JOURNAL CLUB

The Limit of Viability

A Single Regional Unit's Experience

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Objective: To establish the limit between beneficial and futile management in the extremely preterm infant, born at the limit of viability, at 22 to 26 weeks of gestational age (GA).

Design: Retrospective study (11-year study period).

Setting: A tertiary regional neonatal unit.

Participants: Inborn infants (n=841) with a birth weight of 1000 g or less and GA 22 0/7 through 26 6/7 weeks.

Intervention: We compared mortality and neurodevelopmental outcome between 2 periods, epoch 1 (January 1998 to June 2003) and epoch 2 (July 2003 to December 2008). For neurodevelopmental data, epoch 2 extended only to December 2006.

Main Outcome Measures: We reviewed survival rates and adverse neurodevelopmental outcome rates at 18 to 24 months' corrected age.

Results: In the past decade, survival rates continued to increase while neurodevelopmental impairment rates in the extremely preterm infant decreased. From epoch 1 to epoch 2, the increase in survival rate occurred in infants born at 22 weeks' estimated GA, from 20% to 40%, while the decrease in neurodevelopmental impairment (54% to 28%) and severe neurodevelopmental impairment (35% to 8%) occurred in infants born at 23 to 24 weeks' estimated GA.

Conclusions: Novel and aggressive neonatal therapies continue to affect neonatal outcome, mainly in infants born at the limit of viability. Our data suggest that each center offer prospective parents an assessment of the limits of viability based on their updated outcome results.

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THE LIMITS OF VIABILITY, considered to be between 22 and 26 weeks' gestational age (GA),[1-3] vary widely among neonatal centers. The persistent decline in mortality in the extremely low-birth-weight infants (ELBWIs) (birth weight [BW] ≤1000 g and GA <27 weeks), seen from the 1970s to the early 1990s,[4] has gradually lowered these limits. However, concerns about neurodevelopmental outcome have kept these limits broadly defined.[5] Recently, it has been stated that "neonatal mortality for ELBWI has reached an unsurpassable minimum."[6(p1246)] If this were the case, the limit of viability might become easier to determine. However, Itabashi et al[7] recently reported that by 2006, survival rates of infants born at 22 to 23 and 24 to 25 weeks' GA had increased to 49% and 81%, respectively. Do their findings constitute a specific national exception or do they represent a universal phenomenon? This issue is particularly relevant when attempting to establish criteria for what constitutes the limits of viability.[8] To determine the limit of viability in our neonatal referral center, we examined whether a similar decrease in mortality and a parallel decline in neurodevelopmental morbidity occurred in ELBWIs admitted to our neonatal intensive care unit (NICU) over the past decade.

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METHODS

This retrospective medical record review was approved by the institutional review board at the University of South Alabama. Extremely low-birth-weight infants (BW ≤ 1000 g, GA from 22 0/7 to 26 6/7 weeks) were included if they were born alive, from January 1998 through December 2008 (n=841), and were cared for at the tertiary regional NICU at Children's and Women's Hospital of South Alabama. Infants who died in the delivery room (DR), with or without resuscitative efforts,

were also included. We excluded infants transferred to our center (outborn) and infants with multiple congenital malformations.

DATA COLLECTION

For the past 2 decades, the same 2 neonatal nurses collected maternal and infant data as part of ongoing maintenance of an electronic medical database for NICU patients. Neurodevelopmental data were collected from the Neurodevelopmental Clinic.

STUDY DESIGN

The study period was divided into 2 epochs to compare the outcomes of the preterm infant over time. Epoch 1 covered the period from January 1, 1998, through June 30, 2003, while epoch 2 covered from July 1, 2003, through December 31, 2008. Neurodevelopmental data were collected up to the age of 24 months, and thus, the second epoch extends only to December 31, 2006, for those with follow-up data.

LABOR AND DELIVERY DATA

Estimated GA (EGA) was based on last menstrual period or on first-trimester fetal ultrasonography when available. Infants were determined to be alive if cardiac activity was detected at delivery. Except for special circumstances (ie, urgent or unexpected births), parental consultation was always performed prior to delivery in infants born at less than 25 weeks' EGA and resuscitation was not initiated without parental approval. Experienced neonatal nurse practitioners or board-certified neonatologists attended all deliveries of infants born at less than 27 weeks' EGA.

NICU DATA

Cranial ultrasonography was routinely performed on days 7 and 42 and was reviewed by the same neurologist during the study period. The grading of intraventricular hemorrhage (IVH) was based on the Papile et al criteria.[9] White matter injury (WMI) was defined by the presence of 1 of the following ultrasonography findings: grade 3 or 4 IVH or cystic periventricular leukomalacia. Necrotizing enterocolitis (NEC) was diagnosed clinically according to the Bell criteria (≥stage II), during surgery, or from autopsy reports. Bronchopulmonary pulmonary dysplasia (BPD) was defined as the requirement for supplemental oxygen at 36 weeks' postmenstrual age (PMA). Late-onset sepsis was defined as clinical sepsis confirmed by a positive blood culture after the third day of life. Intrauterine growth restriction was defined as BW below the 10th percentile.[10] Major morbidity was defined as the presence of any of the following: WMI, NEC, BPD, or retinopathy of prematurity stage 3 or more.[11]

NEURODEVELOPMENTAL FOLLOW-UP

Serial neurological evaluations were performed at 4, 8, 12 to 18, and 24 months' corrected age. Cerebral palsy (CP) was diagnosed when abnormal movement and posture impeded normal neuromotor function.[12] Cerebral palsy was classified as mild if the infant was able to function without technological devices. Otherwise, CP was classified as moderate/severe. Infants were also evaluated at 12 to 18 months' corrected age by using the revised Bayley Scales of Infant Development (BSID) II or III. Mental developmental index and psychomotor developmental index (BSID II)[13] or cognitive score, language score, and motor score (BSID III) were determined. The BSID II was replaced by BSID III[14] in January 2005. Blindness was defined as the loss of useful vision in one or both eyes. Deafness was defined as the need to use hearing aids.

Neurodevelopmental impairment (NDI) was defined when the infant had any of the following: mental developmental index or cognitive/language score less than 70, psychomotor developmental index or motor score less than 70, CP, or unilateral or bilateral deafness or blindness. Severe NDI was defined by any of the following: mental developmental index or cognitive/language score less than 55, psychomotor developmental index or motor score less than 55, moderate to severe CP, bilateral deafness, or bilateral blindness.

STATISTICAL ANALYSIS

Categorical data were analyzed using the Fisher exact test. Continuous variables were analyzed using the *t* test. Poisson regression was used to evaluate the effects of perinatal and postnatal factors on mortality, NICU morbidity, and NDI rates. The following 5 factors, GA, BW, sex, antenatal steroids, and singleton birth, were maintained in all models.[15] In addition, factors with a $P < .20$ in bivariate analysis were initially included. For survival, these factors were intrauterine growth restriction, cesarean section, race, chorioamnionitis, Apgar score at 5 minutes, surfactant therapy, late-onset sepsis, pneumothorax, ligation of the ductus arteriosus, high-frequency ventilation (HFV), NEC, IVH grade 3 or 4, and epoch. For NDI, we added WMI, steroid use for BPD prevention, BPD, head circumference less than the 10th percentile at 36 weeks' PMA, days of ventilation, and days of total parenteral nutrition to the previous factors. For the final model, all added variables (for survival or for NDI) were sequentially excluded when Bayesian Information Criteria of the depleted model were less than the prior model by an absolute value more than 2.[16] Measures of association in Poisson regression are expressed as relative risk (RR) with a 95% confidence interval (CI).

RESULTS

The distribution of all 841 inborn ELBWIs by BW and by GA is illustrated in the **Figure**. The rate of live-born infants admitted to the NICU increased from 92% to 95% from epoch 1 to epoch 2 (**Table 1**). This increase in NICU admission rate was mainly due to a decrease in mortality rate in the DR in infants born at 22 weeks' EGA with an RR of 0.47 (95% CI, 0.24-0.93) or in infants with a BW less than 500 g with an RR of 0.53 (95% CI, 0.29-0.99). For the entire study population, the survival rate increased from epoch 1 to epoch 2, from 69% to 77%. Within the various GA and BW groups, the increase in survival rate was significant at 22 and 25 weeks' EGA or at BW ranging from 500 to 599 and 700 to 799 g.

The overall rate of NDI decreased from 51% to 32%, and the rate of severe NDI from 31% to 12%, from epoch 1 to epoch 2 (**Table 2**). This decrease in impairment was mainly observed at 23 and 24 weeks' EGA and in infants with BW ranging from 500 to 700 g. **Table 3** lists the components of NDI. Parallel to the decline in the rate of NDI and severe NDI from epoch 1 to epoch 2, the overall rates of CP and moderate/severe CP decreased, with an RR of 0.16 (95% CI, 0.07-0.36) and 0.25 (95% CI, 0.08-0.83), respectively. In the infants born at 23 to 24 weeks' EGA, the decrease in NDI seen in epoch 2 was related to decreases in bilateral deafness, CP, and motor scores less than 70.

Table 4 displays major prenatal and postnatal characteristics in each epoch among infants admitted to the

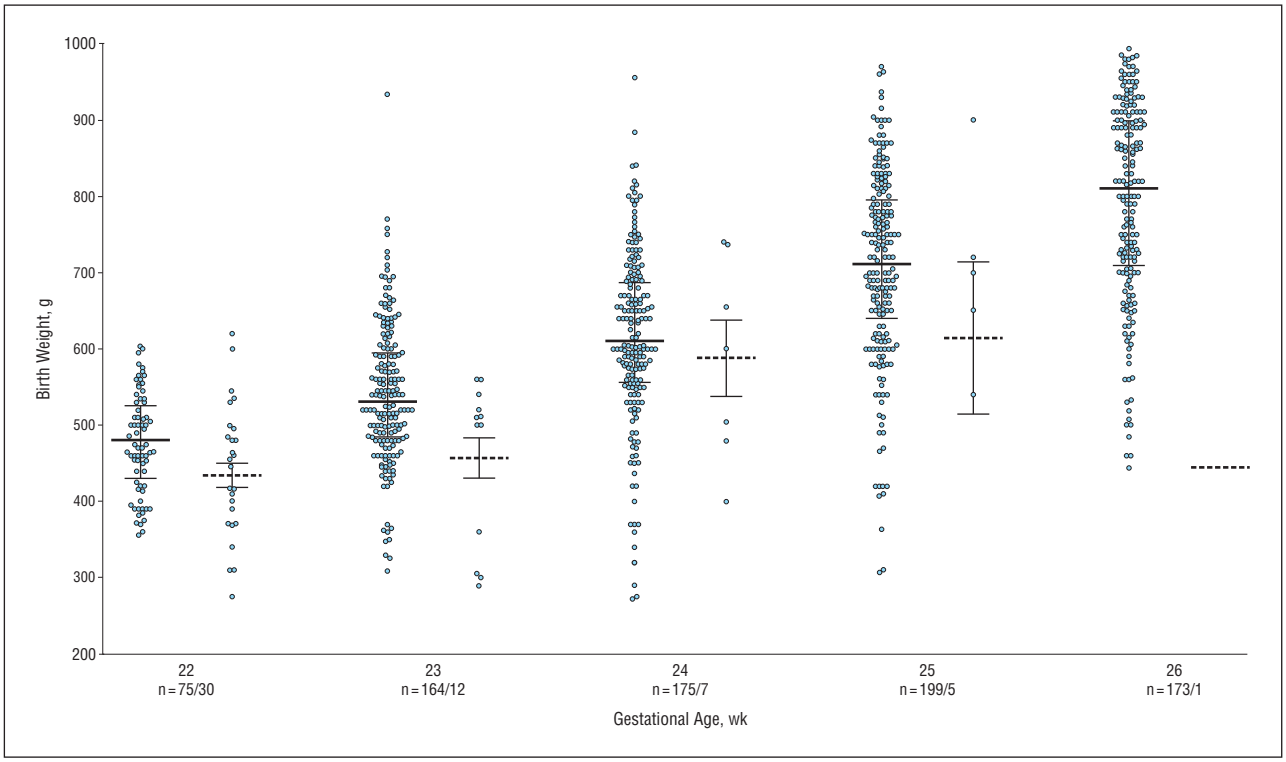

Figure. Dot plot of the population distribution by gestational age and birth weight. Horizontal lines represent median and interquartile range. On the left part of each gestational age is the population admitted to the neonatal intensive care unit (continuous thick line) while on the right (dotted horizontal line) are infants not admitted to the neonatal intensive care unit (died in the delivery room). The number of newborns is summarized by n=survived delivery room/died in delivery room.

Table 1. Survival Rates of All Live-Born Infants

	All Live Births, No.		No. (%) Died in Delivery Room		No. (%) Survived, NICU Admit			Survived, Live Births, No. (%)		
	E1	E2	E1	E2	E1	E2	RR (95% CI)	E1	E2	RR (95% CI)
GA, wk										
22	55	50	21 (38)	9 (18)	11 (32)	20 (50)	1.50 (0.84-2.69)	11 (20)	20 (40)	2.0 (1.06-3.7)
23	95	81	6 (6)	6 (7)	59 (66)	51 (68)	1.02 (0.83-1.27)	59 (62)	51 (63)	1.01 (0.81-1.28)
24	81	101	3 (4)	4 (4)	62 (79)	82 (97)	1.06 (0.92-1.22)	62 (77)	82 (81)	1.06 (0.91-1.23)
25	98	106	5 (5)	0	75 (81)	94 (89)	1.10 (0.97-1.24)	75 (77)	94 (89)	1.16 (1.02-1.3)
26	89	85	0	1 (2)	83 (93)	81 (96)	1.03 (0.96-1.11)	83 (93)	81 (95)	1.02 (0.95-1.10)
BW, g										
300-399	14	26	7 (50)	3 (11)	3 (43)	7 (30)	0.71 (0.24-2.08)	3 (21)	7 (27)	1.25 (0.38-4.10)
400-499	69	77	14 (20)	11 (14)	30 (54)	46 (70)	1.26 (0.94-1.69)	30 (43)	46 (60)	1.37 (0.99-1.90)
500-599	93	87	6 (6)	4 (5)	50 (57)	64 (77)	1.34 (1.09-1.6)	50 (54)	64 (74)	1.36 (1.08-1.7)
600-699	99	87	3 (3)	2 (2)	84 (87)	72 (85)	0.97 (0.86-1.10)	84 (85)	72 (83)	0.96 (0.86-1.12)
700-799	68	74	4 (6)	0	56 (87)	71 (96)	1.11 (1.01-1.2)	56 (82)	71 (96)	1.16 (1.03-1.3)
800-1000	75	72	1 (1)	0	67 (90)	68 (94)	1.03 (0.94-1.24)	67 (89)	68 (94)	1.04 (0.94-1.15)
All	418	423	35 (8)	20 (5)	290 (76)	328 (81)	1.07 (1.00-1.2)	290 (69)	328 (77)	1.14 (1.07-1.2)

Abbreviations: BW, birth weight; CI, confidence interval; E1, epoch 1; E2, epoch 2; GA, gestational age; NICU, neonatal intensive care unit; RR, relative risk.

NICU. The overall rates of chorioamnionitis, delivery by cesarean section, antenatal steroid use, HFV use, and ligation of the ductus arteriosus increased in epoch 2. Additionally, the increase in the use of HFV and ligation of the ductus arteriosus were statistically significant in all infants born at less than 25 weeks' GA. Moreover, the use of antenatal steroids and delivery by cesarean section increased in epoch 2 among all pooled infants born at less than 25 weeks' EGA (RR, 1.29; 95% CI, 1.14-1.46 and RR, 1.18; 95% CI, 1.01-1.40, respectively). The rate of intubation performed in the DR and the rate of surfactant therapy decreased in epoch 2 in all infants born at more than 22 weeks' GA. The incidence of intrauterine growth restriction was higher during epoch 2, especially at 24 weeks' EGA.

Table 5 summarizes the incidence of morbidities in each epoch among infants admitted to the NICU. Rates of late-onset sepsis, NEC, BPD, and severe retinopathy

Table 2. Neurodevelopmental Morbidity

	No. Survived		No. Followed Up		NDI, No. (% of Followed Up)			Severe NDI, No. (%)		
	E1	E2[a]	E1	E2[a]	E1	E2[a]	RR (95% CI)	E1	E2[a]	RR (95% CI)
GA, wk										
22	11	11	9	8	6 (67)	3 (37)	0.56 (0.20-0.59)	3 (33)	3 (37)	1.12 (0.30-4.20)
23	59	27	47	21	29 (62)	10 (48)	0.77 (0.46-1.28)	22 (47)	2 (9)	0.20 (0.05-0.79)
24	62	56	48	37	37 (77)	13 (35)	0.46 (0.28-0.73)	20 (42)	5 (13)	0.32 (0.13-0.79)
25	75	63	56	43	18 (32)	10 (23)	0.72 (0.37-1.41)	10 (18)	3 (7)	0.39 (0.11-1.34)
26	83	52	67	34	25 (37)	10 (29)	0.79 (0.43-1.45)	15 (22)	4 (12)	0.52 (0.19-1.47)
BW, g										
300-399	3	5	3	3	3 (100)	1 (33)	0.33 (0.06-1.92)	3 (100)	1 (33)	0.33 (0.06-1.92)
400-499	30	28	24	20	14 (58)	9 (45)	0.77 (0.42-1.40)	8 (33)	4 (20)	0.60 (0.21-1.72)
500-599	50	40	37	28	25 (68)	11 (39)	0.58 (0.35-0.97)	15 (40)	3 (11)	0.26 (0.08-0.83)
600-699	84	51	66	37	34 (51)	7 (19)	0.39 (0.19-0.80)	20 (30)	2 (5)	0.19 (0.05-0.80)
700-799	55	47	45	31	20 (44)	8 (26)	0.56 (0.27-1.16)	13 (29)	4 (13)	0.37 (0.11-1.20)
800-1000	67	38	51	24	19 (37)	10 (42)	1.05 (0.55-2.01)	11 (22)	3 (12)	0.45 (0.10-1.89)
All	290	209	227	143	115 (51)	46 (32)	0.63 (0.48-0.83)	70 (31)	17 (12)	0.38 (0.24-0.63)

Abbreviations: BW, birth weight; CI, confidence interval; E1, epoch 1; E2, epoch 2; GA, gestational age; NDI, neurodevelopmental impairment; RR, relative risk.
[a]Epoch 2 extends to December 2006.

Table 3. Various Components of Neurodevelopmental Impairment

	No. (% of Followed Up)											
	E1 (5.5 y)					E2 (3.5 y)					All	
	GA 22 wk	GA 23 wk	GA 24 wk	GA 25 wk	GA 26 wk	GA 22 wk	GA 23 wk	GA 24 wk	GA 25 wk	GA 26 wk	E1	E2
Followed up, No.	9	47	48	56	67	8	21	37	43	34	227	143
Mental score <70	4 (44)	15 (32)	12 (25)	7 (12)	9 (13)	2 (25)	7 (33)	10 (27)	8 (19)	8 (23)	47 (21)	35 (24)
Mental score <55	1 (11)	8 (17)	5 (10)	3 (5)	3 (4)	2 (25)	3 (14)	3 (8)	2 (5)	1 (3)	20 (9)	11 (8)
Motor score <70	5 (55)	20 (42)	22 (46)	12 (21)	12 (18)	2 (25)	6 (29)	6 (16)[a]	2 (5)[a]	5 (15)	71 (34)	21 (16)[a]
Motor score <55	3 (33)	10 (21)	8 (17)	6 (11)	5 (7)	2 (25)	2 (9)	3 (8)	2 (5)	2 (6)	32 (15)	11 (8)
CP	3 (33)	8 (17)	13 (27)	9 (16)	8 (12)	1 (12)	2 (9)	2 (5)[a]	0[a]	6 (6)	41 (18)[a]	7 (5)[a]
Moderate/severe CP	3 (33)	6 (13)	3 (6)	5 (9)	2 (3)	1 (12)	0[a]	1 (3)	0[a]	1 (3)	19 (8)	3 (2)
HI	5 (55)	12 (25)	12 (25)	7 (12)	6 (9)	2 (25)	3 (14)	8 (22)	5 (12)	7 (21)	42 (18)	25 (17)
Bilateral HI	0	2 (4)	5 (10)	1 (18)	0	1 (12)	0[a]	0[a]	1 (2)	1 (3)	8 (3)	3 (2)
Blind in 1 eye	0	2 (4)	0	0	0	0	0	0	0	0	2 (1)	0
Blind in both eyes	1 (11)	4 (8)	1 (2)	0	0	1 (12)	1 (5)	0	0	0	6 (3)	2 (1)

Abbreviations: CP, cerebral palsy; E1, epoch 1; E2, epoch 2; GA, gestational age; HI, hearing impairment.
[a]$P < .05$, E1 vs E2 for the same GA.

of prematurity did not differ over time, in contrast to the incidence of severe IVH and periventricular leukomalacia, which declined from 20% to 11% and 6% to 3% for all infants, respectively. In addition, a drop in the rate of "death or BPD" and an increase in the rate of survival without morbidity occurred in epoch 2.

Confounding factors included in Poisson regression are shown in **Table 6**. After adjusting for these factors, the increase in survival of NICU patients from epoch 1 to epoch 2 became statistically significant. Improved overall survival was associated with delivery by cesarean section, larger BW, and higher GA. Increased mortality was associated with the presence of NEC, IVH grade 3 or 4, and the use of HFV. A decrease in NDI and severe NDI occurred in infants born in epoch 2. In addition, singleton birth was associated with a decrease in severe NDI. On the other hand, an increase in NDI and severe NDI were associated with the presence of WMI and head circumference less than the 10th percentile at 36 weeks' PMA. The diagnosis of BPD was associated with an increase in NDI.

The incidence of morbidities between the lost-to-follow-up (LTFU) and the followed-up infants, by epochs, are shown in **Table 7**. Follow-up data were available from 370 infants (74% of survivors born up to December 2006). From epoch 1 to epoch 2, the follow-up rate at 18 to 24 months' corrected age dropped from 79% to 69%.

COMMENT

In contrast to the concept of a leveled outcome of the ELBWIs, survival and adequate neurodevelopment of our ELBWI population continued to rise. During the second epoch, the increase in survival of the infant born at

Table 4. Prenatal and Postnatal Factors by GA and Epoch

	No. (%)											
	GA 22 wk		GA 23 wk		GA 24 wk		GA 25 wk		GA 26 wk		All	
	E1	E2	E1	E2	E1	E2	E1	E2	E1	E2	E1	E2
BW, mean (SD)	480 (68)	459 (63)	539 (83)	526 (94)	626 (94)	604 (115)	706 (120)	705 (134)	805 (122)	764 (136)	643 (152)	630 (156)
DIFFmean (95% CI)	16 (–9 to 42)		13 (–13 to 39)		21 (–10 to 53)		1 (–34 to 36)		41 (2 to 79)		13 (–7 to 34)	
Female	12 (35)	20 (49)	46 (52)	39 (52)	35 (45)	49 (50)	46 (49)	39 (37)	50 (57)	48 (57)	189 (49)	195 (48)
RR (95% CI)	1.38 (0.79 to 2.41)		1.01 (0.75 to 1.35)		1.13 (0.82 to 1.54)		0.74 (0.54 to 1.03)		1.01 (0.78 to 1.31)		0.98 (0.85 to 1.13)	
African American	23 (70)	21 (57)	50 (57)	37 (53)	51 (66)	57 (61)	41 (45)	58 (57)	44 (50)	50 (61)	209 (55)	223 (58)
RR (95% CI)	0.76 (0.52 to 1.11)		0.88 (0.65 to 1.18)		0.90 (0.71 to 1.13)		1.24 (0.93 to 1.65)		1.20 (0.91 to 1.59)		1.01 (0.89 to 1.15)	
Multiparity	5 (15)	12 (29)	26 (29)	22 (29)	17 (22)	18 (18)	26 (28)	22 (21)	19 (21)	16 (19)	93 (24)	90 (22)
Cesarean section	5 (15)	13 (32)	49 (56)	47 (64)	51 (66)	72 (74)	68 (74)	86 (78)	57 (65)	67 (80)	230 (60)	285 (70)
RR (95% CI)	2.16 (0.85 to 5.5)		1.14 (0.88 to 1.47)		1.14 (0.93 to 1.39)		1.07 (0.91 to 1.26)		1.25 (1.03 to 1.5)		1.17 (1.05 to 1.3)	
Antenatal steroids	14 (41)	34 (83)	62 (72)	57 (77)	52 (69)	85 (88)	71 (76)	85 (80)	68 (76)	72 (80)	267 (70)	333 (83)
RR (95% CI)	2.01 (1.31 to 3.1)		1.09 (0.90 to 1.32)		1.31 (1.1 to 1.56)		1.05 (0.91 to 1.22)		1.12 (0.97 to 1.30)		1.19 (1.1 to 1.28)	
IUGR	5 (11)	5 (10)	7 (7)	11 (13)	5 (6)	19 (19)	9 (9)	14 (13)	9 (10)	13 (15)	35 (8)	62 (15)
RR (95% CI)	0.91 (0.26 to 2.71)		1.84 (0.75 to 4.55)		2.73 (1.05 to 7.1)		1.54 (0.67 to 3.5)		1.41 (0.63 to 3.19)		1.93 (1.26 to 3.0)	
Chorioamnionitis	7 (20)	6 (15)	4 (4)	7 (9)	5 (6)	13 (13)	10 (11)	12 (11)	6 (7)	14 (17)	32 (8)	52 (13)
RR (95% CI)	0.71 (0.26 to 1.93)		2.08 (0.63 to 6.85)		2.09 (0.78 to 5.63)		1.05 (0.48 to 2.33)		2.44 (0.98 to 6.08)		1.54 (1.01 to 2.3)	
Apgar score at 5 min ≤3	5 (15)	5 (12)	10 (11)	12 (16)	3 (4)	3 (3)	10 (11)	4 (4)	8 (9)	2 (2)	36 (9)	26 (6)
RR (95% CI)	0.83 (0.26 to 2.65)		1.44 (0.66 to 3.16)		0.81 (0.17 to 3.93)		0.35 (0.11 to 1.08)		0.26 (0.06 to 1.22)		0.69 (0.42 to 1.12)	
Intubation in DR	33 (97)	38 (93)	89 (100)	61 (82)	75 (96)	82 (85)	84 (90)	74 (70)	80 (90)	46 (55)	361 (94)	302 (75)
RR (95% CI)	0.95 (0.86 to 1.06)		0.83 (0.75 to 0.92)		0.88 (0.80 to 0.97)		0.77 (0.67 to 0.89)		0.60 (0.49 to 0.74)		0.79 (0.75 to 0.84)	
Surfactant treatment	34 (100)	40 (97)	88 (99)	68 (92)	77 (99)	90 (93)	91 (98)	91 (86)	84 (94)	66 (79)	374 (98)	356 (88)
RR (95% CI)	0.98 (0.93 to 1.02)		0.93 (0.87 to 1.00)		0.94 (0.88 to 1.00)		0.88 (0.81 to 0.95)		0.82 (0.73 to 0.93)		0.90 (0.87 to 0.94)	
High-frequency ventilation	18 (53)	24 (58)	27 (30)	37 (50)	16 (21)	33 (34)	21 (23)	21 (20)	9 (10)	10 (12)	91 (24)	125 (31)
RR (95% CI)	1.11 (0.73 to 1.67)		1.63 (1.10 to 2.4)		1.66 (0.99 to 2.79)		0.88 (0.51 to 1.50)		1.18 (0.50 to 2.76)		1.31 (1.04 to 1.6)	
PDA ligation	2 (6)	14 (34)	6 (7)	26 (35)	6 (8)	28 (29)	4 (4)	9 (8)	1 (1)	5 (6)	19 (5)	82 (20)
RR (95% CI)	5.8 (1.40 to 24.0)		6.53 (2.6 to 16.1)		3.75 (1.63 to 8.6)		1.95 (0.63 to 6.22)		5.30 (0.63 to 44.7)		4.45 (2.71 to 7.3)	

Abbreviations: BW, birth weight; CI, confidence interval; DIFFmean, difference between the mean of birth weights; DR, delivery room; E1, epoch 1; E2, epoch 2; GA, gestational age; IUGR, intrauterine growth restriction; PDA, patent ductus arteriosus; RR, relative risk.

22 weeks' EGA was mainly due to a decrease in DR mortality and was not associated with an increase in NDI. Infants born at 23 and 24 weeks' EGA during the second epoch had a decrease in NDI but did not experience an increase in survival.

There is no sharp limit of developmental age or weight at which a fetus suddenly becomes viable.[17] Lucey et al[18] found that it is rare for a baby weighing less than 500 g and born between 1996 and 2000 to survive. In our study, infants considered at or below the limit of viability, such as infants born at 22 weeks' EGA or infants with BW less than 500 g, had better survival rates in epoch 2, reaching 40% and 51% survival, respectively. The US Supreme Court has defined the limit of viability as the age at which a fetus becomes potentially able to live outside the mother's womb, albeit with artificial aid.[19] Recently, a commonly stated definition is the fetal age at which a 50% chance of long-term survival outside its mother's womb occurs.[2] In such a case, the viability in our unit, during epoch 2, has shifted down to include infants with BW more than 400 g. A recent survey of the literature on survival of infants born at 22 to 25 weeks' EGA reported that survival rates (mean to 95% upper CI limit) were 1.5% to 2.9% at 22 weeks' EGA, 40% to 59% at 23 weeks' EGA, and 57% to 72% at 24 weeks' EGA.[20] Most of the studies included in this survey did not extend beyond 2000. The striking disparity with our survival rate among the very immature ELBWIs suggests either differences in management and outcome among neonatal centers[21] or a trend toward continued improvement in survival beyond the 1990s.[7]

The improvement in survival of our most immature ELBWIs was associated with the increase in aggressive perinatal management, which is reflected by the overall rise in cesarean section rate and the use of antenatal steroids among infants born at less than 25 weeks' EGA in epoch 2. Previously, the willingness to perform a cesarean section for fetal indication at the "limit of viability" has been shown to increase the survival of these very preterm infants.[22,23] Furthermore, the mortality rate in the DR among the infants born at 22 weeks' EGA and among infants with BW less than 500 g decreased in epoch 2. It would seem that the decision to initiate resuscitation in the DR occurred more frequently in epoch 2. Parental wish was always the determinant factor to initiate treatment in those extremely immature infants. We have not identified any particular reason for the increase in parental desire for a more aggressive approach in epoch 2.

Other definitions of the limit of viability include the ability to work, function, or develop adequately (Merriam-Webster dictionary). Evaluating the ability to work is difficult since it requires examining a distant past during which obstetrical and neonatal practices do not represent our current management. Neurodevelopmental assessment at 18 to 24 months' corrected age has been traditionally used as a possible predictor for infants' future abilities. Available reports on the change in NDI over time among ELBWIs are conflicting. A decrease,[24,25] no im-

Table 5. NICU Morbidities by GA and Epoch

	No. (% Admitted to NICU)											
	GA 22 wk		GA 23 wk		GA 24 wk		GA 25 wk		GA 26 wk		All	
	E1	E2	E1	E2	E1	E2	E1	E2	E1	E2	E1	E2
Late-onset sepsis	9 (26)	17 (41)	54 (61)	38 (51)	42 (54)	44 (45)	41 (44)	33 (31)	21 (24)	16 (19)	167 (44)	149 (37)
RR (95% CI)	1.57 (0.8-3.07)		0.86 (0.65-1.13)		0.84 (0.62-1.14)		0.71 (0.49-1.02)		0.81 (0.45-1.44)		0.85 (0.71-1.01)	
Necrotizing enterocolitis	1 (3)	4 (10)	4 (4)	8 (11)	7 (9)	9 (9)	6 (6)	8 (8)	5 (6)	4 (5)	23 (16)	33 (8)
RR (95% CI)	3.32 (0.38-28.7)		2.37 (0.74-7.60)		1.03 (0.40-2.66)		1.17 (0.42-3.26)		0.85 (0.23-3.06)		1.36 (0.82-2.28)	
IVH, grade 3-4	11 (32)	3 (7)	21 (24)	12 (16)	16 (21)	15 (15)	15 (16)	7 (7)	13 (15)	17 (8)	76 (20)	44 (11)
RR (95% CI)	0.23 (0.07-0.75)		0.68 (0.36-1.29)		0.75 (0.40-1.43)		0.41 (0.17-0.96)		0.57 (0.24-1.36)		0.55 (0.39-0.78)	
Periventricular leukomalacia	2 (4)	2 (5)	4 (4)	2 (3)	8 (10)	3 (3)	5 (5)	1 (1)	5 (6)	4 (5)	24 (6)	12 (3)
RR (95% CI)	0.83 (0.12-5.65)		0.59 (0.11-3.17)		0.30 (0.08-1.10)		0.18 (0.02-1.48)		0.85 (0.23-3.06)		0.48 (0.24-0.94)	
Severe ROP stage ≥3	2 (6)	8 (19)	21 (23)	14 (19)	11 (14)	13 (13)	10 (11)	11 (10)	0	3 (4)	44 (11)	50 (12)
RR (95% CI)	3.32 (0.75-4.74)		0.85 (0.47-1.53)		0.95 (0.45-2.01)		0.97 (0.43-2.17)		(0-3)		1.08 (0.73-1.57)	
BPD	5 (15)	11 (27)	20 (22)	20 (27)	20 (26)	20 (21)	15 (16)	18 (17)	9 (10)	8 (10)	69 (18)	78 (19)
RR (95% CI)	1.82 (0.70-4.77)		1.25 (0.73-2.12)		0.80 (0.47-1.39)		1.05 (0.56-1.97)		0.94 (0.38-2.33)		1.07 (0.80-1.44)	
Death or BPD	28 (82)	32 (78)	50 (56)	42 (56)	36 (46)	34 (35)	33 (35)	28 (26)	14 (16)	11 (13)	161 (42)	147 (36)
RR (95% CI)	0.95 (0.76-1.19)		1.00 (0.76-1.31)		0.76 (0.53-1.09)		0.74 (0.49-1.13)		0.83 (0.40-1.73)		0.87 (0.73-1.03)	
HC <10th percentile at 36 wk PMA	2 (20)	16 (76)	26 (46)	25 (53)	24 (41)	31 (38)	13 (18)	26 (28)	11 (13)	12 (15)	76 (27)	110 (33)
RR (95% CI)	3.8 (1.06-3.75)		1.15 (0.78-1.69)		0.93 (0.61-1.41)		1.53 (0.85-2.76)		1.10 (0.52-2.36)		1.24 (0.97-1.59)	
Survival without morbidity[a]	4 (12)	5 (12)	23 (26)	19 (25)	27 (35)	48 (49)	47 (51)	70 (66)	61 (68)	64 (76)	162 (42)	206 (51)
RR (95% CI)	1.27 (0.16-9.9)		1.01 (0.60-1.7)		1.31 (0.91-.89)		1.34 (1.06-1.7)		1.09 (0.91-1.3)		1.23 (1.07-1.4)	
Survival[b]	11 (32)	20 (50)	59 (66)	51 (68)	62 (79)	82 (84)	75 (81)	94 (89)	83 (93)	81 (96)	290 (76)	328 (81)
RR (95% CI)	1.07 (0.54-2.10)		1.11 (0.91-1.35)		1.08 (0.95-1.23)		1.08 (0.96-1.21)		1.04 (0.98-1.10)		1.08 (1.02-1.2)	

Abbreviations: BPD, bronchopulmonary pulmonary dysplasia; CI, confidence interval; E1, epoch 1; E2, epoch 2; GA, gestational age; HC, head circumference; IVH, intraventricular hemorrhage; NICU, neonatal intensive care unit; PMA, postmenstrual age; ROP, retinopathy of prematurity; RR, relative risk.
[a] Survival without morbidity adjusted for the 5 Tyson et al[15] factors and cesarean section.
[b] Survival was adjusted for the 5 Tyson et al[15] factors, cesarean section, high-frequency ventilation, necrotizing enterocolitis, and IVH grade 3 or 4.

provement,[26] and an increase in adverse developmental outcomes in ELBWIs[27] during the 1990s have been reported. In our ELBWIs, the neurodevelopmental outcome in epoch 2 continued to improve. The decrease in adverse neurodevelopmental outcome occurred in infants born at 23 to 24 weeks' EGA. Of the various components of neurodevelopmental assessment, mental developmental index/cognitive-language score performed at this early age may not be very predictive of later cognitive outcome.[28] The assessment for CP is probably a more robust parameter of neurological morbidity at this early age. The concern for many investigators[5,29,30] is that the increase in survival would increase the prevalence of CP. Many studies[31-33] found a reduced rate of CP in spite of an increase in survival. The rate of CP among our NICU graduates dropped from epoch 1 to epoch 2. The absolute number of infants with CP decreased on average from 7 to 2 per year from epoch 1 to epoch 2.

New therapies for ELBWIs, introduced during epoch 2, could have caused the decrease in NDI. Several interventional factors, such as delayed cord clamping and use of nasal continuous airway pressure in the DR, may have affected neurodevelopmental outcome. In addition, the early use of volume expansion and vasopressors were restricted, and aluminum exposure was reduced. Because these changes started gradually and at different times during epoch 2, we were unable to ascertain their individual roles in the improved outcome of our ELBWIs. It is probable that the increased experience gained from caring for

Table 6. Final Model for Poisson Regression

	Adjusted RR (95% CI)		
	Survival	NDI	Severe NDI
GA	1.05 (1.01-1.10)	0.89 (0.78-1.02)	0.88 (0.71-1.09)
BW per 100 hg	1.05 (1.02-1.08)	0.99 (0.88-1.12)	1.00 (0.82-1.21)
Female	1.05 (0.99-1.13)	0.86 (0.69-1.09)	0.99 (0.68-1.43)
Cesarean section	1.08 (1.01-1.16)	1.00 (0.79-1.27)	1.16 (0.75-1.69)
Antenatal steroids	1.05 (0.96-1.14)	0.93 (0.72-1.20)	1.12 (0.75-1.66)
Singleton birth	1.00 (0.92-1.08)	0.79 (0.61-1.03)	0.66 (0.44-1.00)
African American	1.04 (0.97-1.11)	1.27 (0.98-1.64)	1.37 (0.91-2.05)
High-frequency ventilation	0.67 (0.59-0.77)		
IVH grade 3-4	0.82 (0.72-0.94)		
Necrotizing enterocolitis	0.76 (0.60-0.96)		
Epoch	1.09 (1.02-1.16)	0.68 (0.51-0.90)	0.40 (0.24-0.68)
BPD		1.28 (1.01-1.64)	1.31 (0.87-1.99)
HC <10th percentile at 36 wk PMA		1.31 (1.04-1.66)	1.83 (1.23-2.72)
WMI		1.89 (1.53-2.34)	2.88 (1.98-4.18)

Abbreviations: BPD, bronchopulmonary pulmonary dysplasia; BW, birth weight; CI, confidence interval; GA, gestational age; HC, head circumference; IVH, intraventricular hemorrhage; NDI, neurodevelopmental impairment; PMA, postmenstrual age; RR, relative risk; WMI, white matter injury.

Table 7. Morbidity in Infants LTFU vs Those Followed Up

	No. (%)			
	LTFU (n=122)		Followed Up (n=370)	
	E1	E2	E1	E2
Sample size	57	65	227	143
BPD	18 (32)	22 (34)	47 (21)	28 (20)[a]
WMI	12 (21)	8 (12)	41 (18)	9 (6)[b]
NEC	2 (3)	4 (6)	10 (4)	7 (5)
HC <10th percentile at 36 wk PMA	18 (33)	19 (30)	55 (25)	45 (32)
ROP	10 (17)	11 (17)	30 (13)	20 (14)
Morbidity	29 (51)	27 (41)	95 (42)	50 (35)

Abbreviations: BPD, bronchopulmonary pulmonary dysplasia; E1, epoch 1; E2, epoch 2; HC, head circumference; LTFU, lost to follow-up; NEC, necrotizing enterocolitis; PMA, postmenstrual age; ROP, retinopathy of prematurity; WMI, white matter injury.

[a] $P < .05$, LTFU infants vs those followed up in epoch 2.

[b] $P < .05$, epoch 1 vs epoch 2 among the infants followed up.

a large volume of very immature ELBWIs led to improved staff skills that profited the more mature ELBWIs.[32,34] Aggressive NICU management has increased the survival rate without affecting disability rates. In epoch 2, the rate of WMI declined and the survival without major morbidity increased. A more frequent use of HFV and ligation of the ductus arteriosus may be indicators of our "aggressive" approach. As shown by others,[35-38] factors associated with worse neurodevelopmental outcome were the presence of BPD and head circumference less than the 10th percentile at 36 weeks' PMA. While the rate of BPD was similar for both epochs, there was an increase in the rate of head circumference less than the 10th percentile at 36 weeks' PMA among the infants born at 22 weeks' EGA in epoch 2. In spite of the latter, NDI was not different among those infants; however, there remain concerns about their future learning abilities.[39]

A limitation to our study is the difference in the follow-up rates between epoch 1 and epoch 2. There are conflicting reports as to whether LTFU infants represent a population with lower or higher rates of neurodevelopmental morbidities than infants who undergo follow-up.[40-42] Our LTFU infants had a higher incidence of BPD than the followed-up ones. Consequently, our LTFU group may have had a higher risk for NDI. Thus, we may have underestimated the incidence of NDI. On the other hand, the changes over time in NICU morbidities were similar for both the LTFU and followed-up groups. Hence, the underestimation of the incidence of NDI would be of similar magnitude for both epochs. This similarity in morbidity rate among the LTFU infants should not affect the trend for improvement in NDI rates from epoch 1 to epoch 2. For statistical analysis, assuming the worst-case scenario that all LTFU infants either died or had NDI, the combined undesirable outcome (ie, death or NDI) in infants born at less than 25 weeks' EGA would have still dropped from 76% to 57% (RR, 0.77; 95% CI, 0.63-0.93) from epoch 1 to epoch 2.

To provide consistency and guidance to neonatal and obstetrical staff for counseling parents at the time of previability, Kaempf et al,[3] in 2003, developed a guideline table for initiation of prenatal and neonatal care at 22 to 26 weeks' EGA. Considering our results, if we adopt a similar approach, we will provide NICU care to the majority of the infants born at 24 weeks' EGA, instead of the age of 26 weeks' EGA recommended by Kaempf et al, and we will not offer NICU care for infants born at less than 22 weeks' EGA, instead of less than 23 weeks' EGA. In addition, we will not recommend NICU care at 22 weeks' EGA because of the high incidence of mortality and severe neuromotor disability. It is possible that with continued gain in experience and use of "novel" approaches a further improvement may be expected.[8,34]

Although our findings are encouraging for infants born at or beyond 23 weeks' EGA, further studies are needed to identify reasons for the continued improvement of ELBWIs and for the vast differences in outcome among NICUs.[21] In the interim, we suggest that each center offer prospective parents an assessment of the limits of viability based on the individual center's updated outcome results rather than on "national" statistics.

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Don't underestimate the value of doing nothing, of just going along, listening to all the things you can't hear, and not bothering.
—Winnie the Pooh