Neurodevelopmental and Growth Outcomes of Extremely Preterm Infants with Short Bowel Syndrome

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Objective To determine if preterm infants with surgical necrotizing enterocolitis (sNEC) or spontaneous intestinal perforation (SIP) with short bowel syndrome (SBS) have worse neurodevelopmental and growth outcomes than those with sNEC/SIP without SBS, and those with no necrotizing enterocolitis, SIP, or SBS.

Study design We undertook a retrospective analysis of prospectively collected data from infants born between 22 and 26 weeks of gestation in the National Institute of Child Health and Human Development Neonatal Research Network centers from January 1, 2008, to December 31, 2016. Survivors were assessed at 18-26 months corrected age by standardized neurologic examination and Bayley Scales of Infant and Toddler Development, Third Edition. The primary outcome was moderate-severe neurodevelopmental impairment. Growth was assessed using World Health Organization *z*-score standards. Adjusted relative risks were estimated using modified Poisson regression models.

Results Mortality was 32%, 45%, and 21% in the 3 groups, respectively. Eighty-nine percent of survivors were seen at 18-26 months corrected age. Moderate-severe neurodevelopmental impairment was present in 77% of children with SBS compared with 62% with sNEC/SIP without SBS (adjusted relative risk, 1.22; 95% CI, 1.02-1.45; $P = .03$) and 44% with no necrotizing enterocolitis, SIP, or SBS (adjusted relative risk, 1.60; 95% CI, 1.37-1.88; $P < .001$). Children with SBS had lowcognitive, language, and motor scores than children with sNEC/SIP without SBS. At follow-up, length and head circumference *z*-scores remained more than 1 SD below the mean for children with SBS.

Conclusions Preterm infants with sNEC/SIP and SBS had increased risk of adverse neurodevelopmental outcomes at 18-26 months corrected age and impaired growth compared with peers with sNEC/SIP without SBS or without any of these conditions. *(J Pediatr 2021;230:76-83)*.

Surgical necrotizing enterocolitis (sNEC) requiring extensive bowel resection is the leading cause of short bowel syndrome (SBS) in children born preterm.[1] The incidence of SBS is 0.7% in very low birth weight infants <1500 grams and 1.1% among infants <1000 grams with a mortality rate in affected neonates of ≤50%.[1,2] SBS is associated with a limited intestinal absorption of nutrients needed to maintain growth and fluid and electrolyte balance. Affected children have impaired growth, prolonged use of parenteral nutrition, and cholestasis, and are at increased risk for sepsis, each of which is independently associated with adverse neurologic outcome.[1,3-5] Previous studies have shown that extremely low birth weight infants with sNEC and those with intestinal failure are at an increased risk for poor neurodevelopmental outcomes

Bayley-III	Bayley Scales of Infant and Toddler Development, Third Edition	NICHD	National Institute of Child Health and Human Development
BPD	Bronchopulmonary dysplasia	NRN	Neonatal Research Network
CP	Cerebral palsy	PDA	Patent ductus arteriosus
EOS	Early onset sepsis	RDS	Respiratory distress syndrome
ICH	Intracranial hemorrhage	ROP	Retinopathy of prematurity
LOS	Late-onset sepsis	SIP	Spontaneous intestinal perforation
NEC	Necrotizing enterocolitis	SBS	Short bowel syndrome
		sNEC	Surgical necrotizing enterocolitis

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compared with their unaffected peers.[2,4,6-12] Hintz et al compared neurodevelopmental outcomes of preterm infants with sNEC to those with medical necrotizing enterocolitis (NEC) and found lower cognitive and motor scores on the Bayley Scales of Infant Development, Third Edition (Bayley-III) and an increased risk of cerebral palsy (CP) among those with sNEC.[4] In a cohort of 33 children with intestinal failure and mean gestational age 34 weeks, So et al found that gross motor abnormalities were present in >50% at both 1 and 2 years adjusted age and the majority had early learning deficits by 2 years of age.[11,12]

There are limited reports evaluating the neurodevelopmental outcomes of extremely preterm infants with a history of both sNEC and SBS leaving clinicians to extrapolate predicted outcome based on data from similar cohorts with a diagnosis of sNEC or intestinal failure. We used data from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) to examine in-hospital morbidities, growth at 36 weeks postmenstrual age, and neurodevelopmental outcomes and growth at 18-26 months corrected age in children born prematurely with a history of sNEC or spontaneous intestinal perforation (SIP) and SBS, sNEC/SIP without SBS, and neither NEC, SIP, nor SBS. Infants with a primary diagnosis of NEC or SIP were included in this analysis based on the overlap between these 2 surgical conditions.[13,14] We hypothesized that preterm infants with sNEC/SIP and SBS would have worse neurocognitive performance and poorer somatic growth at 18-26 months corrected age than survivors with sNEC/SIP without SBS and those unaffected by these conditions.

Methods

Study participants were included in a registry of high-risk infants maintained by the NRN. The study population consisted of infants born at 22-26 weeks gestational age at 21 NRN centers who survived >12 hours. Infants with a major birth defect or chromosomal anomaly were excluded. Surviving children who attended follow-up were assessed at 18-22 months corrected age (births before July 2012; 49% of the cohort) or 22-26 months corrected age (births in or after July 2012). The registry and follow-up studies were approved by the institutional review board at each center.

Maternal and neonatal data were collected from birth to discharge, transfer, 120 days, or death. Morbidities were defined in previous NRN publications.[15-18] NEC was defined as Bell stage IIA or greater, with stage IIIB considered sNEC and stages IIA-IIIA considered medical NEC.[19,20] SBS was defined based on documentation in the medical record and/or operative report and included malabsorption, severe diarrhea, gastric hypersecretion, bacterial overgrowth, and failure to thrive. Patients were categorized based on initial clinical impression but updated during the hospitalization if diagnosed with SBS.

The follow-up assessment included a neurologic examination and a developmental evaluation using the Bayley-III. Both were administered by certified examiners who completed annual training to ensure inter-rater reliability.[21]

When the NRN initially transitioned to the Bayley-III in 2006, only the cognitive and language subscales were administered. The motor scale of the Bayley-III was added starting January 1, 2010. More than 99% of children in the cohort were assessed in 2010 or later. The Bayley-III cognitive and motor composite scores are each normalized to mean ± SD scores of 100 ± 15. The gross motor and fine motor subscale scores have a mean ± SD of 10 ± 3. CP was defined using the Gross Motor Function Classification System as mild (level ≤1), moderate (level 2-3), or severe (level 4-5).[22]

Moderate/severe neurodevelopmental impairment was defined as 1 or more of moderate to severe motor impairment defined by a Gross Motor Function Classification System level ≥2, with or without CP; bilateral blindness with corrected vision of <20/200; bilateral hearing impairment defined as permanent hearing loss that did not permit the child to understand directions and communicate, with or without amplification; Bayley-III cognitive composite score of <85; or Bayley-III motor composite score of <85. Severe neurodevelopmental impairment was defined as one or more of a Gross Motor Function Classification System level ≥4, with or without CP; bilateral blindness; bilateral hearing impairment with or without amplification; Bayley-III cognitive composite score of <70; or Bayley-III motor composite score of <70.

Intestinal failure was defined as requiring parenteral nutrition for >60 days.[23] Enteral autonomy was defined as reaching 120 mL/kg/day of feedings. Feeding status at follow-up was determined by caretaker report. Weight, length, and head circumference were assessed by *z*-scores using Olsen standards at birth and 36 weeks postmenstrual age, and using the World Health Organization standards at follow-up based on corrected age.[24-26]

Statistical Analyses

Neurodevelopmental and growth outcomes were considered missing if the follow-up visit occurred at <14 or >32 months corrected age (1.5% of those assessed). Pairwise comparisons were made between infants with sNEC/SIP with SBS vs infants with sNEC/SIP without SBS and unaffected infants. Statistical significance for unadjusted comparisons was determined by χ^2 test (categorical variables) or Wilcoxon test (continuous variables); both are nonparametric tests that do not assume normality of the underlying distributions of the variables. Poisson regression models with robust variance estimators were used to assess the risk of binary outcomes, including in-hospital morbidities, death, the composite outcome death or moderate/severe neurodevelopmental impairment, and moderate/severe neurodevelopmental impairment, for infants with SBS compared with infants in the other groups while adjusting for study center, maternal race/ethnicity, maternal age, antenatal steroid use, multiple birth, infant sex, gestational age, and birth weight.[27]

Maternal education was included in models assessing neurodevelopmental and growth outcomes. Adjusted relative risks (aRR), 95% CIs, and *P* values by the Wald χ^2 test from these models were reported. Normally distributed continuous outcomes, including Bayley-III composite and scaled scores and growth *z*-scores, were compared using linear regression models. Birth weight was not included in the model assessing birth weight *z*-score. To address any concern of bias in our results owing to the inclusion of infants with SIP/SBS, a sensitivity analysis was performed assessing the composite outcome death or moderate/severe neurodevelopmental impairment and the outcome moderate/severe neurodevelopmental impairment in survivors excluding infants with SIP as a primary diagnosis from the sNEC groups. A *P* value of $< .05$ was considered significant. No adjustment was made for multiple comparisons; therefore, one result in 20 may be statistically significant by chance. Analyses were performed using SAS version 9.4 (SAS institute, Cary, N.C.).[28]

Results

Between January 1, 2008, and December 31, 2016, 7999 infants born at NRN centers with a gestational age of 22-26 weeks survived >12 hours, had no major birth defect, and were eligible for follow-up (**Figure 1**; available at www.jpeds.com). Of these infants, 429 diagnosed with medical NEC, 11 with SBS without NEC or SIP, and 7 with inconsistent data were not studied. The remaining 7552 infants were divided into 3 study groups: sNEC or SIP with

Table I. Maternal and neonatal characteristics of children born at 22-26 weeks gestational age who attended follow-up at 18-26 months corrected age

No. (column %) or as shown*	sNEC/SIP + SBS (n = 71)	sNEC/SIP without SBS (n = 373)	No NEC, SIP, or SBS (n = 4684)
Maternal and delivery characteristics			
Maternal age, years, mean (SD)	27.3 (6.1)	27.6 (6.2)	28.1 (6.3)
Maternal education	43	296	3699
Less than high school degree	10 (23.3)	57 (19.3)	769 (20.8)
High school degree	14 (32.6)	101 (34.1)	1062 (28.7)
Partial college, trade or technical school	12 (27.9)	72 (24.3)	940 (25.4)
College degree or more	7 (16.3)	66 (22.3)	928 (25.1)
Race/ethnicity			
Black	28 (39.4)	133 (35.7)	1934 (41.5)
White	27 (38.0)	148 (39.7)	1788 (38.4)
Hispanic	8 (11.3)	75 (20.1)	702 (15.1)
Other	8 (11.3)	17 (4.6)	234 (5.0)
Antenatal steroids	66 (93.0)	339 (90.9)	4253 (90.9)
Cesarean delivery	46 (64.8)	241 (64.6)	3035 (64.8)
Multiple birth	23 (32.4)	101 (27.1)	1174 (25.1)
Infant characteristics			
Gestational age, weeks, mean (SD)	24.8 (1.1)	24.5 (1.1)†	25.0 (1.0)
By gestational age week			
22	1 (1.4)	7 (1.9)†	43 (0.9)
23	8 (11.3)	64 (17.2)	399 (8.5)
24	19 (26.8)	118 (31.6)	1019 (21.8)
25	20 (28.2)	108 (29.0)	1424 (30.4)
26	23 (32.4)	76 (20.4)	1799 (38.4)
Birth weight, g, mean (SD)	735 (163)	714 (139)	763 (160)
SGA (23-26 weeks)	10 (14.3)	39 (10.7)	514 (11.1)
Male sex	39 (54.9)	202 (54.2)	2279 (48.7)
Apgar <5 at 5 minutes	20 (28.2)	107 (28.7)	950 (20.3)
Postnatal steroids for prevention/ treatment of BPD	12 (17.1)	96 (26.4)	1031 (23.2)
Parenteral nutrition during initial hospitalization, days, median (25th-75th percentile)	110 (74-119)	70 (47-96)‡	23 (16-34)‡
Intestinal failure§	60 (84.5)	228 (61.3)‡	178 (3.8)‡
Full enteral feeds achieved during hospital stay (120 mL/kg/day)	52 (73.2)	348 (93.3)‡	4654 (99.4)‡
Hospital stay, days, median (25th-75th percentile)	167 (137-208)	136 (113-168)‡	106 (89-129)‡
PMA at discharge, weeks, median (25th-75th percentile)	49 (45-56)	44 (41-48)‡	41 (38-44)‡

BPD, bronchopulmonary dysplasia; *PMA*, postmenstrual age; *SGA*, small for gestational age.

*Information was missing for maternal education, 1090 infants; maternal race/ethnicity, 26 infants; antenatal steroids, 6 infants; cesarean delivery, 1 infant; birth weight, 1 infant; infant sex, 4 infants; Apgar at 5 minutes, 12 infants; postnatal steroids, 259 infants; parenteral nutrition days, 11 infants; intestinal failure, 12 infants; full enteral feeds achieved, 1 infant; days until full feeds achieved, 78 infants; hospital stay and PMA at discharge, 160 infants (most were transfers with date of discharge to home missing). Among the 5077 infants born at 23-26 weeks of gestation, SGA was missing for 5 infants in the group with no NEC, SIP, or SBS.

†$P \leq .05$, ‡$P \leq .001$ for pairwise comparisons between infants with sNEC/SIP + SBS vs infants in each of the other 2 groups by the Wilcoxon test (maternal age, gestational age, birth weight, days on parenteral nutrition, days until full enteral feeds achieved, hospital stay, PMA at discharge), the row mean score χ^2 test (categorical gestational age), the general association χ^2 or Fisher exact test.

§Defined as requiring >60 days of parenteral nutrition.

SBS (n = 116), sNEC or SIP without SBS (n = 770), and no NEC, SIP, or SBS (n = 6666). Overall, 76% survived to follow-up age (68% of infants with sNEC/SIP with SBS, 55% with sNEC/SIP without SBS, 79% without NEC/SIP/SBS), and 89% of survivors completed a follow-up visit between October 2009 and August 2019, with similar proportions in each group (**Figure 1**). Of the 71 infants with SBS, 56 had sNEC and 15 had SIP; of the 373 infants with sNEC/SIP without SBS, 138 had sNEC and 235 had SIP. The 15 children in the SIP with SBS group underwent a median of 4 additional surgeries during the hospital stay, including bowel resection and ostomy placement.

Maternal and neonatal characteristics of infants with SBS were similar to those of infants in the other groups (**Table I**). Children with sNEC/SIP with SBS were less likely to achieve enteral autonomy, required more days of parenteral nutrition, and had a longer length of stay compared with those without SBS and those who were unaffected.

Rates of complications during the birth hospitalization are shown in **Table II** (available at www.jpeds.com). Rates of late-onset sepsis were higher in infants with NEC/SIP with or without SBS vs infants with no NEC/SIP/SBS (59%, 54%, and 25%, respectively). In contrast, periventricular leukomalacia occurred more frequently in infants with SBS compared with infants with sNEC/SIP without SBS (18% vs 10%; aRR, 2.09; 95% CI, 1.16-3.76; P = .01) and unaffected infants (18% vs 5%; aRR, 3.31; 95% CI, 1.97-5.55; P < .001). Retinopathy of prematurity stage ≥3 was more common in infants with SBS compared with those without NEC/SIP/SBS (43% vs 19%). The proportion of infants with BPD was highest among infants with SBS.

Death before follow-up occurred in 32% of children with sNEC/SIP with SBS vs 45% of children with sNEC/SIP without SBS (aRR, 0.78; 95% CI, 0.57-1.05; P = .10) and 21% of children without NEC/SIP/SBS (aRR, 1.42; 95% CI, 1.06-1.90; P = .02) (**Table III**). **Table IV** (available at www.jpeds.com) provides information on the timing of death in each group and the distribution of deaths before and after discharge. For sNEC/SIP groups with or without SBS, the primary cause of death was NEC with or without proven sepsis (data not shown). Risk for the composite outcome of death or moderate/severe neurodevelopmental impairment was similar for children who had sNEC/SIP with vs without SBS (85% vs 81%, P = .09); children with SBS were at increased risk for death or moderate/severe neurodevelopmental impairment compared with those without NEC/SIP/SBS (85% vs 57%; aRR, 1.43; 95% CI, 1.30-1.58; P < .001) (**Table III**).

Among survivors evaluated at follow-up, 77% of children with SBS had moderate/severe neurodevelopmental impairment compared with 62% of those with sNEC/SIP without SBS (aRR, 1.22; 95% CI, 1.02-1.45; P = .03) and 44% of those without NEC/SIP/SBS (aRR, 1.60; 95% CI, 1.37-1.88; P < .001). About one-half of the children with SBS had severe neurodevelopmental impairment compared with 38% of

Table III. Death and NDI in infants born at 22-26 weeks gestational age who were eligible for follow-up

				aRR (95% CI) for outcome*	
Outcomes, no. (column %)	**sNEC/SIP + SBS**	**sNEC/SIP without SBS**	**No NEC, SIP, or SBS**	**SBS vs sNEC/SIP w/o SBS**	**SBS vs no NEC/SIP/SBS**
No. of children eligible for follow-up	116	770	6666		
Died >12 h after birth and before follow-up	37 (31.9)	348 (45.2)	1402 (21.0)	0.78 (0.57-1.05)	1.42 (1.06-1.90)
No. of children who died before follow-up or survived and had nonmissing moderate/severe NDI	106	715	5923		
Death or moderate/severe NDI	90 (84.9)	576 (80.6)	3402 (57.4)	1.09 (0.99-1.21)	1.43 (1.30-1.58)
No. of children who died before follow-up or survived and had nonmissing severe NDI	104	711	5875		
Death or severe NDI	71 (68.3)	485 (68.2)	2163 (36.8)	1.11 (0.95-1.31)	1.81 (1.55-2.11)
No. of children seen at follow-up with nonmissing moderate/severe NDI	69	367	4521		
Moderate/severe NDI	53 (76.8)	228 (62.1)	2000 (44.2)	1.22 (1.02-1.45)	1.60 (1.37-1.88)
No. of children seen at follow-up with nonmissing severe NDI	67	363	4473		
Severe NDI	34 (50.7)	137 (37.7)	761 (17.0)	1.46 (1.09-1.95)	2.68 (2.05-3.49)

NDI, neurodevelopmental impairment.
*Relative risks and CIs from Poisson regression models fit to each outcome that included the group indicator, study center, maternal age, maternal race/ethnicity (Black, White, Hispanic, other), maternal education at the time of delivery (less than high school degree, high school degree, partial college, college degree or more, missing), maternal antenatal steroid use, multiple birth, infant sex, gestational age (categorical), and birth weight (continuous).

children with sNEC/SIP without SBS and 17% of those with no NEC/SIP/SBS. CP was diagnosed in 31% of children with sNEC/SIP with SBS compared with 28% of those with sNEC/SIP without SBS (aRR, 1.40; 95% CI, 0.96-2.06; $P = .08$) and 13% of those unaffected (aRR, 2.40; 95% CI, 1.69-3.41; $P < .001$) (**Table V**). Children with SBS had lower Bayley-III cognitive, language, and motor composite and subscale scores compared with children in the other 2 groups. When infants with a primary diagnosis of SIP were excluded, the relative risks for death or moderate/severe neurodevelopmental impairment, and moderate/severe neurodevelopmental impairment in survivors, were similar to those observed for the original groups (**Table VI**; available at www.jpeds.com).

At follow-up, 31 of the 71 children with SBS (44%) were independently feeding themselves compared with 65% of children with sNEC/SIP without SBS and 78% of those without NEC/SIP/SBS ($P < .001$). Eight children (11%) with SBS continued to receive parenteral nutrition compared with 1 child (0.3%) with sNEC/SIP without SBS and 7 (0.2%) of those without NEC/SIP/SBS ($P < .001$). Tube feedings were received by 23 children (32%) with SBS, 17% of those with sNEC/SIP without SBS, and 9% of those without these diagnoses. More than one-half of the children with SBS

Table V. Neurodevelopmental outcomes in children who attended follow-up at 18-26 months corrected age

Outcomes, no. (column %)	sNEC/SIP + SBS	sNEC/SIP without SBS	No NEC, SIP, or SBS	aRR (95% CI) for outcome or adjusted *P* value*	
				SBS vs sNEC/SIP w/o SBS	SBS vs no NEC/SIP/SBS
No. of children examined at follow-up†	71	373	4678		
Bilateral blindness	4 (5.6)	15 (4.0)	58 (1.2)	1.57 (0.54-4.61)	4.18 (1.53-11.42)
Hearing impairment	2 (2.8)	18 (4.9)	131 (2.8)	0.62 (0.15-2.64)	0.96 (0.24-3.84)
CP, any grade	22 (31.0)	103 (27.6)	618 (13.2)	1.40 (0.96-2.06)	2.40 (1.69-3.41)
CP, mild	4 (5.6)	35 (9.4)	331 (7.1)	0.63 (0.23-1.72)	0.75 (0.29-1.97)
CP, moderate	11 (15.5)	33 (8.8)	173 (3.7)	1.95 (1.04-3.63)	3.78 (2.17-6.61)
CP, severe	7 (9.9)	35 (9.4)	114 (2.4)	1.20 (0.55-2.61)	3.76 (1.79-7.91)
No. of children with a Bayley-III cognitive test	66	364	4557		
Cognitive CS, mean (SD)	75.2 (15.9)	81.5 (16.6)	88.0 (15.3)	<.001	<.001
Cognitive CS < 85	40 (60.6)	174 (47.8)	1436 (31.5)	1.26 (0.99-1.61)	1.79 (1.43-2.24)
Cognitive CS < 70	22 (33.3)	82 (22.5)	491 (10.8)	1.61 (1.08-2.40)	2.67 (1.86-3.85)
No. of children with a Bayley-III language test‡	65	362	4547		
Language CS, mean (SD)	71.9 (17.1)	77.6 (18.2)	83.4 (17.1)	.009	<.001
Language CS < 85	45 (70.3)	222 (62.0)	2246 (50.3)	1.08 (0.89-1.31)	1.24 (1.04-1.48)
Language CS < 70	31 (48.4)	122 (34.1)	891 (20.0)	1.48 (1.07-2.04)	2.14 (1.60-2.87)
Expressive communication scaled score, mean (SD)	5.8 (3.7)	6.5 (3.0)	7.3 (3.0)	.09	<.001
Receptive communication scaled score, mean (SD)	5.5 (2.6)	6.6 (3.0)	7.2 (3.0)	.008	<.001
No. of children with a Bayley-III motor test§	66	360	4515		
Motor CS, mean (SD)	70.6 (19.1)	77.9 (18.8)	87.1 (16.0)	<.001	<.001
Motor CS < 85	47 (73.4)	192 (54.4)	1492 (33.7)	1.34 (1.09-1.63)	1.94 (1.62-2.33)
Motor CS < 70	29 (45.3)	114 (32.3)	543 (12.3)	1.52 (1.09-2.11)	3.27 (2.42-4.43)
Gross motor scaled score, mean (SD)	5.0 (3.4)	6.0 (3.0)	7.4 (2.7)	.006	<.001
Fine motor scaled score, mean (SD)	5.6 (3.3)	7.2 (3.3)	8.5 (2.9)	<.001	<.001

CS, composite score.

*RRs and CIs from Poisson regression models fit to each outcome that included the group indicator, study center, maternal age, maternal race/ethnicity (Black, White, Hispanic, other), maternal education at the time of delivery (less than high school degree, high school degree, partial college/trade or technical school, college degree or more, missing), maternal antenatal steroid use, multiple birth, infant sex, gestational age (categorical), and birth weight (continuous), except as noted. RRs for blindness, hearing impairment, mild CP, moderate CP, and severe CP were adjusted for gestational age and birth weight only owing to small numbers in some groups. Adjusted *P* values by *t* test from linear regression models that included the covariates listed above.

†Among children seen at follow-up with a child examination form, information was missing for blindness, 10 children; hearing impairment, 38 children; and CP, 10 children.

‡Among children with at least 1 Bayley-III language composite, expressive communication, or receptive communication score, information was missing for language composite score, 87 children; expressive communication score, 163 children; and receptive communication score, 141 children.

§Among children with at least 1 Bayley-III motor composite, gross motor, or fine motor score, information was missing for motor composite score, 92 infants; gross motor score, 165 infants; and fine motor score, 122 infants.

were receiving high calorie supplements (63%) compared with 42% and 27% in the other 2 groups ($P < .001$). Mean *z*-scores for weight, length, and head circumference were close to zero at birth in all groups, and decreased between 1 and 2 SDs at 36 weeks postmenstrual age (**Figure 2**). Decreases for infants with SBS did not differ significantly compared with infants with sNEC/SIP without SBS, but were lower on all measures compared with infants with no NEC/SIP/SBS ($P < .001$ for each). At 18-26 months corrected age, the *z*-scores had improved in all groups but continued to be lower than at birth. Length and head circumference z-scores were significantly lower at 18-26 months for children with SBS compared with those with no NEC/SIP/SBS ($P = .002$ and $P < .001$, respectively).

Discussion

Despite many advances in neonatal care, NEC continues to be a major complication of premature birth and children with NEC/SIP are at increased risk for adverse neurodevelopmental outcome compared with unaffected peers.[4,8,9,12] However, limited data are available on the neurodevelopmental outcomes of those who develop SBS as a consequence of this disease process.

Using the NRN database, Wadhawan et al found surviving preterm infants with a history of sNEC or SIP had a 2-fold increased risk of death and/or moderate/severe neurodevelopmental impairment at 18-22 months compared with those who were unaffected.[29] We now report that SBS further modifies these outcomes; the proportion of children with moderate/severe neurodevelopmental impairment was greater and the mean cognitive, language, and motor scores lower for children with sNEC/SIP and SBS than for children with sNEC/SIP without SBS. Our data are consistent with previous analyses by So and Chesley who reported that motor and cognitive delays are common in children with a history of neonatal intestinal failure in early childhood.[10,11]

NEC continues to be an important cause of neonatal mortality in preterm infants. In our cohort, the proportion of infants who died before follow-up was greatest among those with sNEC/SIP without SBS (45%) with smaller proportions among infants with sNEC/SIP and SBS (32%) and in those unaffected (21%). These patterns are similar to a prior 2008 report from the NRN and a recent meta-analysis of infants with NEC.[1,2] Infants with sNEC/SIP without SBS may include those who died before or shortly after surgical intervention that could have preceded a diagnosis of SBS. Therefore, surviving infants without SBS may have been those with less severe disease. This potential selection bias may have impacted our findings.

There is a complex relationship between prematurity, neonatal morbidity, and brain injury. In our study, infants with SBS were more likely to have neonatal morbidities such as BPD, late-onset sepsis, and periventricular leukomalacia, all known to be independently associated with adverse neurodevelopmental outcome. The additive effect of premature birth, compromised nutrition, and increased risk of exposure to proinflammatory states owing to bowel injury, chronic inflammation, or blood stream infection is unknown. Animal and clinical models demonstrate that the developing white matter in the preterm brain is vulnerable to cytotoxic injury.[30,31] We speculate that morbidities associated with a proinflammatory state likely modify the risk for adverse neurodevelopmental outcome in this population.

There is a positive correlation between nutrition, brain volume, and neurodevelopmental outcomes at 2 years of age in children born preterm.[32] We tracked longitudinal growth outcome data in this high-risk population of premature children with a history of sNEC/SIP, and found deficits in weight, length, and head circumference measurements for infants with and without SBS that were sustained at follow-up. Children with sNEC with or without SBS were also more likely to have abnormal feeding at follow-up, which highlights the importance of close postdischarge nutritional management in these children.

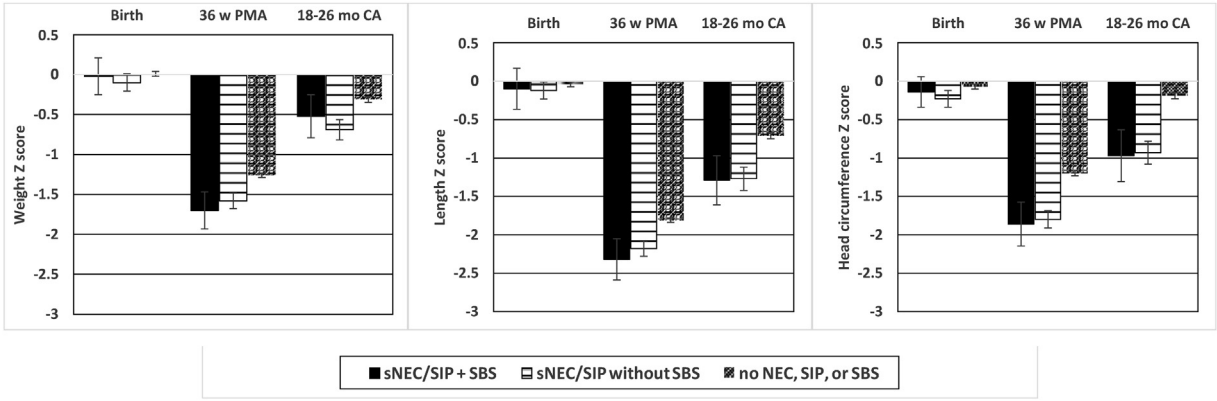

Figure 2. Mean *z*-scores for sex and age at birth, 36 weeks postmenstrual age (PMA), and 18-26 months corrected age in children who attended follow-up. Narrow bars show 95% CIs.

A strength of our study was the ability to include comprehensive, prospectively collected data for preterm infants from 21 centers. Even though sNEC is a common complication of prematurity, infants with SBS comprise a rare subgroup that is difficult to study. However, a limitation of our data collection was that we lacked detailed surgical data, including remaining bowel length or presence of an ileocecal valve. The definition of SBS was based on abstraction from the medical record, which could result in over- or under-representation of the disease population. We have limited data on the use of lipid minimization strategies and, therefore, are unable to interpret any potential impact on outcome.

In conclusion, surviving preterm infants with sNEC/SIP and SBS were at greater risk for neurodevelopmental impairment and cognitive, language, and motor deficits at 18-26 months corrected age than children with sNEC/SIP without SBS. The impact of suboptimal nutrition during critical periods of brain development in this population needs further study to understand whether it independently modifies long-term outcome in this population. ■

*We are indebted to our medical and nursing colleagues (**Appendix**) and the infants and their parents who agreed to take part in this study.*

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Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *The Journal of Pediatrics*

Searching for Survivors–Chemotherapy for Treatment of Acute Myelogenous Leukemia

Freedman MH, Finklestein JZ, Hammond GD, Karon M. The effect of chemotherapy on acute myelogenous leukemia. J Pediatr 1971;78:526-32

Until the late-1950s, acute myelogenous leukemia (AML) in children was a death sentence. Most were offered supportive care and survived only a few months. This seminal publication by Freedmen et al reported a high morphologic remission rate of 70% and prolonged median survival of 9.5 months in 60 patients with AML treated from 1956 to 1968 with combination chemotherapy. This study was the start of 50 years of effective combination chemotherapy regimens used for AML.

Since then, we have optimized the chemotherapy backbone to include high-dose cytarabine and anthracyclines. We can now better stratify patients at high risk of relapse by measuring minimal residual disease by flow cytometry and identify chemoresistance-conferring mutations with next-generation sequencing.[1] Stem cell transplant, which was just being investigated at the time of Freedman et al's study, has since been found to be curative even in the end stages of AML by the 1970s[2] and is currently the treatment of choice for high-risk AML. Second-generation molecular inhibitors of fms-related receptor tyrosine kinase 3 internal tandem duplications and activating tyrosine kinase domain mutations, DNA methyltransferase, and isocitrate dehydrogenase, B-cell lymphoma 2, along with antibody-drug conjugates and bispecific targeted antibodies such as gemtuzumab ozogamicin and flotetuzumab have been developed and are beginning to change the treatment paradigm in AML. Based on 50 years of treatment advances in AML, the 5-year event-free survival rates for childhood AML are now 60%-70%, with survivors living late into adulthood. Despite these advances, high-risk AML is still associated with poor outcomes and presents a major challenge to oncologists. With the advances in CAR (chimeric antigen receptor)-T technology, immunology, pharmacogenomic research, and novel targeted agents, just imagine how pediatric AML therapy will change in the next 50 years!

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Appendix

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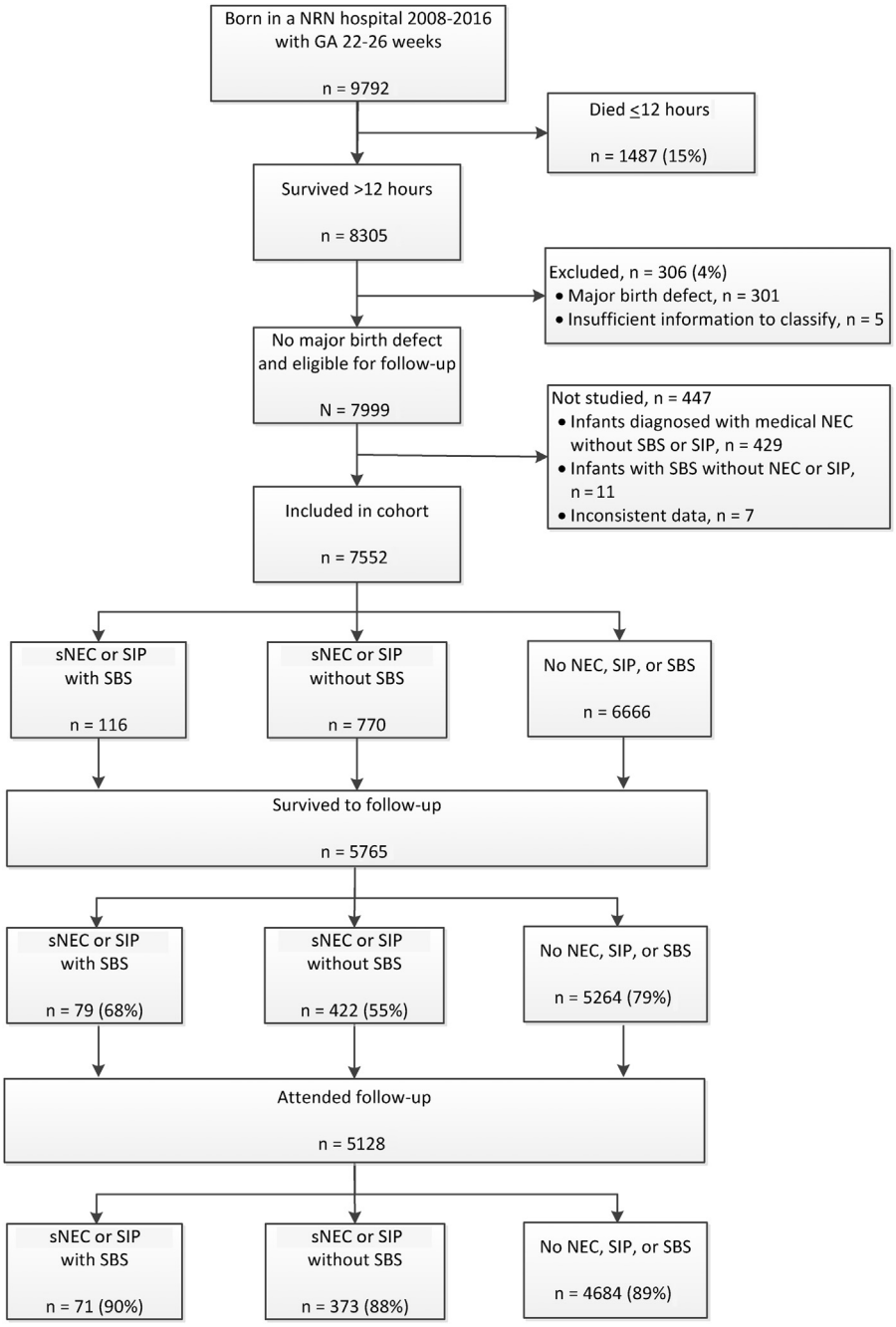

Figure 1. Study population flow diagram. Attendance at follow-up was defined based on the presence of 2 key study forms: Infant Examination Form and Bayley-III Scales Summary Score Sheet. Infants without these forms but with other limited data reported were considered to have incomplete follow-up. Owing to missing information, moderate/severe neurodevelopmental impairment could not be determined for all infants who attended follow-up. Survivors to follow-up included sNEC/SIP with SBS—69 with nonmissing moderate/severe neurodevelopmental impairment, 2 with key forms but missing moderate/severe neurodevelopmental impairment, 1 with incomplete follow-up, and 7 lost to follow-up; sNEC/SIP without SBS—367 nonmissing moderate/severe neurodevelopmental impairment, 6 with key forms but missing moderate/severe neurodevelopmental impairment, 9 with incomplete follow-up or late visit outside of the allowable time frame, and 40 lost to follow-up; and no NEC, SIP, or SBS—4521 with nonmissing moderate/severe neurodevelopmental impairment, 163 with key forms but missing moderate/severe neurodevelopmental impairment, 110 with incomplete follow-up or late visit, and 470 lost to follow-up.

Table II. In-hospital morbidities for infants born at 22-26 weeks gestational age who attended follow-up

Outcomes, no. (column %)*	sNEC/ SIP + SBS (n = 71)	sNEC/SIP without SBS (n = 373)	No NEC, SIP, or SBS (n = 4684)	aRR (95% CI) for outcome†	
				SBS vs sNEC/SIP w/o SBS	SBS vs no NEC/SIP/SBS
RDS	67 (94.4)	368 (98.7)	4578 (97.7)	0.96 (0.91-1.02)	0.96 (0.91-1.02)
PDA	41 (57.7)	231 (61.9)	2606 (55.6)	0.85 (0.69-1.03)	0.94 (0.78-1.13)
EOS	2 (2.8)	13 (3.5)	96 (2.0)	0.86 (0.20-3.68)	1.31 (0.34-5.04)
LOS	42 (59.2)	200 (53.6)	1186 (25.3)	1.19 (0.95-1.47)	2.20 (1.80-2.68)
No. of infants with cranial ultrasound examinations within 28 d	71	371	4665		
Severe ICH	12 (16.9)	88 (23.7)	661 (14.2)	0.91 (0.54-1.55)	1.27 (0.77-2.09)
No. of infants with cranial imaging within 28 d and/or closest to 36 weeks	71	373	4678		
PVL	13 (18.3)	36 (9.7)	249 (5.3)	2.09 (1.16-3.76)	3.31 (1.97-5.55)
No. of infants evaluated for severe ICH or PVL‡	71	371	4666		
Severe ICH or PVL	22 (31.0)	102 (27.5)	750 (16.1)	1.37 (0.93-2.01)	1.98 (1.40-2.82)
No. of infants in hospital at 28 d examined for ROP	70	373	4645		
ROP	62 (88.6)	330 (88.5)	3270 (70.4)	1.06 (0.97-1.17)	1.23 (1.13-1.35)
ROP stage ≥ 3	30 (42.9)	153 (41.0)	888 (19.1)	1.19 (0.86-1.66)	2.04 (1.49-2.79)
No. of infants evaluated for BPD§	71	373	4666		
BPD (oxygen use at 36 weeks)	51 (71.8)	247 (66.2)	2741 (58.7)	1.11 (0.95-1.29)	1.16 (1.01-1.33)
No. of infants evaluated for physiologic BPD	69	370	4645		
BPD by physiologic definition	49 (71.0)	252 (68.1)	2639 (56.8)	1.05 (0.90-1.23)	1.16 (1.00-1.34)

BPD, bronchopulmonary dysplasia; *EOS*, early onset sepsis; *ICH*, intracranial hemorrhage; *LOS*, late-onset sepsis; *PDA*, patent ductus arteriosus; *PVL*, periventricular leukomalacia; *RDS*, respiratory distress syndrome defined as clinical features within 24 hours of birth and/or surfactant use within 72 hours; *ROP*, retinopathy of prematurity.

*Information was missing for PDA, 1 infant.

†Relative risks and CIs from Poisson regression models fit to each outcome that included the group indicator, study center, maternal age, maternal race/ethnicity (Black, White, Hispanic, other), maternal antenatal steroid use, multiple birth, infant sex, gestational age (categorical), and birth weight (continuous), except as noted. The RRs comparing risk of RDS, EOS, and PVL were adjusted for gestational age and birth weight only owing to small numbers in some groups.

‡Presence of ICH and/or PVL was determined for infants with nonmissing ICH and PVL outcomes, except that a diagnosis of either condition was sufficient to set the outcome.

§Of infants evaluated for BPD, 93% were still in the hospital at 36 weeks PMA, 4% had been discharged home, and 3% had been transferred to another hospital.

Table IV. Death before follow-up in infants eligible for follow-up

Groups	Proportion of infants who died, n/N (%)			Timing of death (day of life)	
	All deaths before follow-up	Deaths before discharge	Deaths after discharge	Mean (SD)	Median (p25, p75)
1: sNEC/SIP + SBS	37/116 (31.9)	32/116 (27.6)	5/116 (4.3)	141 (134.0)	76 (30, 229)
2: sNEC/SIP without SBS	348/770 (45.2)	334/770 (43.4)	14/770 (1.8)	53.4 (92.7)	26 (13, 48)
3: No NEC, SIP or SBS	1402/6666 (21.0)	1333/6666 (20.0)	69/6666 (1.0)	40.6 (85.9)	9 (3, 23.5)
1: sNEC + SBS*	33/96 (34.4)	29/96 (30.2)	4/96 (4.2)	123 (127)	64 (29, 178)
1: SIP + SBS†	4/20 (20.0)	3/20 (15.0)	1/20 (5.0)	288 (106)	291 (203, 372.5)
2: sNEC‡	206/365 (56.4)	201/365 (55.1)	5/365 (1.4)	50.5 (77.4)	28 (19, 48)
2: SIP	142/405 (35.3)	133/405 (32.8)	9/405 (2.2)	57.5 (111)	16 (10, 45)

*The difference in the proportion of infants who died before follow-up, 34% vs 20%, was not significant ($P = .29$). However, the median age at death differed between these subgroups ($P = .02$).

†These 4 infants died on day of life 165, 241, 341, and 404.

‡The difference in the proportion of infants who died before follow-up, 56% vs 35%, was significant ($P < .001$), and median age at death differed between these subgroups ($P < .001$).

Table VI. Death and NDI in infants born at 22-26 weeks gestational age who were eligible for follow-up excluding infants with SIP without sNEC

Outcomes, no. (column %)	sNEC + SBS	sNEC without SBS	No NEC, SIP, or SBS	aRR (95% CI) for outcome*	
				SBS vs sNEC w/o SBS	SBS vs no NEC/SIP/SBS
No. of children eligible for follow-up	96	365	6666		
Died ≥ 12 h after birth and before follow-up	33 (34.4)	206 (56.4)	1402 (21.0)	0.66 (0.47-0.92)	1.54 (1.12-2.12)
No. of children who died before follow-up or survived and had nonmissing moderate/severe NDI	87	342	5923		
Death or moderate/severe NDI	76 (87.4)	290 (84.8)	3402 (57.4)	1.08 (0.97-1.21)	1.47 (1.33-1.63)
No. of children who died before follow-up or survived and had nonmissing severe NDI	85	339	5875		
Death or severe NDI	58 (68.2)	260 (76.7)	2163 (36.8)	0.99 (0.82-1.19)	1.84 (1.54-2.19)
No. of children seen at follow-up with nonmissing moderate/severe NDI	54	136	4521		
Moderate/severe NDI	43 (79.6)	84 (61.8)	2000 (44.2)	1.27 (1.03-1.57)	1.61 (1.36-1.90)
No. of children seen at follow-up with nonmissing severe NDI	52	133	4473		
Severe NDI	25 (48.1)	54 (40.6)	761 (17.0)	1.24 (0.86-1.78)	2.44 (1.79-3.32)

NDI, neurodevelopmental impairment.
*RRs and CIs from Poisson regression models fit to each outcome that included the group indicator, study center, maternal age, maternal race/ethnicity (Black, White, Hispanic, other), maternal education at the time of delivery (less than high school degree, high school degree, partial college/trade or technical school, college degree or more, missing), maternal antenatal steroid use, multiple birth, infant sex, gestational age (categorical), and birth weight (continuous).