outcomes remain to be clarified.

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APPENDIX

NICHD NEONATAL NETWORK VERY LOW BIRTHWEIGHT REGISTRY CENTRES 1991–2001

- Alan Jobe, MD Chairman
- Case Western Reserve University 1991–2001 (U10 HD21364)

  – Avroy A Fanaroff, MB, BCh
  – Nancy Newman, RN

- University of Texas-Dallas 1991–2001 (U10 HD21373)

  – Jon E Tyson, MD, MPH
  – Susie Madison, RN

- Wayne State University 1991–2001 (U10 HD21385)

  – Seetha Shankaran, MD
  – Geraldine Muran, RN

- University of Tennessee 1991–2001 (U10 HD21415)

  – Sheldon B Korones, MD
  – Tina Hudson, RN

- University of Miami 1991–2001 (U10 HD21397)

  – Charles R Bauer, MD
  – Amy Mur Worth, RN, MSN

- Emory University 1991–2001 (U10 HD27851)

  – Barbara J Stoll, MD
  – Ellen Hale, RN

- University of New Mexico 1991–2001 (U10 HD27881; M01 RR 00997)

  – Lu-Ann Papile, MD
  – Conra Backstrom, RN

- University of Cincinnati 1991–2001 (U10 HD27853; M01 RR 08084)

  – Edward F Donovan, MD
  – Marcia Mersman, RN

- Indiana University 1991–2001 (U10 HD27856; M01 RR 00750)

  – James A Lemons, MD
  – Diana Appel, RN

- Yale University 1991–2001 (U10 HD27871; M01 RR 06022)

  – Richard A Ehrenkranz, MD
  – Patricia Gettner, RN

- Brown University 1991–2001 (U10 HD27904)

  – William Oh, MD
  – Angelita Hensman, RN

- Stanford University 1991–2001 (U10 HD27880; M01 RR 00070)

  – David K Stevenson, MD
  – M Bethany Ball, CCRC

- University of Alabama-Birmingham 1996–2001 (U10 HD34216)

  – Waldemar A Carlo, MD
  – Monica Collins, RN

- Harvard University 1996–2000 (U10 HD34167; M01 RR02635; M01 RR 02172; M01 RR02032)

  – Ann R Stark, MD
  – Kerri Fournier, RN

- National Institute of Child Health and Human Development

  – Linda L Wright, MD
  – Elizabeth McClure, Med

- Research Triangle Institute, Inc 1998–2001 (U01 HD36790)

  – W Kenneth Poole, PhD
  – Betty Hastings

- George Washington University 1991–1998 (U01 HD 19897)

  – Joel Verter, PhD
  – Tonya Powers

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