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Outcomes at 18 to 22 Months of Corrected Age for Infants Born at 22 to 25 Weeks of Gestation in a Center Practicing Active Management

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Objective To assess the outcomes in actively managed extremely preterm infants after admission to a neonatal intensive care unit.

Study design Retrospective cohort of 255 infants born at 22-25 weeks of gestation between 2006 and 2015 at a single study institution. Infants were excluded for congenital anomaly, death in delivery room, or parental request for palliation (n = 7). Neurodevelopmental outcomes were analyzed for 169 of 214 survivors (78.9%) at 18-22 months of corrected age. Outcomes were evaluated using the Mann-Whitney *U*, χ^2, or Fisher exact test, where appropriate. In addition, cognitive scores of the Bayley Scales of Infant-Toddler Development (3rd edition) were assessed using generalized estimating equations.

Results Seventy infants born at 22-23 weeks of gestation (22 weeks, n = 20; 23 weeks, n = 50) and 178 infants born at 24-25 weeks of gestation (24 weeks, n = 79; 25 weeks, n = 99 infants) were included. Survival to hospital discharge of those surviving to NICU admission was 78% (55/70; 95% CI, 69%-88%) at 22-23 weeks and 89% (159/178; 95% CI, 84%-93% at 24-25 weeks; *P* = .02). No or mild neurodevelopmental impairment in surviving infants was 64% (29/45; 95% CI, 50%-77%) at 22-23 weeks and 76% (94/124; 95% CI, 68%-83%; *P* = .16) at 24-25 weeks.

Conclusions Although survival was lower in infants born at 22-23 weeks than at 24-25 weeks of gestation, the majority of survivors in both groups had positive outcomes with no or mild neurodevelopmental impairments. Further evaluation of school performance is warranted. *(J Pediatr 2020;217:52-8)*.

See editorial, p 9

The decision to resuscitate preterm infants is based on many factors, including gestational age at delivery. At present, resuscitation at less than 24 weeks of gestation is not uniformly offered owing to concerns for futility or poor outcomes. Active measures, such as antenatal corticosteroid administration, are often reserved for infants past 24 weeks of gestation.[1,2] Several studies have demonstrated that an active approach at the hospital level could have a positive impact on infant outcomes,[1,3-7] and that antenatal steroids may have efficacy as early as 22 weeks.[8] In a recent study of outcomes across the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN), Rysavy et al found that differences in outcomes for infants born at 22-23 weeks could largely be explained by rates of active resuscitation offered by each institution.[1] Given the discrepancy in outcomes associated with center attitude toward resuscitation, we sought to delineate the outcomes of infants born at 22-23 weeks of gestation at a center in which an active approach is taken both antenatally and postnatally.

The purpose of this study was to describe survival and toddler age neurodevelopmental outcomes of infants born at 22-23 weeks compared with those born at 24-25 weeks of gestation in a center whose obstetricians and neonatologists provide both antenatal steroids and active resuscitation when desired by parents. We hypothesized that infants born at 22-23 weeks would be less likely to survive to hospital discharge than those born at 24-25 weeks, but that survivors would experience similar rates of in-hospital morbidity and neurodevelopmental outcomes at 18-22 months corrected age.

BSID-II	Bayley Scales of Infant-Toddler Development
NDI	Neurodevelopmental impairment
NEC	Necrotizing enterocolitis
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NICU	Neonatal intensive care unit
NRN	Neonatal Research Network

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Methods

After institutional review board approval, we conducted a retrospective cohort analysis of infants born at our institution from April 1, 2006, to December 31, 2015 at 22-25 weeks of completed gestation. Potential subjects were identified by a live birth registry maintained locally. No records are kept of fetuses alive at the onset of labor who are stillborn; thus, this study includes only those born alive, defined as any heart rate present at birth. All infants with gestational ages of 22-25 weeks are assessed routinely for a heart rate at birth by obstetric or pediatric providers, unless fetal demise is confirmed during labor, regardless of intent to resuscitate. We do not limit resuscitation based on size or weight at birth. Gestational age was assessed by best obstetrical estimate recorded in the maternal medical record. During the study period, all parents of fetuses at 22-23 weeks of gestation were offered active resuscitation. Throughout the same period, infants born at 24-25 weeks of gestation were resuscitated routinely. Neonatology fellows, with staff neonatologist on call as needed, attended the delivery when parents elected active treatment at 22-23 weeks, and for all births at 24-25 weeks. Infants were excluded from the present study if parents declined active resuscitation, the infant did not survive to admission to the neonatal intensive care unit (NICU), or if major congenital anomalies were present at birth.

In-Hospital Morbidity and Mortality

In-hospital data were recorded in a de-identified research database created in the RedCap system administered by the University of Iowa containing demographic, treatment, and outcome factors obtained from maternal and infant medical records.

Prenatal care was defined as at least 1 visit before admission for delivery of the infant. Antenatal steroid therapy was defined as any corticosteroids administered during the present pregnancy for the purpose of enhancing fetal lung maturity. Ideal antenatal steroid therapy was defined as at least 2 doses of corticosteroid with the first dose administered at least 48 hours before delivery and not more than 7 days before delivery. Delayed antenatal steroid therapy was defined as corticosteroid administration more than 7 days before delivery. Patent ductus arteriosus was defined as patent ductus arteriosus confirmed by echocardiography after 4 days of age. Intraventricular hemorrhage grade was reported based upon the Papile classification system.[9] Retinopathy of prematurity was defined as the highest stage reported during hospitalization by the examining ophthalmologist, using the International Classification of Retinopathy of Prematurity guidelines.[10] Bronchopulmonary dysplasia was defined as the use of supplemental oxygen at 36 weeks postmenstrual age. Necrotizing enterocolitis (NEC) was defined as neonatologist-diagnosed NEC or medical record documentation consistent with NEC stage 2 or greater based on the modified Bell criteria.[11] Survival to hospital discharge was defined at the time of hospital discharge or transfer to lower acuity NICU.

Neurodevelopmental Outcomes

NICHD NRN Follow-up Study data prospectively collected during the study period were reviewed retrospectively to evaluate neurodevelopmental outcomes at 18-22 months of corrected age. Infants who did not present for a follow up visit were considered lost to follow up; death after discharge could not be excluded in these infants. Neurodevelopmental outcomes were assessed by trained staff according to NRN guidelines. Neurologic examiners and those administering the Bayley Scales of Infant-Toddler Development, 3rd edition (BSID-III) were certified annually per NRN procedures.[12]

The follow-up visit at 18-22 months included a parent questionnaire, a neurologic examination, and neurodevelopmental testing including the BSID-III. The normative mean score for all BSID-III Scales is set at 100, with an SD of 15 points. Neurodevelopmental impairment (NDI) was defined as none or mild if infants were free from hearing impairment, visual impairment, and cerebral palsy and had BSID-III cognitive composite scores of 85 or greater (up to 1 SD below the mean). Because there is no standard definition of no impairment, and a developmental test score of 1 deviation below the mean or greater is considered normal, we have classified all children who were free of sensory impairment and had cognitive scores of more than 85 as no or mild NDI to highlight that these children, despite normal test scores, are still at long-term developmental risk owing to extremely preterm birth. Moderate NDI was classified as 1 or more of mild or moderate cerebral palsy, Gross Motor Function Classification System level 2-3, or cognitive composite score of 70-84 (1-2 SD below the mean). Severe NDI was classified as blindness, deafness, severe cerebral palsy, Gross Motor Function Classification System level 4 or 5, or cognitive composite score of less than 70 (>2 SD below the mean). If values were missing, a chart review was performed to obtain the data for NDI classification; if data could not be verified via chart review, follow-up data were considered incomplete for that infant. Autism data were obtained through an NRN questionnaire asking the parent if the child had been diagnosed with autism by a physician (yes/no); formal autism screening was not performed as a part of the present study.

Statistical Analyses

Demographic, treatment, and outcome factors were compared between infants with gestational ages of 22-23 weeks and 24-25 weeks using the Wilcoxon test for continuous and dichotomous variables and the χ^2 or Fisher exact test for categorical variables with more than 1 level. Nonparametric tests were used owing concern for non-normality of distribution at the extremes of BSID-III composite scores. Differences were considered significant when *P* values were less than .05. The impact of gestational age on BSID-III composite cognitive score expressed as a continuous variable was also assessed using generalized estimating equations with gestational age expressed as a continuous variable. Secondary

Table I. Demographic data

Factors	Infants delivered at 22-23 weeks (n = 70)	Infants delivered at 24-25 weeks (n = 178)	*P* value
Female	36/70 (51)	93/178 (52)	.87
Gestational age, wk	23.3 (22.9 to 23.6)	25.0 (24.6 to 25.6)	<.001
Birth weight, g	546 (495 to 638)	716 (322 to 816)	<.001
Birth weight z-score	0.005 (−0.83 to 0.58)	0.19 (−0.74 to 0.68)	.42
Birth head circumference, cm	20.5 (20 to 21)	22.5 (21.5 to 23.25)	<.001
Birth head circumference z-score	−0.45 (−0.63 to 0.27)	−0.12 (−0.72 to 0.48)	.23
Discharge weight, g	3790 (2880 to 4290)	3365 (2880 to 3990)	.23
Discharge weight z-score	−0.44 (−1.01 to 0.08)	−0.49 (−1.1 to 0.07)	.66
Discharge head circumference, cm	35 (33 to 36)	34.3 (33 to 35.5)	.24
Discharge head circumference z-score	−1.01 (−1.54 to −0.31)	−0.70 (−1.35 to 0.11)	.21
Maternal age, y	26 (22 to 32)	28 (23 to 32.5)	.48
Maternal race/ethnicity			.75
White	47/70 (67)	128/178 (72)	
Black	11/70 (16)	23/178 (13)	
Other	12/70 (17)	27/178 (15)	
Gravidity	2 (1 to 3)	2 (1 to 4)	.55
Singleton gestation	47/69 (68%; 58%-79%)	139/176 (79%; 73%-85%)	.02
Cesarean delivery*	22/70 (31%; 20%-42%)	123/178 (69%; 62%-76%)	<.001
Any prenatal care†	65/70 (93%; 87%-99%)	169/178 (95%; 92%-98%)	.55
Antenatal steroids	64/70 (91%; 87%-99%)	166/173 (96%; 93%-98%)	.33
Doses of antenatal steroids	2 (1 to 2)	2 (2 to 2)	.01
Ideal antenatal steroids‡	27/54 (50%; 37%-63%)	56/132 (42%; 33%-51%)	.35

Data are presented as number/total (%; 95% CI) or median (IQR).
*No 22-week infants were delivered by cesarean, 22 of the 50 infants delivered at 23 weeks were delivered by cesarean.
†At least 1 prenatal visit before admission for delivery.
‡2 doses of steroids given 24 hours apart and completed > 24 hours but < 7d prior to birth.

analyses were performed with infants grouped by gestational week. SAS 9.4 (SAS Institute, Cary, North Carolina) and SPSS version 21 (SPSS Inc, Chicago, Illinois) were used for analyses.

Results

A total of 255 infants with gestational ages of 22-25 completed weeks were born at the study institution during the study period and entered into the locally maintained live birth registry (**Figure**; available at www.jpeds.com); 248 were included in the study. Seven infants were excluded for congenital anomaly (n = 1), no resuscitation performed per parent request (n = 4; 2 at 22 weeks and 2 at 23 weeks), and failure to survive to NICU admission (n = 2). Both infants who did not survive to NICU admission were delivered at 22 weeks of gestation; these infants had resuscitation initiated upon delivery, with a decision made by parents or providers in the delivery room that further resuscitation should not be pursued. All infants resuscitated at grater than 22 weeks survived to NICU admission. All included infants 22-25 weeks born with a heart rate are thus accounted for as follows: 70 infants were born at 22-23 weeks (22 weeks, n = 20; 23 weeks, n = 50) and 178 infants were born at 24-25 weeks (24 weeks, n = 79; 25 weeks, n = 99).

A comparison of demographic factors between infants born at 22-23 weeks and 24-25 weeks is presented in **Table I**. There was no significant difference in the overall receipt of antenatal steroid therapy. Receipt of prenatal care was similar in both groups and almost universal (93% at 22-23 weeks and 95% at 24-25 weeks with ≥1 prenatal clinic visit before the hospital admission for delivery). Of note, cesarean delivery was not performed at 22 weeks of gestation, whereas 44% of infants (95% CI, 31%-58%) born at 23 weeks of gestation were born by cesarean delivery. Maternal race was predominantly white in all groups (67%-72%), with no difference in reported race between mothers with infants delivered at 22-23 and 24-25 weeks.

In-Hospital Morbidity and Mortality

All infants were managed with high-frequency ventilation immediately on NICU admission, in a dedicated section of the NICU staffed with nurses, dieticians, and pharmacists who specialize in the care of extremely preterm infants. In-hospital treatment factors and outcomes for the two study groups are presented in **Table II**. Infants born at 22-23 weeks of gestation had a longer duration of mechanical ventilation (P = .001) than infants born at 24-25 weeks, with higher rates of surgical ligation of a patent ductus arteriosus (P = .04) and surgical NEC or spontaneous intestinal perforation (P = .01). There were no other differences in major neonatal morbidities between the 2 groups. In-hospital growth was similar in both groups of infants, with birth weight and head circumference z-scores in the normal range both at admission and discharge and loss of approximately 0.5 SD in z-score for weight and head circumference during hospitalization.

Infants in the 24-25 week group had higher survival (159/178 [89%]; 95% CI, 84-93%) than their 22-23 week counterparts (55/70 [78%]; 95% CI, 69-88%, P = .02; **Table II**). Among infants admitted to the NICU, survival was lowest in the infants born at 22 weeks of gestation, of whom 70% (95% CI, 48%-86%) survived, and highest in those born at 25 weeks, with 90% survival (95% CI, 82%-95%; P = .06; **Table III**; available at www.jpeds.com). Including the 2 infants born at 22 weeks who did not survive to NICU admission but had resuscitation attempted in the delivery

Table II. Survival and hospital morbidity

Factors	Infants delivered at 22-23 weeks (n = 70)	Infants delivered at 24-25 weeks (n = 178)	*P* value
Survival to discharge	55/70 (78%; 69%-88%)	159/178 (89%; 84%-93%)	.02
Surfactant administered	70/70 (100)	173/175 (99)	1.0
Length ventilation, d	63 (47-78)	48 (33-61)	.001
PDA	45/60 (75%; 64%-86%)	124/173 (72%; 65%-78%)	.62
PDA ligation performed	29/45 (64%; 50%-78%)	58/124 (47%; 38%-56%)	.04
IVH	18/65 (28%; 17%-39%)	47/173 (27%; 21%-34%)	.94
IVH grade			.84
I	4/18 (22%; 8%-46%)	15/46 (33%; 21%-47%)	
II	4/18 (22%; 8%-46%)	10/46 (22%; 12%-36%)	
III	4/18 (22%; 8%-46%)	10/46 (22%; 12%-36%)	
IV	6/18 (33%; 16%-56%)	11/46 (24%; 14%-38%)	
IVH grade III or IV	10/65 (15%; 8%-26%)	21/173 (12%; 8%-18%)	.51
Retinopathy of prematurity	45/55 (81%; 72%-92%)	117/161 (73%; 66%-80%)	.18
Retinopathy of prematurity stage ≥3			.72
3	7/45 (16%; 7%-29%)	13/117 (11%; 6%-18%)	
4	0/45 (0)	0/117 (0)	
5	0/45 (0)	0/117 (0)	
Laser photocoagulation	4/45 (9%; 1%-17%)	14/114 (12%; 6%-18%)	.54
Periventricular leukomalacia	3/61 (5%; 0%-10%)	16/169 (9%; 5%-14%)	.27
Bronchopulmonary dysplasia	54/55 (98%; 95%-100%)	156/160 (98%; 95%-100%)	1.0
NEC	9/64 (14%; 6%-22%)	16/169 (9%; 5%-14%)	.31
NEC Bell stage			.01
IIA	0/9 (0)	3/16 (19%; 6%-44%)	
IIB	1/9 (11%; 0%-46%)	9/16 (56%; 33%-77%)	
IIIA	1/9 (11%; 0%-46%)	0/16 (0)	
IIIB*	7/9 (78%; 44%-95%)	4/16 (25%; 10%-50%)	
Length of hospitalization, d	123 (95-150)	107 (88-130)	.06
Tracheostomy	1/42 (2%; 0%-12%)	3/125 (2%; 0%-7%)	.99
Ventriculoperitoneal shunt	3/42 (7%; 2%-20%)	3/121 (3%; 1%-7%)	.17

IVH, intraventricular hemorrhage; *PDA*, patent ductus arteriosus.
Data are presented as the proportion (%; 95% CI) or median (IQR).
*Includes spontaneous intestinal perforation.

room, survival at 22 weeks was 64% (95% CI, 43%-80% [14/22 vs 14/20]).

Neurodevelopmental Outcomes at 18-22 Months

Of the 248 infants originally included in the present study, 214 survived to 18-22 months and were eligible for neurodevelopmental follow-up. The follow-up visit was completed in 45 of 55 infants born at 22-23 weeks (82%; 95% CI, 69%-90%) and 124 of 159 of those born at 24-25 weeks (78%; 95% CI, 71%-84%). Vital status at 18-22 months corrected age was not formally assessed; however, 59% of infants who did not attend their neurodevelopmental follow-up visit were confirmed alive after 18-22 months corrected age, based on visits recorded in the electronic medical record. At 18-22 months corrected age, no infants born at 22-23 weeks and 2% of those born at 24-25 weeks had been diagnosed with autism, as assessed by parent questionnaire. Two percent of infants in each gestational category had undergone

Table IV. Survival and neurodevelopmental composite by week of gestational age

Characteristics	All	22 weeks	23 weeks	24 weeks	25 weeks	*P* value
Eligible	248	20	50	79	99	
Died	34 (14%; 10%-19%)	6/20 (30%; 14%-52%)	9/50 (18%; 10%-31%)	9/79 (11%; 6%-20%)	10/99 (10%; 5%-18%)	.06
Survived to hospital discharge	214 (86%; 81%-90%)	14/20 (70%; 48%-86%)	41/50 (82%; 69%-90%)	70/79 (89%; 80%-94%)	89/99 (90%; 82%-95%)	
Survived with no/mild NDI*,†	123/203 (61%; 54%-67%)	6/17 (35%; 17%-59%)	23/43 (53%; 39%-67%)	42/62 (68%; 55%-78%)	52/81 (64%; 53%-74%)	.33
Survived with mod/severe NDI*,†	46/203 (23%; 17%-29%)	5/17 (29%, 95% CI)	11/43 (26%; 15%-40%)	11/62 (18%; 10%-29%)	19/81 (23%; 15%-34%)	
Lost to follow-up	45/214 (21%; 16%-27%)	3/14 (21%; 7%-48%)	7/41 (17%; 8%-32%)	17/70 (24%; 16%-36%)	18/89 (20%; 13%-30%)	.83
Follow-up	169/214 (79%; 73%-84%)	11/14 (79%; 52%-93%)	34/41 (83%; 68%-92%)	53/70 (76%; 64%-84%)	71/89 (80%; 70%-87%)	
NDI among survivors (excludes survivors lost to follow-up)						
No/mild NDI	123/169 (73%; 66%-79%)	6/11 (55%; 28%-79%)	23/34 (68%; 51%-81%)	42/53 (79%; 66%-88%)	52/71 (73%; 62%-83%)	.33
Moderate NDI	36/169 (21%; 16%-28%)	3/11 (27%; 9%-57%)	8/34 (24%; 12%-40%)	9/53 (17%; 9%-29%)	16/71 (23%; 14%-34%)	.80
Severe NDI	10/169 (6%; 3%-11%)	2/11 (18%; 4%-49%)	3/34 (9%; 2%-24%)	2/53 (4%; 0%-13%)	3/71 (4%; 1%-12%)	.23

Data are presented as number or proportion (%; 95% CI).
The number of survivors with follow-up (169) + infants who died (34) = 203 in the total sample.
*Moderate or severe NDI corresponds with the definition of NDI used by Younge et al[16]; no or mild ND corresponds with the definition of unimpaired used by Younge et al.[16]
†Excludes infants without follow-up data.

tracheostomy; however, 1 infant born at 24-25 weeks used a home ventilator. No infants required total parenteral nutrition for nutrition.

Results of neurodevelopmental testing and classification of NDIs at 18-22 months corrected age are presented in Table IV. There were no significant differences in overall rates of moderate or severe NDI between infants born at 22-23 or 24-25 weeks ($P = .16$), however cerebral palsy was more prevalent in those born at 22-23 weeks than at 24-25 weeks ($P = .02$). Vision and hearing were normal in the majority of infants, with more than 98% of infants in each group requiring no vision correction or corrective lenses only. One child born at 24-25 weeks required hearing aids. The median BSID-III cognitive composite scores were similar between infants born at 22-23 weeks and those born at 24-25 weeks ($P = .18$). Univariable linear regression analysis demonstrated no significant effect of gestational age on cognitive score (beta, 1.348; $P = .19$). Likewise, there was no significant difference in the proportion of infants with cognitive composite scores of less than 70 ($P = .09$) or in those with scores of less than 85 ($P = .10$). Although not included in the overall classification of NDI, BSID-III language and motor composite scores were significantly lower in the infants born at 22-23 weeks (Table III). Table III describes the composite developmental outcomes by gestational week. The overall distribution of NDI categories did not differ by gestational week.

Discussion

In our almost 10-year cohort of actively treated infants born at 22-25 weeks of gestation, cognitive scores among survivors were similar between infants born at 22-23 weeks and 24-25 weeks. Additionally, the median BSID-III cognitive scores for both groups were in the range typically considered as unimpaired or mildly impaired (90 in both cohorts), rather than those typically considered as moderately or severely impaired. In our center, actively managed periviable infants born at 22-23 weeks survived at a lower rate (78%; 95% CI, 69%-88%) than those born at 24-25 weeks (89%; 95% CI, 84%-93%) for whom active management is the North American standard of care. The survival rate at 22-23 weeks significantly exceeded rates reported elsewhere.[13-16] Despite the increased number of periviable survivors, rates of either moderate or severe NDI among our survivors were similar at 22-23 weeks and 24-25 weeks. Additionally, our rate of unimpaired or mildly impaired survival at 22-23 weeks exceeded that described by other investigators[5,16]; 64% (95% CI, 50%-77%) of 22- to 23-week survivors had no or mild NDI at 18-22 months. Although there is debate concerning the ability of the BSID-III to predict outcomes in older children,[17] we note that the median cognitive composite score was the same in infants born at 22-23 weeks as those born at 24-25 weeks gestation. Although infants born at 22-23 weeks had higher rates of cerebral palsy and lower language and motor scores on the BISD-III than those born at 24-25 weeks, we did not find a large disparity in overall neurodevelopmental outcomes between infants for whom palliation is often recommended, compared with those for whom resuscitation is routinely recommended. This highlights the possibility of positive outcomes in infants born at 22-23 weeks with active prenatal and postnatal management. Indeed, the majority of surviving infants in our study experienced no or mild NDI (73% in the full cohort) at 18-22 months corrected age. This finding is consistent with trends throughout the NRN,[1,4,18] as well as outside of the US.[3,5,19] Most recently, a comparison of 22-week survival in a setting of universal resuscitation vs selective resuscitation based upon parental request showed that higher survival rates were achieved when 22 weeks infants were more commonly resuscitated.[7] Although our institution does selectively resuscitate based on parental request, our center's reputation for active management attracts a larger than average cohort of parents desiring resuscitation, broadening our experience in caring for these infants.

Before 1990, survival for infants born at 22-23 weeks was less than 10%.[20] By the mid-1990s, survival had improved to approximately 50%,[13-15,21-23] approaching our own survival data; however, neurodevelopmental outcomes in these early studies remained suboptimal,[13] possibly attributable to lack of antenatal steroid administration.[22,23] Younge et al reviewed outcomes of infants born at 22-24 weeks who were treated from 2000 to 2011 in the NRN.[16] Comparing outcomes across 4-year epochs, the authors found a significant increase in survival without NDI with advancing epoch, concomitant with increased rates of antenatal steroid administration.

Our center's practice of antenatal steroid administration, with antenatal steroids provided to 91% (22-23 weeks) and 96% (24-25 weeks) of mothers, may have contributed to the outcomes here reported. This high rate of steroid administration has been achieved through consensus among neonatologists and obstetricians that actively managed infants may achieve survival without NDI. There is also consensus that antenatal steroid administration can be uncoupled from the need for emergent cesarean delivery for neonatal distress at 22-23 weeks of gestation when this procedure carries disproportionately high morbidity for mothers.[24,25] In our study population, no cesarean deliveries were performed at 22 weeks, and fewer infants at 23 weeks (44%) were delivered by cesarean than those at 24-25 weeks (69%). Antenatal steroid use at the study institution stands in contrast to NICHD NRN centers as a whole, who in 2008-2012 reported delivery of antenatal steroids to only 14% of women delivering at 22 weeks and 63% at 23 weeks.[26] The impact of antenatal steroid administration on survival has been well-documented,[8,18,19,27-30] as has the tendency to limit this therapy for births at 22 weeks.[23,31,32] The impact of hospital-level attitude toward active management of infants at the limit of viability has likewise been established in the US[1] and elsewhere.[3,7,19]

The present study is limited by its single institution demographic; however, this limitation allowed for consistent neurodevelopmental testing at 18-22 months by NRN-trained examiners, as well as uniform perinatal management. The study institution's participation in the NRN facilitated this retrospective analysis with prospective collection of data on neurodevelopmental outcomes and 79% follow-up of treated children. Because the NRN does not perform follow-up on outborn infants, our study is limited to inborn infants. It is also important to note that our sample size is low, with only 20 infants born and 11 followed at 22 weeks and 50 infants born and 34 followed at 23 weeks. We have accounted for all inborn infants with a heart rate at birth, regardless of intent to resuscitate and our sample size reflects the population size of our state. Although we do not have complete data, if all lost subjects were classified as severe NDI, the rates of severe NDI would be 36%, 24%, 27%, and 23% at 22, 23, 24, and 25 weeks, respectively. As the loss to follow-up rate was similar in all gestational age week groups, we have no reason to suspect that the reasons for loss to follow-up differed by gestational week.

In addition to the exclusion of outborn infants, our study population characteristics create further limitations which impact the ability to generalize our results broadly. The majority (70%) of our study population was white. Maternal race did not vary by gestational age group, and is reflective of the population of the state of Iowa as a whole. The overall low racial diversity limits the ability to translate to a more diverse population. Our mothers also received at least one prenatal visit at extremely high rates (>90% in all groups); thus, our results are not generalizable to populations with low rates of prenatal care.

Because our population was identified retrospectively from a locally maintained database of live births, we were unable to track the course of each fetus alive at 22-25 weeks whose mother presented to and delivered at our hospital. Although it is standard in our institution for an obstetric or pediatric provider to assess all births at these gestations for a heart rate unless fetal demise was confirmed during labor, we cannot be certain this was done in all cases, and thus we may have missed some live births that were classified as stillbirths. However, every fetus delivered at 22-25 weeks that was assessed and had a heart rate at birth was entered into the database, and we did not exclude any from the initial study sample.

The present investigation demonstrates favorable survival and neurodevelopmental outcomes for a contemporary cohort of infants born at 22-25 weeks of gestation managed actively in a tertiary referral center. We speculate that the institutional philosophy of active management in this population by both obstetricians and neatologists and high rates of antenatal steroids may be related to these findings. Because outcomes may change over time, further investigation of the school performance of actively managed infants born at 22-23 weeks of gestation will be important. ■

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References

1. Rysavy MA, Das A, Hintz SR, Stoll BJ, Vohr BR, et al. Between-hospital variation in treatment and outcomes in extremely preterm infants. N Engl J Med 2015;372:1801-11.
2. Management of preterm labor. Practice Bulletin No. 159. American College of Obstetricians and Gynecologists. Obstet Gynecol 2016;127:e29-38.
3. Hakansson S, Holmgren PA, Serenius F, Hogberg U. Proactive management promotes outcome in extremely preterm infants: a population-based comparison of two perinatal management strategies. Pediatrics 2004;114:58-64.
4. Kyser KL, Bell EF, Klein JM, Dagle JM. Improving survival of extremely preterm infants born between 22 and 25 weeks of gestation. Obstet Gynecol 2012;119:795-800.
5. Mehler K, Oberthuer A, Keller T, Becker I, Valter M, Roth B, et al. Survival among infants born at 22 or 23 weeks' gestation following active prenatal and postnatal care. JAMA Pediatr 2016;170:671-7.
6. Kono Y, Yonemoto N, Nakanishi H, Kusuda S, Fujimura M. Changes in survival and neurodevelopmental outcomes of infants born at <25 weeks' gestation: a retrospective observational study in tertiary centres in Japan. BMJ Paediatr Open 2018;2:e000211.
7. Backes CH, Soderstrom F, Agren J, Sindelar R, Bartlett CW, Rivera BK, et al. Outcomes following a comprehensive versus a selective approach for infants born at 22 weeks of gestation. J Perinatol 2019;39:39-47.
8. Ehret DEY, Edwards EM, Greenberg LT, Bernstein IM, Buzas JS, Soll RF, et al. Association of antenatal steroid exposure with survival among infants receiving postnatal life support at 22 to 25 weeks' gestation. JAMA Network Open 2018;1:e183235.
9. Papile LA, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500gm. J Pediatr 1978;92:529-34.
10. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005;123:991-9.
11. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. Pediatr Clin North Am 1986;33:179-201.
12. Newman JE, Bann CM, Vohr BR, Dusick AM, Higgins RD. Improving the Neonatal Research Network annual certification for neurologic examination of the 18-22 month child. J Pediatr 2012;161:1041-6.
13. Wood NS, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. N Engl J Med 2000;343:378-84.
14. Lee SK, Ohlsson A, Pendray M, Synnes A, Whyte R, Chien LY, et al. Variations in practice and outcomes in the Canadian NICU network: 1996-1997. Pediatrics 2000;106:1070-9.
15. Vanhaesebrouck P, Allegaert K, Bottu J, Debauche C, Devlieger H, Docx M, et al. The EPIBEL study: outcomes to discharge from hospital for extremely preterm infants in Belgium. Pediatrics 2004;114:663-75.
16. Younge N, Goldstein RF, Bann CM, Hintz SR, Patel RM, Smith PB, et al. Survival and neurodevelopmental outcomes among periviable Infants. N Engl J Med 2017;376:617-28.
17. Hack M, Taylor HG, Drotar D, Schuchter M, Cartar L, Wilson-Costello D, et al. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. Pediatrics 2005;116:333-41.
18. Smith BP, Li L, Cotten CM, Laughon M, Walsh MC, Das A, et al. Approach to infants born at 22 to 24 weeks' gestation: relationship to outcomes of more mature infants. Pediatrics 2012;129:e1508-16.
19. Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, et al. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol 2007;196:e141-8.
20. Tin W, Wariyar U, Hey E. Changing prognosis for babies of less than 28 weeks' gestation in the north of England between 1983 and 1994. Northern Neonatal Network. BMJ 1997;314:107-11.
21. Outcome at 2 years of children 23-27 weeks' gestation born in Victoria in 1991-92. The Victorian Infant Collaborative Study Group. J Paediatr Child Health 1997;33:161-5.

22. Wood NS, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR. The EPICure study: associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. Arch Dis Child Fetal Neonatal Ed 2005;90:F134-40.
23. Costeloe HE, Gibson AT, Marlow N, Wilkinson AR. The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability. Pediatrics 2000;106:659-71.
24. Blanc J, Resseguier N, Goffinet F, Lorthe E, Kayem G, Delorme P, et al. Association between gestational age and severe maternal morbidity and mortality of preterm cesarean delivery: a population-based cohort study. Am J Obstet Gynecol 2019;220:399.e1-9.
25. Kilpatrick SJ, Abreo A, Gould J, Greene N, Main EK. Confirmed severe maternal morbidity is associated with high rate of preterm delivery. Am J Obstet Gynecol 2016;215:233.e1-7.
26. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. JAMA 2015;314:1039-51.
27. Abbasi S, Gerdes J, Sedhev H, Ludmir J. Antenatal corticosteroids prior to 24 weeks' gestation and neonatal outcome of extremely low birth weight infants. Am J Perinatol 2010;27:61-6.
28. Carlo WA, McDonald SA, Fanaroff AA, Vohr BR, Stoll BJ, Ehrenkranz RA, et al. Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. JAMA 2011;306:2348-58.
29. Ochiai M, Kinjo T, Takahata Y, Iwayama M, Abe T, Ihara K, et al. Survival and neurodevelopmental outcome of preterm infants born at 22-24 weeks of gestational age. Neonatology 2014;105:79-84.
30. Zayek MM, Hamm CR, Peevy KJ, Benjamin JT, Eyal FG. The limit of viability: a single regional unit's experience. Arch Pediatr Adolesc Med 2011;165:126-33.
31. Fellman V, Hellström-Westas L, Normal M, Westgren M, Kallen K, Lagercrantz H, et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. JAMA 2009;301:2225-33.
32. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics 2010;126:443-56.

50 Years Ago in *The Journal of Pediatrics*

Acceptance of Unsalted Strained Foods by Normal Infants

Fomon S, Thomas LN, Filer LJ. J Pediatr 1970;76:242-6

The World Health Organization recommends starting complementary feeding at approximately 6 months of age, when "breast milk alone is no longer sufficient to meet all nutritional requirements."[1] Over time, there has been increased consensus on the proper timing of complementary feeding, as well as its content.

This 1970 study by Fomon et al compared consumption of salted and unsalted foods by 4-month-old and 7-month-old infants. Salt content did not appear to affect food intake in both groups; however, the mean intake of sodium was 4 times greater when salted foods were given. The authors concluded that, given the ready acceptance of unsalted foods by infants, there is no justification for adding salt to infant foods, and that the practice leads to higher than recommended daily salt intake.

Today, there is greater awareness of the effects of high salt consumption on the body. The Daily Recommended Value for sodium in infants (6-12 months) ranges from 120 to 370 mg/day.[2] In comparison, the 7-month-old subjects in the study by Fomon et al consumed an average of 632 mg of sodium from food; this calculation did not include the salt intake from cow's milk or formula, which is 86 and 52 mg of sodium/100 kcal, respectively. At the time, cow's milk consumption before 12 months of age was an accepted practice.

Today, commercially available foods in the US have significantly less sodium than the foods highlighted in the 1970 study. The American Academy of Pediatrics currently recommends that no salt (or sugar) be added to infant foods. Although there has been progress in the last 50 years in reducing infant sodium consumption, there are still many complementary foods currently marketed for infants (eg, infant snacks) that have high sodium content.[3] As a result, pediatricians may still need to counsel parents about this topic.

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References

1. World Health Organization. Complementary feeding: Summary of guiding principles. Report of the Global Consultation, Geneva, Switzerland, December 10-13, 2001. https://www.who.int/nutrition/publications/Complementary_Feeding.pdf. Accessed August 20, 2019.
2. European Food Safety Authority, Panel on Dietetic Products, Nutrition, and Allergies. Scientific opinion on nutrient requirements and dietary intakes of infants and young children in the European Union. EFSA J 2013;11:3408.
3. Maalouf J, Cogswell ME, Bates M, Yuan K, Scanlon KS, Pehrsson P, et al. Sodium, sugar and fat content of complementary infant and toddler foods sold in the United States, 2015. Am J Clin Nutr 2017;105:1443-52.

Table III. Outcomes at 18-22 months of corrected age among survivors with follow-up data

Outcomes	Infants delivered at 22-23 weeks (n = 45)	Infants delivered at 24-25 weeks (n = 124)	*P* value
Home ventilator	0/42 (0%; 0%-1%)	1/124 (1%; 0%-5%)	.56
Supplemental oxygen	7/42 (17%; 8%-31%)	8/124 (6%; 3%-12%)	.05
Total parenteral nutrition	0/41 (0%; 0%-10%)	0/124 (0%; 0%-4%)	1
Gastrostomy tube	3/40 (8%; 2%-21%)	19/125 (15%; 10%-22%)	.21
Oral diet consisting of solids	41/41 (100%; 90%-100%)	119/124 (96%; 91%-99%)	.19
Autism	0/41 (0%; 0%-10%)	2/89 (2%; 0%-8%)	.34
Gross motor function level <2	27/34 (79%; 63%-90%)	104/121 (86%; 79%-91%)	.09
Vision (normal or corrected with glasses)	35/35 (100%; 88%-100%)	112/114 (98%; 93%-100%)	.58
Hearing (normal or corrected with hearing aids)*	34/34 (100%; 88%-100%)	115/115 (100%; 96%-100%)	1
Cerebral palsy	7/38 (18%; 9%-34%)	14/124 (11%; 7%-18%)	.02
BSID-III Cognitive composite	90 (80-95)	90 (85-95)	.18
BSID-III Language composite	83 (74-94)	91 (77-97)	.01
BSID-III Motor composite	82 (78-87)	85 (79-91)	.04
BSID-III Cognitive Score <70	5/45 (11%; 4%-24%)	5/124 (4%; 2%-9%)	.09
BSID-III Cognitive Score <85	15/45 (33%; 21%-48%)	26/124 (21%; 15%-29%)	.10
NDI classification†			
No/mild NDI	29/45 (64%; 50%-77%)	94/124 (76%; 68%-83%)	.16
Moderate NDI	11/45 (24%; 14%-39%)	25/124 (20%; 14%-28%)	
Severe NDI	5/45 (11%; 4%-24%)	5/124 (4%; 1%-9%)	

Data are presented as a proportion (%; 95% CI) or median (IQR).
*One child in the 24-25 weeks group uses hearing aids; there are no cochlear implants in either group.
†NDI classification per Younge et al.[16]

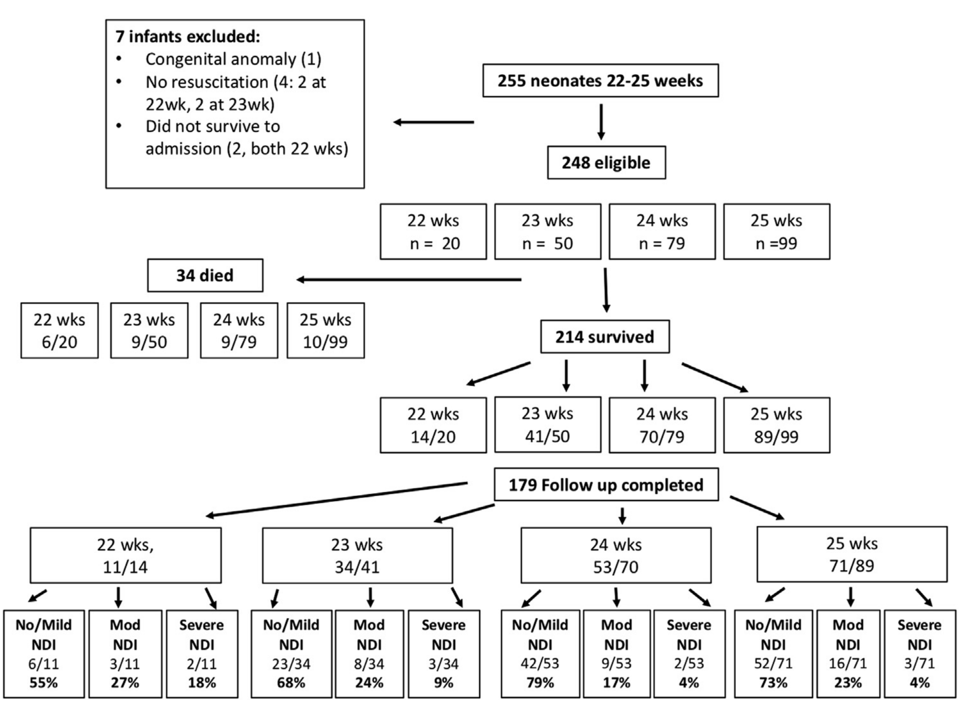

Figure. Flowchart of study population, survival, and developmental outcomes at 18-22 months of corrected age.