EDITORIAL

Neonatal Intensive Care — The Only Constant Is Change

Prakesh S. Shah, M.D.

The rate of survival of infants born extremely early — previously considered to be periviable (≤24 weeks) — has increased with advances in perinatal–neonatal care. However, concerns regarding higher rates of neurodevelopmental impairment among survivors have been raised. A precise interpretation of outcomes in periviable neonates requires an understanding of competing outcomes bias, differences in outcome reporting, denominators used in the calculation of rates, and health care philosophies at the personal, institutional, regional, and national level that influence care provision.

In this issue of the *Journal*, Younge et al.[1] report data on 4227 neonates born at 22 to 24 weeks of gestation from 11 neonatal centers in the United States. The data were compared across three consecutive birth-year epochs (2000–2003 [epoch 1], 2004–2007 [epoch 2], and 2008–2011 [epoch 3]). Survival free of neurodevelopmental impairment increased between epoch 1 and epoch 3 (adjusted relative risk, 1.59; 95% confidence interval, 1.28 to 1.99). When the data are analyzed according to gestational age, improvements in survival are still not seen for infants born at 22 weeks; epoch 2 was the turning point for infants born at 23 weeks, and random variations in outcomes characterized infants born at 24 weeks of gestation. There was a 4 percentage point increase in the rate of survival without clinically significant neurodevelopmental impairment from epoch 1 to epoch 3 ($P=0.001$) and a 1 percentage point increase in the rate of survival with clinically significant neurodevelopmental impairment from epoch 1 to epoch 3 ($P=0.29$). The study attempts to signal a progressive change in neonatal intensive care by reporting on the largest cohort of periviable neonates from the United States and, more importantly, shows variability across centers. However, limitations include the exclusion of neonates not born in the 11 centers, evaluation of outcomes by arbitrary segmental epochs rather than by process control charts, and lack of generalizability — the study population represents only 4 to 5% of periviable neonates born in the United States.

In addition to the study by Younge et al., other multicenter studies have reported on periviable neonates (Table 1). Reported rates of death or clinically significant neurodevelopmental impairment were greater than 94% for infants born at 22 weeks, between 80% and 90% for infants born at 23 weeks, and between 51% and 72% for infants born at 24 weeks of gestation, with the exception of Japan and Sweden (Table 1). There is wide variation in these rates, but the key to a correct interpretation lies in the denominator used, as well as the differing definitions of neurodevelopmental impairment in these reports. For example, in the study from Japan,[7] data were from selected neonatal units, whereas in the studies from Sweden,[4] France,[3] and the United Kingdom,[2] data included all births within a defined period. The classification of motor, cognitive, and sensory impairments that composed clinically significant neurodevelopmental impairment differed among studies. Therefore, it is difficult to counsel families on the basis of these different population bases and different outcomes. Studies from the United Kingdom and France have attempted to overcome such limitations and provided results using several denominators — all alive fetuses, all births, live births, neonates in whom active intervention was at-

Table 1. Multicenter Reports of Outcomes of Neonates Born between 22 and 24 Weeks of Gestation.*

Region or Country, Year (Base Population)	Exclusion Criteria	Outcomes	Definition of Clinically Significant NDI†	Denominator‡	Gestational Age		
					22 wk	23 wk	24 wk
					no./total no. (%)		
United Kingdom, 2006 (entire region)[2]	Not reported	Death or severe impairment at 3 yr	GMFCS level 3 to 5, DQ >3 SDs below the mean, blindness, sensorineural hearing loss not improved by aids	Alive at the onset of labor	270/272 (99)	370/416 (89)	354/494 (72)
				Live births	150/152 (99)	293/339 (86)	302/442 (68)
				Admission to neonatal ICU	17/19 (89)	181/217 (83)	241/381 (63)
France, 2011 (98% of entire population)[3]	None	Death before discharge	Not applicable	All births (live and stillbirths)	58/58 (100)	88/89 (99)	128/186 (69)
Sweden, 2004–2007 (all 7 regions in the country)[4]	Refusal to provide data	Death or clinically significant NDI at 2.5 yr	Nonambulatory cerebral palsy, Bayley-III score 3 SDs below the mean, blindness in both eyes, deafness in both ears	Live births (inborn and outborn)	48/51 (94)	57/94 (61)	60/135 (44)
Victoria, Australia, 2010–2011 (all hospitals in the state)[5]	Major congenital anomalies, termination of pregnancy	Death before discharge from neonatal ICU	Not applicable	Live births (inborn and outborn)	40/40 (100)	44/55 (80)	43/84 (51)
United States, 2006–2011 (24 hospitals)[6]	Congenital malformation	Death or clinically significant NDI at 18 to 22 mo	GMFCS level 4 to 5, Bayley-III score in any domain of <70, blindness in both eyes, severe hearing impairment in both ears	Live births (inborn)	345/357 (97)	624/755 (83)	665/1152 (58)
United States, 2000–2011 (11 neonatal units)[1]	Not enrolled in the registry	Death or severe NDI at 18 to 22 mo	GMFCS level 2 to 5, MDI score <70 (Bayley-II) or Cognitive Composite score <85 (Bayley-III), visual acuity <20/200 in both eyes, hearing amplification in both ears	Live births (inborn)	740/749 (99)	1287/1435 (90)	1504/2090 (72)
Japan, 2003–2005 (48 centers in network)[7]	Admission after 28 days of age	Death or profound NDI at 36 to 42 mo	GMFCS level 4 to 5, DQ <70, blindness in either eye, hearing deficit requiring aids	Admission to neonatal ICU in the first 28 days	55/75 (73)	136/245 (56)	99/232 (43)
Canada, 2009–2011 (25 of 30 units in the country)[8]	Death in delivery room, major congenital anomalies, not assessed, not linked§	Clinically significant NDI at 18 to 21 mo	GMFCS level 3 to 5, Bayley-III score <70 in any domain, hearing aid, visual impairment in both eyes	Survivors who were followed up	23/62 (37)¶	—¶	54/186 (29)

* Bayley-II and Bayley-III denotes Bayley Scales of Infant and Toddler Development (second edition and third edition, respectively), DQ developmental quotient, GMFCS Gross Motor Function Classification System, ICU intensive care unit, MDI Mental Developmental index, NDI neurodevelopmental impairment, and SDs standard deviations.

† A child was considered to have clinically significant NDI if any of the components of the disability were present. GMFCS levels range from 1 (mild impairment) to 5 (most severe impairment). Domains of the Bayley-II and Bayley-III have a mean ±SD score of 100±15, with lower scores indicating greater degree of impairment. DQ was calculated by dividing the developmental age by the chronological age and multiplying by 100. In the study from Japan,[7] a DQ of less than 70 was considered to represent clinically significant delayed performance.

‡ Inborn denotes neonates delivered in participating hospitals; and outborn, neonates delivered in other hospitals and then transferred to participating or tertiary hospital for expert care.

§ "Not linked" indicates infants who were seen in follow-up clinic but who could not be linked to the neonatal database and vice versa.

¶ Values for infants born at 22 and 23 weeks of gestation are combined.

tempted, and neonates who were admitted to neonatal units. However, caution is needed when counting all births; the termination of pregnancies at 22 to 24 weeks of gestation because of major congenital malformations may artificially increase the calculated mortality rate.

As neonatal care advances, new reports of survival and outcomes at periviable gestational ages will emerge. A consistent reporting framework is needed to permit comparisons of results and to use them to create benchmarks and pursue quality improvement. Death and neurodevelopmental impairment are competing outcomes, and reports need to delineate them in combination and in isolation. Determination of what constitutes neurodevelopmental impairment and whose perspectives are considered (health care workers, parents, or children) remains debatable. Undoubtedly, our obligations to society will be unfulfilled if survivors are not followed longitudinally to better guide neonatal, postneonatal, infantile, and childhood care and to improve the quality of life for patients and families.

No discussion on neonatal outcomes is complete without consideration of the philosophy of care provision at these gestational ages. Of the national guidelines reviewed previously,[9] none have suggested active care for neonates born at 22 to 23 weeks of gestation. Differences in the initiation of resuscitation for such neonates have explained a significant proportion of variation in outcomes between centers.[10] "Gentler" approaches to provision of care have initiated a mini-revolution in neonatology. In providing care for periviable neonates, opportunities for testing several organ-protective strategies (e.g., less invasive respiratory support, tolerance in permitting levels of physiological measures that are outside the normal range, melatonin therapy, and administration of erythropoietin) in a rigorous manner should be a priority. Nonetheless, one must not forget the implementation of proven interventions, because outcomes can be greatly improved if we act on existing knowledge.[6] Reports of outcomes in periviable neonates, such as the study by Younge et al., remind us that the only constant thing in neonatal intensive care is change.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Department of Pediatrics and Institute of Health Policy, Management, and Evaluation, Mount Sinai Hospital, and the University of Toronto — both in Toronto.

1. Younge N, Goldstein RF, Bann CM, et al. Survival and neurodevelopmental outcomes among periviable infants. N Engl J Med 2017;376:617-28.
2. Moore T, Hennessy EM, Myles J, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. BMJ 2012;345:e7961.
3. Ancel PY, Goffinet F, EPIPAGE-2 Writing Group. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. JAMA Pediatr 2015;169:230-8.
4. Serenius F, Källén K, Blennow M, et al. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. JAMA 2013;309:1810-20.
5. Boland RA, Davis PG, Dawson JA, Doyle LW. Outcomes of infants born at 22-27 weeks' gestation in Victoria according to outborn/inborn birth status. Arch Dis Child Fetal Neonatal Ed 2016 August 16 (Epub ahead of print).
6. Zeitlin J, Manktelow BN, Piedvache A, et al. Use of evidence based practices to improve survival without severe morbidity for very preterm infants: results from the EPICE population based cohort. BMJ 2016;354:i2976.
7. Ishii N, Kono Y, Yonemoto N, Kusuda S, Fujimura M. Outcomes of infants born at 22 and 23 weeks' gestation. Pediatrics 2013;132:62-71.
8. Synnes A, Luu TM, Moddemann D, et al. Determinants of developmental outcomes in a very preterm Canadian cohort. Arch Dis Child Fetal Neonatal Ed 2016 October 6 (Epub ahead of print).
9. Guillén Ú, Weiss EM, Munson D, et al. Guidelines for the management of extremely premature deliveries: a systematic review. Pediatrics 2015;136:343-50.
10. Rysavy MA, Li L, Bell EF, et al. Between-hospital variation in treatment and outcomes in extremely preterm infants. N Engl J Med 2015;372:1801-11.

DOI: 10.1056/NEJMe1616539