Published in final edited form as:
*Pediatrics*. 2010 April ; 125(4): 813–816. doi:10.1542/peds.2010-0194.

# Evidence-Based Treatment Decisions for Extremely Preterm Newborns

**Nehal A. Parikh, DO, MS**[a], **Cody Arnold, MD, MSc, MPH**[a], **John Langer, MS**[b], and **Jon E. Tyson, MD, MPH**[a,c]

[a] Division of Neonatal-Perinatal Medicine, Department of Pediatrics, University of Texas Medical School at Houston, Houston, Texas

[b] Research Triangle Institute, Research Triangle Park, North Carolina

[c] Center for Clinical Research and Evidence-Based Medicine, University of Texas Medical School at Houston, Houston, Texas

Few treatment decisions in any area of medicine have greater consequences than the decisions made shortly after birth to give intensive care or comfort care to extremely preterm infants. Obstetricians and neonatologists continue to struggle with ethical questions such as “How can we formulate better evidence-based treatment thresholds in judging when intensive care is ethically mandatory, unwarranted, or optional?”[1] and “How can parents be best informed and counseled?”

Results of the cohort study by Bader et al, published in this issue of *Pediatrics*,[2] are an important addition to the evidence base for these decisions. Theirs is one of only a few recent population-based studies that are free of the referral biases in virtually all center-based studies. Other important strengths include prospective data collection and entry into a computerized database with error checks. Prenatal and post-natal risk factors were related to predischarge mortality for >99% of the 3768 infants born alive at 23 to 26 weeks’ gestational age (GA) in Israel between 1995 and 2006. A limitation of the study is their lack of analyses to assess the extent to which mortality was affected by center differences or decisions to forego intensive care. In addition, there were no data about longer-term outcomes, including profound impairment, an outcome that some people consider worse than death.[3,4]

In multivariable regression models, the likelihood of death decreased with not only increasing GA but also higher birth weight (BW), female gender, singleton gestation, and antenatal steroid treatment. These same factors were also associated recently with a reduced mortality rate in large population-based analyses in California[5] and center-based analyses in the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN).[6]

Bader et al[2] found that the decrease in mortality rate with antenatal steroid treatment and with a higher BW (per 100-g increase) was comparable to that of a 1-week increase in GA. In the California[5] and NRN studies,[6] this was true for not only higher BW and antenatal steroid treatment but also for female gender and singleton gestation. The reduction in risk of

Address correspondence to Jon E. Tyson, MD, MPH, University of Texas Medical School at Houston, 6431 Fannin St, MSB 2.106, Houston, TX 77030. jon.e.tyson@uth.tmc.edu.

**FINANCIAL DISCLOSURE:** *The authors have indicated they have no financial relationships relevant to this article to disclose.*

Opinions expressed in this commentary are those of the author and not necessarily those of the American Academy of Pediatrics or its Committees.

impairment and of profound impairment at 18 to 22 months' corrected age (postterm) associated with each of these 4 factors was also comparable to a 1-week increase in GA in the NRN study.

Bader et al[2] used BW and gender to classify infants into 3 categories on the basis of gender-specific BW percentiles and then developed simple tables for clinicians to use in assessing prognosis. This approach involves some uncertainty in determining appropriate BW standards[7] and introduces approximations in grouping infants with different percentiles into the same category. Although this categorization was necessary for prediction tables, the infant's exact BW can be used as one of multiple factors in assessing prognosis on Web-based tools such as that on the NICHD Web site (www.nichd.nih.gov/neonatalestimates).[8]

What are the implications of these and other recent outcome studies[9–12] for decision-making in the care of extremely preterm fetuses or newborn infants? With the editors' encouragement, we offer the following thoughts.

## IMPLICATIONS FOR CURRENT TREATMENT GUIDELINES AT OR BEFORE BIRTH[13–15]

1. In the absence of randomized trials that evaluate the benefits of antenatal corticosteroids before 26 weeks' gestation,[16] large, carefully risk-adjusted cohort studies allow the most rigorous assessment. Results of the 3 studies noted above support administration of antenatal corticosteroids before delivery at 23 to 25 weeks' gestation, although the associated benefits are likely to be partly a result of an obstetric commitment to optimize pregnancy outcome.
2. Several problems make it difficult to use the results of published studies to infer the probability that initiating intensive care will benefit extremely preterm infants. This probability is likely to be intermediate between the percentage with a favorable outcome among all these infants (some of whom died without receiving intensive care) and the percentage among those selected to receive intensive care. At a minimum, researchers in future studies should report both percentages. More sophisticated approaches, such as those used for the NICHD Web site, can be used to address this problem.[6] Another problem is that outcome with intensive care differs in different centers. In principle, the likelihood of a favorable outcome estimated from multi-center studies could be adjusted on the basis of local outcomes. However, few centers have the large populations, standardized follow-up assessments, and low attrition rates needed to adjust estimates for survival without impairment or profound impairment. A low predischarge mortality rate does not necessarily indicate a high rate of survival without profound impairment.[6]
3. There is a need to replace GA-based guidelines with probability-based guidelines to promote decisions to initiate intensive or comfort care that are better informed, more individualized, and less influenced by the frequent errors in assessing GA.[17–19] The most recent guidelines from the American Academy of Pediatrics emphasized the need for each institution to develop "comprehensive and consistent guidelines for antenatal counseling" that are based on multiple factors.[13]

## DEVELOPMENT OF PROBABILITY-BASED GUIDELINES FOR CARE AT BIRTH

Approaches such as the following can be considered.

1. Use probability thresholds that are implicit in current GA-based treatment guidelines already being used. GA has been used as a proxy (albeit imperfect) to indicate the overall probability of a favorable (or unfavorable) outcome with intensive care. Current GA-based guidelines take into consideration parental autonomy, infant suffering, and resource availability and reflect implicit clinical judgments about when the probability of benefit is so high that intensive care should be mandatory and when the probability is so low that intensive care is unwarranted.[1] These judgments can be better applied to individual infants when their probability of a favorable outcome is assessed more accurately.

   In many centers, intensive care has been viewed as mandatory for infants born at ≥25 weeks' GA.[20] With the NRN data, the overall probability of survival with intensive care for 401- to 1000-g infants born at 25 weeks' gestation would be estimated to be 75% to 76%; the probability of survival without profound impairment, 62% to 63%; and the probability of survival without impairment, 46%.[6] In centers with outcomes equivalent to those across the NRN and in which intensive care has been considered mandatory at ≥25 weeks' gestation, such care might be considered mandatory, irrespective of GA, when the estimated probability of a favorable outcome exceeded values such as those discussed above.

   At 22 weeks, a GA at which intensive care has often been considered unwarranted, the probability of survival with intensive care was estimated to be 5% to 20%; the likelihood of survival without profound impairment was estimated to be 2% to 10%; and the likelihood of survival without impairment was estimated to be 1% to 5% in the NRN study.[8] As a measure of both the total infant suffering and resource use resulting from intensive care at this GA, a mean of 197 ventilator-days and 365 hospital-days (including days for infants who died) were needed per infant who survived without profound impairment (values represent estimates for male and female infants combined; for gender-specific values, see Table 4 in ref [6]). In centers at which intensive care has been judged to be unwarranted at ≤22 weeks' gestation, such care might be judged to be unwarranted irrespective of GA when, say, the estimated probability of survival without profound impairment is ≤10% (ie, a >90% likelihood of death or profound impairment). Whatever thresholds were used, intensive care would then be considered optional (as decided with the parents) at probability estimates intermediate between the thresholds for mandatory and unwarranted care.

2. Develop probability thresholds on the basis of a broad consensus. Development of new guidelines within individual centers or groups of centers may be best done by actively engaging obstetric and neonatal caregivers, follow-up clinic personnel, and parents in a process similar to that used by Kaempf et al.[21,22] It is difficult to weigh the infant suffering, parental distress, and short-term and long-term resource needs associated with intensive care against the potential benefits. Different centers may differ in the importance ascribed to different outcomes and the probability thresholds that would be selected in designating intensive care as unwarranted, mandatory, or optional. An argument can be made that intensive care should be considered investigational in the lower portion of what might otherwise be the optional range.[1] (This designation could help foster a well-defined approach to informing parents and involving them in decision-making and a commitment to carefully assess and publish neonatal and follow-up outcomes.)

Table 1 lists probability estimates of outcome and resource use of ventilated infants in the NRN. It is provided to stimulate discussion of the threshold probability estimates that may be considered in designating intensive care as unwarranted, investigational, or optional.

Whatever guidelines are developed, they obviously should be reconsidered as new information emerges.

## NEED FOR ADDITIONAL RESEARCH

Despite the advances in assessing the prognosis of extremely preterm infants, much additional study is needed to promote better informed parental counseling and treatment decisions for extremely preterm infants. Although beyond the scope of this commentary, promising areas of investigation have been suggested elsewhere.[1,23]

## Acknowledgments

This work was supported in part by National Institutes of Health grant U10HD021373-22.

Funded by the National Institutes of Health (NIH).

## ABBREVIATIONS

| | |
|---|---|
| **GA** | gestational age |
| **BW** | birth weight |
| **NICHD** | Eunice Kennedy Shriver National Institute of Child Health and Human Development |
| **NRN** | Neonatal Research Network |

## References

1. Tyson JE, Stoll BJ. Evidence-based ethics and the care and outcome of extremely premature infants. Clin Perinatol. 2003; 30(2):363–387. [PubMed: 12875360]
2. Bader D, Kugleman A, Boyko V, et al. Israel Neonatal Network. Risk factors and estimation tool for mortality among extremely preterm infants: a national population-based study. Pediatrics. 2010; 125(4):696–703. [PubMed: 20351002]
3. Saigal S, Stoskopf BL, Burrows E, Streiner DL, Rosenbaum PL. Stability of maternal preferences for pediatric health states in the perinatal period and 1 year later. Arch Pediatr Adolesc Med. 2003; 157(3):261–269. [PubMed: 12622676]
4. Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function for a comprehensive health status classification: Health Utilities Index Mark 2. Med Care. 1996; 34(7):702–722. [PubMed: 8676608]
5. Lee, HC.; Green, C.; Hintz, SR.; Tyson, JE.; Langer, J.; Gould, JB. Predictors of mortality for extremely premature infants: a population based cohort. [Accessed February 9, 2010]. E-PAS2009;4352.381. Available at: www.pasmeeting.org
6. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD. National Institute of Child Health and Human Development Neonatal Research Network. Intensive care for extreme prematurity: moving beyond gestational age. N Engl J Med. 2008; 358(16):1672–1681. [PubMed: 18420500]
7. Kramer, MS.; Platt, RW.; Wen, SW., et al. Fetal/Infant Health Study Group of the Canadian Perinatal Surveillance System. A new and improved population-based Canadian reference for birth weight for gestational age; Pediatrics. 2001. p. 2Available at: www.pediatrics.org/cgi/content/full/108/2/e35
8. National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development. NICHD Neonatal Research Network (NRN): extremely preterm birth outcome data. [Accessed January 10, 2010]. Available at: www.nichd.nih.gov/neonatalestimates
9. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. N Engl J Med. 2000; 343(6):378–384. [PubMed: 10933736]

10. Hack M, Taylor HG, Drotar D, et al. Chronic conditions, functional limitations, and special health care needs of school-aged children born with extremely low-birth-weight in the 1990s. JAMA. 2005; 294(3):318–325. [PubMed: 16030276]
11. Saigal S, Feeny D, Rosenbaum P, Furlong W, Burrows E, Stoskopf B. Self-perceived health status and health-related quality of life of extremely low-birth-weight infants at adolescence. JAMA. 1996; 276(6):453–459. [PubMed: 8691552]
12. Fellman V, Hellström-Westas L, et al. EXPRESS Group. One-year survival of extremely preterm infants after active perinatal care in Sweden. JAMA. 2009; 301(21):2225–2233. [PubMed: 19491184]
13. Batton DG. American Academy of Pediatrics, Committee on Fetus and Newborn. Clinical report: antenatal counseling regarding resuscitation at an extremely low gestational age. Pediatrics. 2009; 124(1):422–427. [PubMed: 19564329]
14. International Liaison Committee on Resuscitation. The International Liaison Committee on Resuscitation (ILCOR) consensus on science with treatment recommendations on pediatric and neonatal patients: neonatal resuscitation. Pediatrics. 2006. Available at: www.pediatrics.org/cgi/content/full/117/5/e978
15. Griswold, KJ.; Fanaroff, JM. An evidence-based overview of prenatal consultation with a focus on infants born at the limits of viability. Pediatrics. 2010. Available at: www.pediatrics.org/cgi/content/full/125/4/e931
16. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2006; (3):CD004454. [PubMed: 16856047]
17. Gjessing HK, Skjoerven R, Wilcox AJ. Errors in gestational age: evidence of bleeding early in pregnancy. Am J Public Health. 1999; 89(2):213–218. [PubMed: 9949752]
18. Kramer, MS.; Platt, RW.; Wen, SW., et al. Fetal/Infant Health Study Group of the Canadian Perinatal Surveillance System. A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics. 2001. Available at: www.pediatrics.org/cgi/content/full/108/2/e35
19. Donovan EF, Tyson JE, Ehrenkranz RA, et al. Inaccuracy of Ballard scores before 28 weeks' gestation. J Pediatr. 1999; 135(2 pt 1):147–152. [PubMed: 10431107]
20. Pignotti, MS.; Donzelli, G. Perinatal care at the threshold of viability: an international comparison of practical guidelines for the treatment of extremely preterm births. Pediatrics. 2008. Available at: www.pediatrics.org/cgi/content/full/121/1/e193
21. Kaempf JW, Tomlinson M, Arduza C, et al. Medical staff guidelines for periviability pregnancy counseling and medical treatment of extremely premature infants. Pediatrics. 2006; 117(1):22–29. [PubMed: 16396856]
22. Kaempf JW, Tomlinson MW, Campbell B, Ferguson L, Stewart VT. Counseling pregnant women who may deliver extremely premature infants: medical care guidelines, family choices, and neonatal outcomes. Pediatrics. 2009; 123(6):1509–1515. [PubMed: 19482761]
23. Saigal S, Tyson J. Measurement of quality of life of survivors of neonatal intensive care: critique and implications. Semin Perinatol. 2008; 32(1):59–66. [PubMed: 18249241]

**TABLE 1**

Outcomes and Resource Used According to Estimated Probability of Survival Without Profound Neurodevelopmental Impairments Among Infants of 22 to 25 Week' Gestation (401–1000 g) Treated With Mechanical Ventilation in the NICHD NRN Study[6]

| | <5% | 5%–9% | 10%–14% | 15%–24% | 25%–32% | 33%–49% | 50%–66% | ≥67% |
|---|---|---|---|---|---|---|---|---|
| Total No. of ventilated subjects[a] | 18 | 93 | 137 | 391 | 326 | 897 | 932 | 625 |
| No. (%) of survivors | 3 (17) | 12 (13) | 24 (18) | 131 (34) | 142 (44) | 485 (54) | 657 (70) | 516 (83) |
| No. (%) of survivors without profound impairment | 1 (6)[b] | 7 (8) | 18 (13) | 84 (21) | 113 (35) | 357 (40) | 574 (62) | 468 (75) |
| No. of ventilator-days per survivor without profound impairment[c] | 395 | 221 | 140 | 139 | 95 | 94 | 52 | 36 |
| No. of hospital-days per survivor without profound impairment[c] | 591 | 378 | 238 | 303 | 210 | 204 | 140 | 114 |

[a] The number of all subjects (including infants who received comfort care and died) in each column was 149, 307, 242, 562, 377, 947, 954, and 649, respectively.

[b] This infant weighed 522 g at birth, was 22 weeks' gestation according to the best obstetric estimate, had an estimated probability of survival without profound impairment of 0.046, developed cerebral palsy, and had a Bayley Mental Developmental Index of 53 but did not meet criteria for profound impairment.

[c] Total days for all infants (including deaths) "invested" at that week divided by the number who survived without profound impairment.