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Intensive Care for Extreme Prematurity — Moving Beyond Gestational Age

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Abstract

Background—Decisions regarding whether to administer intensive care to extremely premature infants are often based on gestational age alone. However, other factors also affect the prognosis for these patients.

Methods—We prospectively studied a cohort of 4446 infants born at 22 to 25 weeks' gestation (determined on the basis of the best obstetrical estimate) in the Neonatal Research Network of the National Institute of Child Health and Human Development to relate risk factors assessable at or before birth to the likelihood of survival, survival without profound neurodevelopmental impairment, and survival without neurodevelopmental impairment at a corrected age of 18 to 22 months.

Results—Among study infants, 3702 (83%) received intensive care in the form of mechanical ventilation. Among the 4192 study infants (94%) for whom outcomes were determined at 18 to 22 months, 49% died, 61% died or had profound impairment, and 73% died or had impairment. In multivariable analyses of infants who received intensive care, exposure to antenatal corticosteroids, female sex, singleton birth, and higher birth weight (per each 100-g increment) were each associated with reductions in the risk of death and the risk of death or profound or any neurodevelopmental impairment; these reductions were similar to those associated with a 1-week increase in gestational age. At the same estimated likelihood of a favorable outcome, girls were less likely than boys to receive intensive care. The outcomes for infants who underwent ventilation were better predicted with the use of the above factors than with use of gestational age alone.

Conclusions—The likelihood of a favorable outcome with intensive care can be better estimated by consideration of four factors in addition to gestational age: sex, exposure or nonexposure to antenatal corticosteroids, whether single or multiple birth, and birth weight. (ClinicalTrials.gov numbers, NCT00063063 and NCT00009633.)

Decisions to initiate or forgo intensive care for extremely premature infants are highly controversial.[1-7] In some centers, intensive care is provided to all very premature infants. In most centers, intensive care is provided selectively on the basis of specific gestational-age thresholds. Such care is likely to be routinely administered at 25 weeks' gestation but may be provided only with parental agreement at 23 to 24 weeks, and only “comfort care” may be given at 22 weeks. The evidence base providing support for these decisions is limited,[5,6] and

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the measurement error in assessing pregnancy length[8-13] may exceed the 1-to-2-week difference in gestational age that often prompts different treatment decisions.[2,3,5,7,14-16]

To facilitate more informed and better justified decisions, we assessed a large cohort of infants born at 22 to 25 weeks' gestation in the Neonatal Research Network of the National Institute of Child Health and Human Development to relate gestational age and other risk factors assessable at or before birth to the likelihood of death or adverse neurodevelopmental outcomes.

Methods

Eligibility Criteria

We assessed infants born in 19 centers of the Neonatal Research Network at 22 to 25 completed weeks[17] of gestation (25 completed weeks are equivalent to 25 weeks 0 days to 25 weeks 6 days of postmenstrual age) between January 1, 1998, and December 31, 2003. We excluded infants with a major anomaly, a birth weight greater than 1000 g or the 97th percentile for gestational age (suggesting that the gestational age was underestimated[9,12]), or a birth weight of less than 401 g (below which few infants receive intensive care). Because we adopted the perspective of a physician deciding whether to initiate mechanical ventilation for infants considered very likely to die otherwise, we excluded the 31 infants who survived without mechanical ventilation (described below).

Risk Factors

We recorded the type of delivery, whether the birth was single or multiple, the child's sex, exposure or nonexposure to antenatal corticosteroid treatment within 7 days before delivery, race or ethnic group assigned by maternal report (black [not Hispanic], white [not Hispanic], Hispanic, or other), and birth weight. On the basis of previous findings,[13] the best obstetrical estimate based on the last menstrual period, early ultrasonographic examination, or other important prenatal findings was used to calculate gestational age, except in unusual circumstances when only an estimate by the pediatrician[18] was available. Details about the mother's menstrual history and ultrasonographic findings were not collected. We considered intensive care to have been provided if mechanical ventilation was initiated. (Nasal continuous positive airway pressure was unlikely to be administered or successfully used to avoid mechanical ventilation at 22 to 25 weeks' gestation.[19])

Outcome Assessments

Research nurses using standardized definitions collected data before discharge. Standardized neurodevelopmental assessments were performed at a corrected age of 18 to 22 months by certified examiners trained in a 2-day hands-on workshop.[20] Neurodevelopmental impairment was defined as a score of 70 or below on either the Psychomotor Developmental Index or the Mental Developmental Index of the Bayley Scales of Infant Development, second edition (on a scale of 50 to 150, with 150 indicating the most advanced development), moderate or severe cerebral palsy,[20] bilateral blindness, or bilateral hearing loss requiring amplification. Profound impairment was defined as a Bayley score below 50 (untestable) or a level of 5 for gross motor function according to the modified criteria of Palisano et al.[21] (on a scale of 0 to 5, with 5 indicating that adult assistance is required to move).[20]

Benefits of Intensive Care

We assessed the percentage of infants with the following prespecified primary outcomes: survival, survival without impairment, and survival without profound impairment. To avoid underestimating the potential benefits of intensive care, the maximum potential percentage of

infants with favorable outcomes, had all infants received intensive care, was estimated. This estimation was calculated with the assumption that the percentage of infants with a potentially favorable outcome among those who had died without undergoing mechanical ventilation would be the same as the percentage of infants in the same risk category who had a favorable outcome and who underwent mechanical ventilation. Because infants who did not undergo ventilation tended to be smaller, sicker, and less mature than infants in the same risk category who underwent ventilation (data not shown), this approach provides an optimistic estimate. This estimate can be considered the upper bound for the maximum potential percentage of study infants with a favorable outcome. These estimates were not intended to indicate the best outcomes achievable under ideal or future circumstances.

Burdens of Intensive Care

We divided the total number of hospital days or ventilator days before death or discharge home by the number of survivors in order to calculate an index of the infant distress, resource use, and costs[22] incurred per survivor. Similar calculations were performed to express the burdens of intensive care per survivor without profound impairment.

We estimated the number of additional hospital or ventilator days that would have been required if all study infants had been given intensive care, assuming that the additional survivors would require no fewer mean days per survivor than infants in the same risk category who were given intensive care. We regard this estimate as being conservative because the infants who died without receiving intensive care tended to be quite small and immature and might well have required more resources per survivor. The additional number of hospital or ventilator days per additional survivor without profound impairment was estimated in a similar manner.

Statistical Analysis

Each outcome for infants who received intensive care was analyzed with the use of a logistic mixed model[23,24] performed with the GLIMMIX procedure in SAS software, version 9.1.2 (SAS Institute). Gestational age, birth weight, sex, exposure or nonexposure to antenatal corticosteroids, and single or multiple birth were selected a priori as predictor variables on the basis of previous studies of extremely premature infants.[6,25-27] Race or ethnic group as described above was unrelated to the three outcomes in bivariable and multivariable analyses and was not included. The type of delivery was also unrelated to death or to either impairment or profound impairment. The center entered the model as a random intercept to adjust for center differences while providing parameter estimates to permit center-free predictions.[21,22] Each completed week of gestation was entered as a categorical variable rather than a continuous variable because the latter resulted in inaccurate estimates of the outcome at 22 and 23 weeks' gestation. A comparison of observed parameter estimates with distributions derived from a bootstrap procedure involving 10,000 resamples provided support for the validity of the final model coefficients. For models of the three main outcomes, the variable estimates were within 0.4 to 2.3% of the median of the bootstrap estimates.

There were no significant interactions between gestational age and other risk factors. Data on infants not examined at 18 to 22 months were excluded from the denominator in analyses including neurodevelopmental impairment but were not excluded in analyses of death alone.

In assessing differences among centers, the expected proportion of infants who underwent ventilation with an adverse outcome was estimated for each center by applying our regression models to the population of infants who underwent ventilation in that center. The ratio of the observed to the expected rate was then calculated for each center.

To compare prognostic assessments based on multiple factors with those based on gestational age alone, we categorized all infants who underwent ventilation into 24 risk groups according to birth weight (≤25th, 26th to 75th, and >75th percentile for gestational age), sex, exposure or nonexposure to antenatal corticosteroids, and single or multiple birth. For each group, the percentage of infants with an unfavorable outcome was predicted with the use of gestational age alone and according to gestational age, birth weight, sex, exposure or nonexposure to antenatal corticosteroids, and single or multiple birth. The observed and estimated rates were then compared. No adjustment for multiple comparisons was performed. Two-sided P values of less than 0.05 were considered to indicate statistical significance. We used our models to develop a simple Web-based tool to estimate the likelihood of a favorable outcome.

Results

The study population of 4446 patients is described in Table 1. The 31 relatively mature infants (0.7%) who were excluded because they survived without mechanical ventilation had a mean gestational age of 24.7 weeks and a birth weight of 765 g; 68% were female; 87% were singletons; and 97% had received antenatal corticosteroids. At 18 to 22 months, none had died; 5 of the 27 examined (19%) had impairment, and none had profound impairment.

As expected, the study infants who did not receive intensive care differed from those who received intensive care with respect to birth weight, gestational age, exposure or nonexposure to antenatal corticosteroids, and type of delivery (Table 1). The groups also differed with regard to race or ethnic group (P = 0.04); the proportion of infants born at 22 and 23 weeks was highest in the centers with the largest population of black infants. No significant difference in race or ethnic group was present after adjustment for gestational age and center (P = 0.74). Among infants who did not survive, the mean (±SD) age at death was 2.0±4.1 hours in the group of infants who did not receive intensive care and 22.4±45.2 days in the group of infants who did receive intensive care.

At 18 to 22 months, 49% of the study infants had died, 61% had died or had profound impairment, and 73% had died or had impairment. The rates for these outcomes according to the week of gestation were 95%, 98%, and 99%, respectively, among study infants born at 22 weeks; 74%, 84%, and 91% among study infants born at 23 weeks; 44%, 57%, and 72% among study infants born at 24 weeks; and 25%, 38%, and 54% among study infants born at 25 weeks.

Predictors of Outcome With Intensive Care

The benefit of a 1-week increase in gestational age varied somewhat at different weeks and for different outcomes (Table 2). In multivariable analyses, increased birth weight (per each 100-g increment), female sex, any use of antenatal corticosteroids, and singleton birth were each associated with reductions in risks of death and of death or profound or any neurodevelopmental impairment that were similar to the reductions associated with a 1-week increase in gestational age. (The regression equations relating these risk factors to outcomes are provided in Table A of the Supplementary Appendix, available with the full text of this article at www.nejm.org.)

Depending on these risk factors, the estimated probability of an adverse outcome with intensive care varied considerably among infants at the same gestational age (see Fig. A and B of the Supplementary Appendix). For example, among infants born midway between 24 and 25 completed weeks of gestation, the estimated likelihood of death or profound impairment was 33% for a 750-g, appropriate-for-gestational-age female singleton who received antenatal corticosteroids but 87% for a 525-g, small-for-gestational-age male twin who did not receive antenatal corticosteroids.

Outcomes for infants who underwent ventilation varied among centers (P<0.001). Among centers that contributed data on 100 or more infants who underwent ventilation, the ratio of the observed to the expected rate of adverse outcomes ranged from 0.60 to 1.38 for death, 0.75 to 1.23 for death or profound impairment, and 0.85 to 1.17 for death or impairment.

Use of Intensive Care and Infant Risk

As expected, the percentage of study infants who received intensive care increased progressively with increasing gestational age (from 23% at 22 weeks' gestation to 99% at 25 weeks' gestation) and birth weight (from 49% at 401 to 500 g to ≥97% at 701 to 1000 g). Intensive care was administered to more infants who received antenatal corticosteroids than to those who did not (94% vs. 58%). However, the percentage of infants who received intensive care was not significantly greater for singletons than for multiples (83% and 84%, respectively) or for female infants than for male infants (84% and 83%, respectively). This was also true at the lowest gestational ages (for female and male infants: 21% and 25%, respectively, at 22 weeks and 65% and 74%, respectively, at 23 weeks). For each major outcome, the percentage of infants who received intensive care was lower for female infants than male infants and for singletons than for multiples, after adjustment for the predicted likelihood of a favorable outcome with intensive care (P<0.01).

Outcome Prediction

The outcomes of the infant risk groups were predicted more accurately with the use of five factors (gestational age, birth weight, sex, exposure or nonexposure to antenatal corticosteroids, and single or multiple gestation) than with the use of gestational age alone, particularly for some subgroups (P<0.001 for the mean absolute difference between predicted and observed values and for the area under the receiver-operating-characteristic curve) (Table 3). (See Tables B and C of the Supplementary Appendix for specific subgroup data.)

Benefits of Intensive Care For Small Immature Infants

Even among the study infants at 24 weeks' gestation or less and with a birth weight of 600 g or less, outcomes varied considerably among different risk groups. The observed and maximum potential rates of survival without profound impairment were as low as 2 and 5%, respectively, for boys who weighed 401 to 500 g at 22 weeks' gestation and as high as 37 and 38%, respectively, for girls who weighed 501 to 600 g at 24 weeks' gestation (Fig. 1).

Burdens of Intensive Care

Among all study infants, the total resource use per survivor and per survivor without profound impairment was high, particularly at the lowest gestational ages. The total resource use was consistently greater for male than for female infants (Table 4).

Benefits and Burdens of Universal Intensive Care For Infants at 22 to 23 Weeks

We estimate that providing universal intensive care to all infants who were born at 22 to 23 weeks' gestation would have resulted in at least 1749 extra hospital days and 0 to 9 additional survivors per 100 infants treated. We estimate that of 0 to 9 additional survivors per 100 infants treated, 0 to 5 would have survived without profound impairment and 0 to 3 would have survived without impairment.

Discussion

Our findings challenge the widespread use of gestational-age thresholds alone in deciding whether to administer intensive care to extremely premature infants. In multivariable models of infants who received intensive care, female sex, exposure to antenatal corticosteroid therapy,

singleton birth, and increased birth weight (per 100-g increment) were each associated with benefits similar to those of an increase in gestational age of approximately 1 week. In bivariable analyses as well as analyses adjusted for the center and the factors described above, race or ethnic group had no significant association with outcomes; these findings are similar to those in a previous Neonatal Research Network study.[25] At the same estimated likelihood of a favorable outcome, the likelihood of receiving intensive care was lower for girls than for boys and for singletons than for multiples. The likelihood of death or adverse developmental outcomes among different risk groups was more accurately estimated with the use of multiple risk factors than with the use of gestational age alone.

Outcomes are likely to be more closely related to gestational age in populations that virtually always undergo an early ultrasonographic assessment.[9,28] Estimates based on ultrasonographic examinations have been reported to have an error (±2 SD) of approximately 4 days at 12 to 14 weeks[29] and 7 days at 14 to 22 weeks.[30] However, even early estimates based on ultrasonographic examinations are subject to both systematic and random error,[10, 31-33] and their accuracy has generally been assessed in relatively healthy populations evaluated by ultrasonographers who are aware of other indicators of pregnancy length. The error under field conditions at 20 to 30 weeks' gestation may be as great as 2 weeks.[14] For many extremely premature infants, the measurement error in assessing pregnancy length[8-14,29-31] is more than the 1-to-2-week difference in gestational age that would change treatment decisions with the use of current gestational-age thresholds. The error in estimating fetal weight should also be considered in antepartum counseling.

For multiple reasons, the effects of intensive care on extremely premature infants are unlikely to be determined in randomized trials. Observational studies are more subject to bias, particularly at the lowest gestational ages, when intensive care is used most selectively. Our study is also limited by the unavailability of data indicating how the obstetrical estimate of gestational age was assigned, the inability to determine the outcome for 6% of the study infants, and the use of center-based samples. A population-based study is needed to verify the absence of an important effect of race or ethnic group on the outcome for extremely premature infants. The better outcomes for infants who received antenatal corticosteroids result at least in part from their use when obstetricians are committed to optimizing outcomes.[34] Whether the use of corticosteroids has a benefit before 26 weeks' gestation remains to be determined in randomized trials.[35]

The strengths of our study include a prospective evaluation of a large, heterogeneous cohort and assessment of profound impairment, an outcome that some persons consider to be worse than death.[36,37] Total ventilator days or hospital days before discharge per infant with a favorable outcome were computed as indexes of cost, resource use, parental distress, and infant suffering due to painful procedures, prolonged intubation, and such complications as intracranial hemorrhage, necrotizing enterocolitis, and recurrent episodes of hypoxia.[5] Conventional analyses of cost-effectiveness are problematic for neonatal intensive care,[5] and we did not attempt to measure short-term or long-term financial costs. However, current costs before discharge may be estimated at approximately $3,400 per hospital day (2007 U.S. dollars, based on the estimates of Schmitt et al.[22] and adjusted for inflation[38]). Barring major therapeutic advances, our findings indicate that extending intensive care to all of the most immature infants would entail considerable suffering, resource use, and cost in order to benefit only a small proportion of infants.

When are the burdens of intensive care justified by the likelihood of benefit? Traditional estimates of this likelihood are based on the proportion of births of infants in the highest-risk groups with a good outcome. Because some infants die without receiving intensive care, this approach underestimates the likelihood of a benefit from intensive care. To avoid this problem

and provide an upper bound for the likelihood of such a benefit, we assessed the maximum potential benefit, assuming the same outcome among infants who died without receiving intensive care as among infants who received intensive care in the same risk category. In any risk category, the true likelihood of a benefit from intensive care is likely to be intermediate between the observed and maximum potential percentage of infants with a favorable outcome. Whether intensive care should be considered mandatory (i.e., given even if the parents object), optional, investigational, or unwarranted (i.e., not given even if requested by the parents) can be considered in terms of the likelihood of a benefit.[5]

In deciding whether to administer intensive care, Paris[39] contends that "The best one can do … is to make a human judgment based on probabilities." Physicians should do their best to estimate and interpret these probabilities in counseling parents.[40]

Whatever minimum probability of a favorable outcome is judged to warrant intensive care, consideration of multiple factors is likely to promote treatment decisions that are less arbitrary, more individualized, more transparent, and better justified than decisions based solely on gestational-age thresholds. A simple Web-based tool (www.nichd.nih.gov/neonatalestimates) allows clinicians to use our findings in estimating the likelihood that intensive care will benefit individual infants, after considering the extent to which outcomes in their center might differ from those we identified.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

In addition to the authors, the following investigators participated in the Generic Database Study of the National Institute of Child Health and Human Development Neonatal Research Network: A. Jobe (chair); *Brown University and Women and Infants Hospital of Rhode Island, Providence* — A.R. Laptook, W. Oh, A. Hensman, B. Vohr, L. Noel; *Case Western Reserve University and Rainbow Babies and Children's Hospital, Cleveland* — A.A. Fanaroff, M.C. Walsh, N.S. Newman, D. Wilson-Costello, B.S. Siner; *Duke University, University Hospital, Alamance Regional Medical Center, Duke Raleigh Hospital, and Durham Regional Hospital, Raleigh, NC* — R.N. Goldberg, C.M. Cotten, K. Auten, R. Goldstein, M. Lohmeyer; *Emory University, Grady Memorial Hospital, Emory Crawford Long Hospital, and Children's Healthcare of Atlanta, Atlanta* — B.J. Stoll, L. Jain, E. Hale; *Harvard University, Boston* — A.R. Stark, K. Fournier, K.G. Lee, C. Driscoll; *Indiana University, Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services, Indianapolis* — B.B. Poindexter, J.A. Lemons, D.D. Appel, L. Miller, A.M. Dusick, L. Richard; *RTI International, Research Triangle Park, NC* — A. Das, W.K. Poole, C.P. Huitema, K. Zaterka-Baxter; *Stanford University, Dominican Hospital, El Camino Hospital, and Lucile Packard Children's Hospital, Palo Alto, CA* — D.K. Stevenson, K.P. Van Meurs, M.B. Ball,

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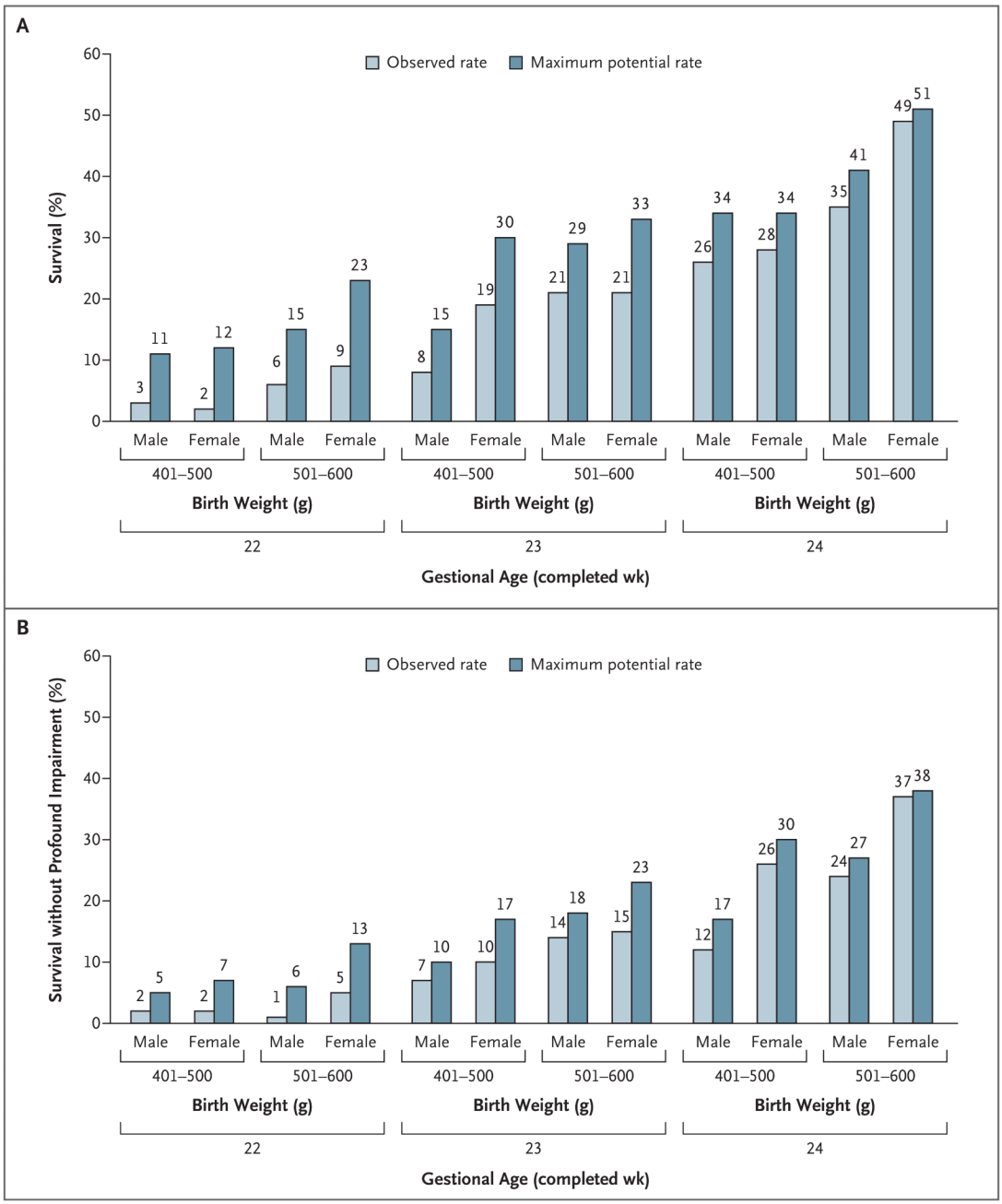

Figure 1. Observed and Maximum Potential Rates of Survival and Survival without Profound Impairment

Panel A shows observed and maximum potential survival, and Panel B shows survival without profound impairment. Both rates are shown for an adjusted age of 18 to 22 months and calculated according to gestational age, sex, and birth weight for all of the smallest and most immature infants in the study.

Table 1

Characteristics at Birth, Outcomes before Discharge, and Outcomes at a Corrected Age of 18 to 22 Months*

Variable	All Infants (N = 4446)	Infants Who Received Intensive Care (N = 3702)	Infants Who Did Not Receive Intensive Care (N = 744)
Characteristics at birth			
Prenatal care (%)	92	93	90†
Delivery by cesarean section (%)	42	48	9‡
Use of antenatal corticosteroids (%)	71	80	28‡
Race or ethnic group (%)†§			
Black	45	45	48
White	35	36	31
Hispanic	17	17	17
Singleton birth (%)	76	76	78
Female sex (%)	46	47	44
Gestational age (wk)	23.9±0.99	24.2±0.82	22.7±0.78‡
Birth weight (g)	648±124	670±118	536±84‡
Apgar score ≤3 (%)			
At 1 min	58	50	98‡
At 5 min	28	15	98‡
Predischarge outcomes			
Death (%)	49	38	100¶
Major morbidity (%)‖	50	60	NA¶
Death or major morbidity (%)‖	66	76	100¶
Median no. of ventilator days (5th–95th percentile)	19 (0–83)	26 (0–87)	0 (0–0)¶
Median no. of hospital days (5th–9th percentile)	72 (0–168)	88 (0–177)	0 (0–0)¶
Outcomes at 18–22 mo**			
Death (%)	49	42	100¶
Death or profound impairment (%)	61	53	100¶
Death or impairment (%)	73	67	100¶

*The study infants excluded 57 infants with a birth weight of more than 1000 g, 7 with ambiguous sex, 127 with major anomalies, 82 with a birth weight that exceeded the 97th percentile for gestational age, and 31 survivors who did not undergo mechanical ventilation. (The percentage of infants with each predischarge outcome was virtually identical for study infants and for all infants at 22 to 25 weeks of gestational age, including exclusions.) Plus–minus values are means ±SD. NA denotes not applicable.

†P<0.05 for infants given intensive care as compared with infants not given intensive care.

‡P<0.001 for infants given intensive care as compared with infants not given intensive care.

§Race or ethnic group was assigned by maternal report.

¶The P value is not meaningful for this comparison.

‖Major morbidity was defined as bronchopulmonary dysplasia requiring oxygen administration at 36 weeks' gestation, necrotizing enterocolitis requiring surgery, retinopathy of prematurity requiring laser therapy or surgery, grade III or IV intracranial hemorrhage, or white-matter injury detected on ultrasonographic examination.

**Outcomes were determined for 4165 infants, including 3421 who received intensive care. Data for infants not examined at 18 to 22 months were excluded from the denominator in analyses of death or profound impairment or death or impairment, but they were not excluded from analyses of death.

Table 2

Relation of Major Risk Factors to Observed Outcomes at a Corrected Age of 18 to 22 Months among Infants Who Underwent Mechanical Ventilation*

Variable	Death		Death or Profound Impairment		Death or Impairment	
	Odds Ratio (95% CI)	Gestational-Age Equivalent Effect	Odds Ratio (95% CI)	Gestational-Age Equivalent Effect	Odds Ratio (95% CI)	Gestational-Age Equivalent Effect
Gestational age						
25 vs. 24 wk	0.62 (0.53–0.74)	1.00	0.66 (0.55–0.78)	1.00	0.70 (0.59–0.84)	1.00
24 vs. 23 wk	0.61 (0.52–0.73)	1.02	0.58 (0.46–0.73)	1.13	0.56 (0.42–0.74)	1.26
23 vs. 22 wk	0.54 (0.32–0.92)	1.15	0.50 (0.26–0.98)	1.31	0.56 (0.22–1.44)	1.25
Birth weight (per 100-g increase)	0.60 (0.55–0.65)	1.04	0.61 (0.56–0.66)	1.08	0.61 (0.56–0.66)	1.16
Female sex	0.64 (0.55–0.75)	0.97	0.55 (0.48–0.65)	1.19	0.48 (0.41–0.56)	1.47
Use of antenatal corticosteroids	0.55 (0.45–0.66)	1.14	0.54 (0.44–0.66)	1.23	0.53 (0.42–0.66)	1.33
Singleton birth	0.77 (0.65–0.92)	0.81	0.76 (0.64–0.91)	0.87	0.70 (0.58–0.85)	1.00

*The gestational-age equivalent effect indicates the reduction in risk for an adverse outcome with a particular risk factor relative to the reduction in risk with an increase in gestational age from 24 to 25 weeks (the reference group). The gestational-age equivalent risk for a given outcome is calculated by dividing the odds ratio for the reference group by the odds ratio for the factor of interest.

Table 3

Comparison of Models Using Gestational Age Alone with Models Using Five Factors*

Outcome	Gestational-Age Model	Five-Factor Model	P Value
Death			
Mean absolute difference (%)†	11.9	2.8	<0.001
Range of values for observed minus estimated outcomes (%)†	−21 to 35	−11 to 16	NA
Area under the ROC curve (95% CI)‡	0.709 (0.692–0.726)	0.753 (0.737–0.769)	<0.001
Death or profound impairment			
Mean absolute difference (%)†	11.2	3.2	<0.001
Range of values for observed minus estimated outcomes (%)†	−27 to 30	−7 to 14	NA
Area under the ROC curve (95% CI)‡	0.704 (0.686–0.721)	0.751 (0.735–0.767)	<0.001

* The five factors are birth weight, gestational age, sex, exposure or nonexposure to antenatal corticosteroids, and singleton or multiple birth. NA denotes not applicable, and ROC receiver operating characteristic.

† The range of values for observed minus estimated percent differences are for 24 subgroup combinations of the five risk factors. P values were determined by chi-square analysis.

‡ The statistical comparison between the areas under the ROC curves is based on chi-square analysis, calculated with the use of a modified ROC macro in SAS software (SAS Institute). The ROC analysis indicates that the five-factor models were superior. Hosmer–Lemeshow goodness-of-fit tests derived from an equivalent fixed-effects model were not significant; these findings also provide support for the five-factor models.

Table 4

Mean Resource Use per Survivor and per Survivor without Profound Impairment at a Corrected Age of 18 to 22 Months

Resource Use	Gestational Age (wk)			
	22	23	24	25
Per survivor				
Total no. of ventilator days				
Male	119	88	63	43
Female	90	73	58	37
Total no. of hospital days				
Male	222	181	145	121
Female	168	163	136	111
Per survivor without profound impairment				
Total no. of ventilator days				
Male	266	135	85	53
Female	113	103	70	43
Total no. of hospital days				
Male	498	272	193	149
Female	206	231	164	127