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Neurodevelopmental and Growth Outcomes of Extremely Low Birth Weight Infants After Necrotizing Enterocolitis

Susan R. Hintz, MD*; Douglas E. Kendrick, MStat‡; Barbara J. Stoll, MD§; Betty R. Vohr, MD‖; Avroy A. Fanaroff, MB BCh¶; Edward F. Donovan, MD#; W. Kenneth Poole, PhD‡; Martin L. Blakely, MD**; Linda Wright, MD‡‡; and Rosemary Higgins, MD‡‡, for the NICHD Neonatal Research Network

ABSTRACT. *Objectives.* **Necrotizing enterocolitis (NEC) is a significant complication for the premature infant. However, subsequent neurodevelopmental and growth outcomes of extremely low birth weight (ELBW) infants with NEC have not been well described. We hypothesized that ELBW infants with surgically managed (SurgNEC) are at greater risk for poor neurodevelopmental and growth outcomes than infants with medically managed NEC (MedNEC) compared with infants without a history of NEC (NoNEC). The objective of this study was to compare growth, neurologic, and cognitive outcomes among ELBW survivors of SurgNEC and MedNEC with NoNEC at 18 to 22 months' corrected age.**

Methods. **Multicenter, retrospective analysis was conducted of infants who were born between January 1, 1995, and December 31, 1998, and had a birth weight <1000 g in the National Institute of Child Health and Human Development Neonatal Research Network Registry. Neurodevelopment and growth were assessed at 18 to 22 months' postmenstrual age. χ^2, *t* test, and logistic regression analyses were used.**

Results. **A total of 2948 infants were evaluated at 18 to 22 months, 124 of whom were SurgNEC and 121 of whom were MedNEC. Compared with NoNEC, both SurgNEC and MedNEC infants were of lower birth weight and had a greater incidence of late sepsis; SurgNEC but not MedNEC infants were more likely to have received a diagnosis of cystic periventricular leukomalacia and bronchopulmonary dysplasia and been treated with postnatal steroids. Weight, length, and head circumference <10 percentile at 18 to 22 months were significantly more likely among SurgNEC but not MedNEC compared with NoNEC infants. After correction for anthropometric measures at birth and adjusted age at follow-up, all growth parameters at 18 to 22 months for SurgNEC but not MedNEC infants were significantly less than for NoNEC infants. SurgNEC but not MedNEC was a significant independent risk factor for Mental Developmental Index <70 (odds ratio [OR]: 1.61; 95% confidence interval [CI]: 1.05–2.50), Psychomotor Developmental Index <70 (OR: 1.95; 95% CI: 1.25–3.04), and neurodevelopmental impairment (OR: 1.78; 95% CI: 1.17–2.73) compared with NoNEC.**

Conclusions. **Among ELBW infants, SurgNEC is associated with significant growth delay and adverse neurodevelopmental outcomes at 18 to 22 months' corrected age compared with NoNEC. MedNEC does not seem to confer additional risk. SurgNEC is likely to be associated with greater severity of disease.** *Pediatrics* **2005;115:696–703;** ***necrotizing enterocolitis, extremely low birth weight, neurodevelopmental outcome, cerebral palsy, Bayley Scales of Infant Development, growth.***

ABBREVIATIONS. NEC, necrotizing enterocolitis; ELBW, extremely low birth weight; VLBW, very low birth weight; SurgNEC, surgically managed necrotizing enterocolitis; MedNEC, medically managed necrotizing enterocolitis; NICHD, National Institute of Child Health and Human Development; NoNEC, no history of necrotizing enterocolitis; IRB, Institutional Review Board; cPVL, cystic periventricular leukomalacia; BPD, bronchopulmonary dysplasia; CP, cerebral palsy; BSID II, Bayley Scales of Infant Development II; NDI, neurodevelopmental impairment; MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index; HC, head circumference; ROM, rupture of membranes; PNS, postnatal steroid; OR, odds ratio; CI, confidence interval.

Necrotizing enterocolitis (NEC) continues to be a potentially devastating complication for the extremely low birth weight (ELBW) premature infant.[1,2] Although survival rates of >80% have been reported in some premature populations,[3,4] ELBW patients fare much worse with survival ranging from 41% to 55%.[4,5] Short-term medical and surgical complications associated with NEC have been found to be more prevalent and life-threatening among extremely premature and lower birth weight infants.[6–8]

Neurodevelopmental outcomes in ELBW patients with NEC have not been widely reported.[9] Previous single-center and multi-institutional studies have variably found the diagnosis of NEC to be associated with a nonsignificant trend toward[10] or an independent risk factor for[11,12] adverse neurodevelopmental outcomes. To date, outcomes studies of ELBW or very low birth weight (VLBW) survivors of NEC have included only single-center reviews with small

From the *Division of Neonatal and Developmental Medicine, Stanford University School of Medicine, Palo Alto, California; ‡Research Triangle Institute, Research Triangle Park, North Carolina; §Department of Pediatrics, Emory University, Atlanta, Georgia; ‖Department of Pediatrics, Women and Infants Hospital, Providence, RI; ¶Department of Pediatrics, Case Western Reserve University, Cleveland, Ohio; #Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio; **Department of Pediatric Surgery, University of Texas, Houston, TX; and ‡‡National Institute of Child Health and Human Development, Washington, DC.

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Reprint requests to (S.R.H.) Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University School of Medicine, 750 Welch Rd, Suite 315, Palo Alto, CA 94304. E-mail: srhintz@stanford.edu

numbers of patients. Sonntag et al[13] found significant neurodevelopmental delay in 20 VLBW survivors of NEC at 12 and 20 months compared with gestational age–matched control subjects. Infants who require surgery for NEC are likely to be more severely ill with the disease and may be at even higher risk for neurodevelopmental and neuromotor delay. Single-center analyses have suggested that motor delay at 15 months' corrected age may be more prevalent in VLBW NEC survivors who require abdominal incisions than in those who were medically managed[14] and that VLBW and ELBW survivors of surgically managed NEC (SurgNEC) have significantly worse neurodevelopmental outcome and growth than control subjects or infants with medically managed NEC (MedNEC).[15,16]

The extent to which NEC has an impact on long-term somatic growth has been debated. Early small studies reported normal anthropometric measurements at 1 year in the absence of short-bowel syndrome.[17] Sonntag et al[13] found no somatic growth differences between VLBW NEC survivors and control subjects at 12 or 20 months. However, others have found that infants who require surgery for NEC have a higher incidence of growth delay than control subjects.[18,19] Walsh et al[20] also found that a higher stage of NEC was associated with both severe growth restriction and neurodevelopmental delay at 20 months' adjusted age compared with lower stage of NEC or control subjects.

In this analysis of ELBW infants who were in the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network VLBW Registry and born form 1995 to 1998, we sought to compare neurodevelopmental and growth outcomes of ELBW infants with SurgNEC and MedNEC with infants without a history of NEC (NoNEC) at 18 to 22 months' corrected age and, through regression analysis, to assess whether SurgNEC or MedNEC was an independent risk factor for adverse neuromotor, neurosensory, and cognitive outcomes.

METHODS

This was an analysis of infants who had birth weight of 401 to 1000 g, were born from January 1, 1995, through December 31, 1998, and were in the multicenter NICHD Neonatal Research Network VLBW Registry. The registry was developed to survey practice, assess morbidity and mortality, and provide information for the planning of randomized clinical trials. Each center's Institutional Review Board (IRB) reviewed the data collection procedures, and waivers of consent were granted. Infants qualified for inclusion in the VLBW registry when they were admitted to a network center within 14 days of birth or were liveborn but died in the delivery room. Research nurses collected demographic, perinatal, and infant data at each participating center using common definitions developed by the investigators and described in previous publications.[21,22] Antenatal antibiotics was defined as administration of any antibiotics to the mother during the admission that resulted in delivery. Antenatal steroids were defined as administration of any corticosteroids to accelerate fetal lung maturity in the present pregnancy. Estimated gestational age in completed weeks was determined by best obstetric estimate using last menstrual period, standard obstetric parameters, and ultrasonography. When there was a 2-week range of gestational age among obstetric estimates, the lowest estimate was used. When there was a ≥3-week range of when several estimates existed, the median estimate of gestational age was used. Small for gestational age was defined as weight <10th percentile for gestational age using the fetal growth curves of Alexander et al.[23] Data were also collected on diagnoses (including patent ductus arteriosus), treatments, and in-hospital morbidities until death, discharge, or 120 days; after 120 days or if the patient was transferred, then data were collected regarding death or discharge to home. Surfactant treatment was defined as 1 or more doses of any surfactant during hospitalization. Indomethacin was defined as treatment with the drug for closure of a patent ductus arteriosus. Intraventricular hemorrhage was reported according to the classification of Papile et al.[24] Cystic periventricular leukomalacia (cPVL) was defined specifically as diagnosis by head ultrasound performed after 2 weeks of age; if a head ultrasound was not obtained after 2 weeks of age, then no report was made as to the presence or absence of cPVL. Cranial ultrasounds were not interpreted by a central reader but rather by radiologists at individual network centers. Early sepsis was defined as a positive blood culture at ≤72 hours of age, and late sepsis was defined as a positive blood culture at >72 hours of age. Data regarding NEC were collected for infants who survived >12 hours and was defined as Modified Bell's classification stage IIA or greater.[25] Surgery for NEC was at the discretion of each individual network center and included any surgical intervention (drain, laparotomy, or both). Bronchopulmonary dysplasia (BPD) was defined as receiving supplemental oxygen at 36 weeks' postmenstrual age as determined by best obstetric estimate.

Comprehensive follow-up at 18 to 22 months' postmenstrual age was considered standard of care for ELBW infants at network sites. The IRBs at each center approved participation in the follow-up study. Waivers of consent were granted, or informed consent was sought per the specifications of each center's IRB. Contact to schedule the follow-up visit was made by telephone call, postcard, or letter. The elements of the follow-up visit have been previously described in detail.[11] All neurologic assessments were performed by certified, masked developmentalists who had been trained in the examination procedure in an annual 2-day workshop. The neurologic examination was based on the Amiel-Tison[26] assessments, and the gross motor skills examination was developed from the work of Russell et al[27] and Palisano et al.[28] Cerebral palsy (CP) was defined as a nonprogressive central nervous system disorder characterized by abnormal muscle tone in at least 1 extremity and abnormal control of movement and posture. The Bayley Scales of Infant Development-II (BSID-II)[29] was administered by experienced testers at each site who had been certified by 1 of 4 gold standard examiners. BSID-II scores of 100 ± 15 represent the mean ± 1 SD. Scores of <70 are 2 SDs below the mean. Scores of 49 were assigned to infants whose extremely severe neurologic or neurodevelopmental impairment prevented their examination. Examiners noted the reasons for unsuccessful BSID-II testing. Deafness was defined as using hearing aids in both ears. Blindness was defined as no useful vision in either eye. Neurodevelopmental impairment (NDI) was defined as 1 or more of the following: Mental Developmental Index (MDI) <70, Psychomotor Developmental Index (PDI) <70, CP, deafness, or blindness. Weight, length, and head circumference (HC) measurements were also made at the time of the 18- to 22-month follow-up visit. Determinations of weight, length, and HC percentiles for age were based on age corrected for prematurity, using growth charts developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (published May 30, 2000). Socioeconomic status information, including highest level of education attained by the primary caregiver, was also obtained at the time of the follow-up visit.

Statistical analyses were performed using continuity-adjusted χ^2 or Fisher exact test for categorical data, and t test, analysis of variance, or analysis of covariance was used for continuous data. Logistic regression models were developed to evaluate NEC management-related risk for CP, BSID-II MDI <70, BSID-II PDI <70, and the combined outcome of NDI (defined as deafness, blindness, CP, MDI <70, or PDI <70) while adjusting for differences in perinatal and neonatal variables. Demographic, maternal, and neonatal risk factors that are known to be associated with neurodevelopmental outcomes were entered into the regression models. These factors included network center, use of antenatal glucocorticoids, rupture of membranes (ROM) >24 hours, outborn status, estimated gestational age, gender, race, birth weight, small for gestational age, surfactant therapy, intraventricular hemorrhage grade 3 or 4 or cPVL, sepsis, postnatal steroid (PNS) treatment,

BPD, and highest level of education attained by the primary caregiver.

RESULTS

During the study period (January 1, 1995, to December 31, 31, 1998), a total of 5553 ELBW infants were entered into the NICHD VLBW Registry, 4933 of whom survived >12 hours. Of those, 4401 were NoNEC, 3496 (79.4%) of whom survived to discharge; 239 were MedNEC, 156 (65.3%) of whom survived to discharge ($P < .0001$ compared with NoNEC); and 293 were SurgNEC, 162 (55.3%) of whom survived to discharge ($P < .0001$ compared with NoNEC). The progression of study patients through hospital discharge and reasons for no follow-up are shown in Fig 1. Of the 3420 NoNEC infants who were alive at 18 to 22 months, 2703 completed follow-up (79.1% follow-up rate). Of 305 NEC infants who were alive at 18 to 22 months, 245 completed follow-up (80.3% follow-up rate).

Demographic and perinatal characteristics of the SurgNEC, MedNEC, and NoNEC follow-up groups are presented in Table 1. SurgNEC and MedNEC groups were significantly smaller than NoNEC infants at birth. There were also small but significant differences in HC at birth between both SurgNEC and MedNEC infants compared with NoNEC infant. The SurgNEC group was more likely than the NoNEC group to have been delivered after ROM >24 hours.

Common in-hospital treatments and morbidities among the follow-up groups are presented in Table 2. Late sepsis was significantly more common in both SurgNEC and MedNEC compared with NoNEC infants. cPVL, PNS, and the diagnosis of BPD were significantly more prevalent for SurgNEC but not MedNEC compared with NoNEC infants. Hospital stay was significantly longer for both SurgNEC and MedNEC compared with NoNEC infants.

Major growth outcomes at the 18- to 22-month follow-up examination are shown in Table 3, including weight, length, and HC <10th percentile for adjusted age. SurgNEC was significantly more likely to be associated with substantial growth delay (<10th percentile) in all 3 parameters assessed compared with NoNEC. Analysis of covariance was also performed for each growth parameter, adjusting for differences in anthropometric measurements at birth and corrected age at follow-up. Weight, length, and HC in SurgNEC infants all were significantly less than in NoNEC infants, even after adjustment for those variables (weight: $P = .0019$; length: $P = .0016$; HC: $P = .0003$). MedNEC and NoNEC infants were not significantly different for any growth parameter after adjustment for birth measures and corrected age at follow-up (weight: $P = .21$; length: $P = .18$; HC: $P = .13$).

The incidence of CP, deafness, and blindness

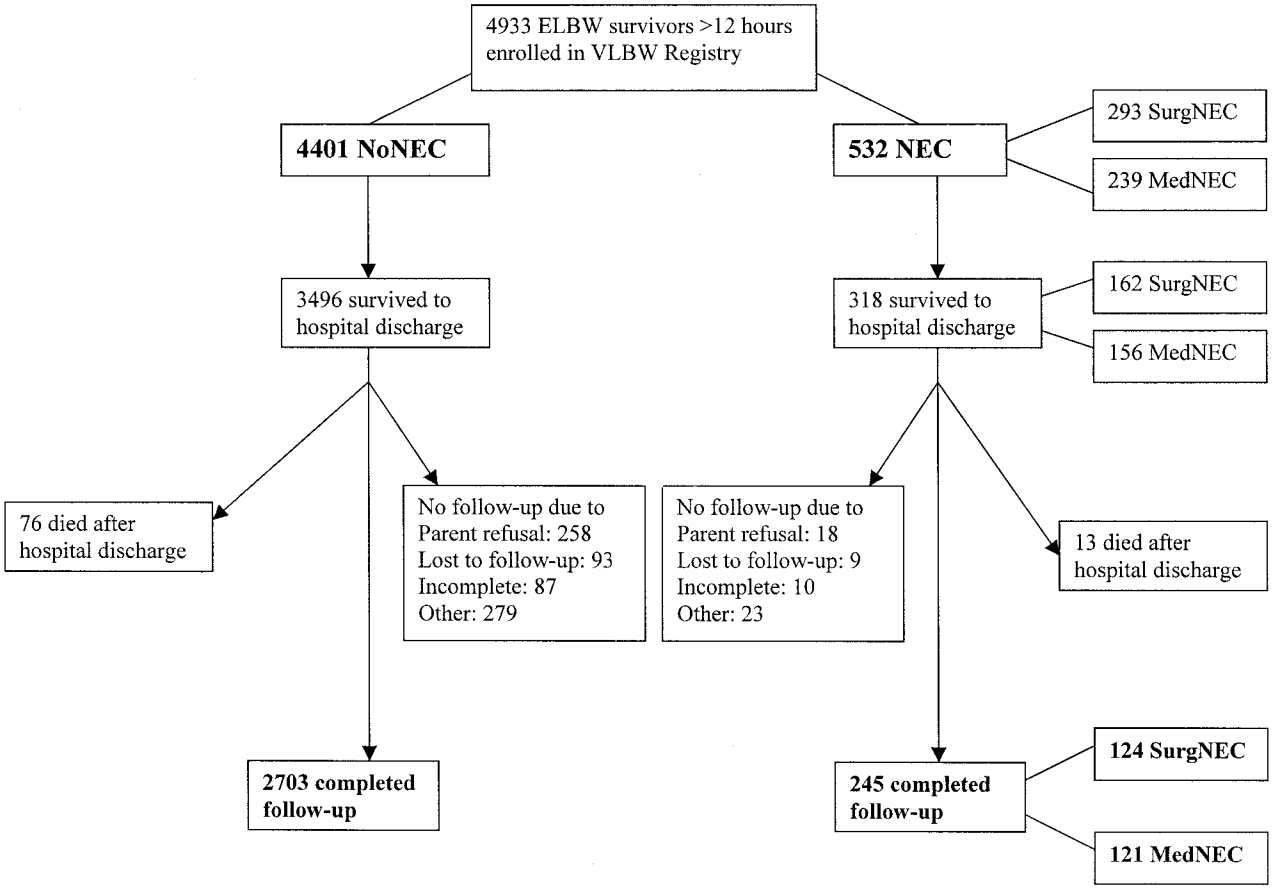

Fig 1. Flow of NEC (SurgNEC and MedNEC) and NoNEC ELBW infants who survived >12 hours through hospital discharge to neurodevelopmental follow-up at 18 to 22 months' corrected age.

TABLE 1. Demographic and Perinatal Characteristics of SurgNEC, MedNEC, and NoNEC Follow-up Groups

	SurgNEC	MedNEC	NoNEC	SurgNEC Versus NoNEC	MedNEC Versus NoNEC
Birth weight, g, mean ± SD	757 ± 129	762 ± 133	792 ± 132	$P = .003$	$P = .01$
HC at birth, cm, mean ± SD	23.2 ± 1.6	23.2 ± 1.4	23.6 ± 1.6	$P = .0016$	$P = .01$
EGA <28 wk, *n* (%)	102 (82)	101 (83)	2092 (77)	NS	NS
ROM >24 h, *n* (%)*	43 (35)	32 (27)	653 (25)	$P = .014$	NS
AABX, *n* (%)†	84 (68)	90 (75)	1793 (66)	NS	$P = .07$
Inborn, *n* (%)	108 (87)	107 (88)	2461 (91)	NS	NS
Male, *n* (%)	64 (52)	59 (49)	1269 (47)	NS	NS
Race, *n* (%)				NS	NS
Black	52 (42)	62 (51)	1191 (44)		
White	48 (39)	44 (36)	1090 (40)		
Hispanic	20 (16)	11 (9)	338 (13)		
Multiple, *n* (%)	30 (24)	30 (25)	608 (22)	NS	NS
SGA, *n* (%)	17 (14)	21 (17)	481 (18)	NS	NS
ANS, *n* (%)‡	91 (73)	97 (81)	2071 (77)	NS	NS

EGA indicates estimated gestational age; AABX, Antenatal antibiotics; SGA, small for gestational age; ANS, antenatal steroids. SurgNEC $N = 124$, MedNEC $N = 121$, NoNEC $N = 2703$.. $P > .1$ is reported as not significant (NS).
* SurgNEC $N = 123$, MedNEC $N = 118$, NoNEC $N = 2640$.
† SurgNEC $N = 124$, MedNEC $N = 120$, NoNEC $N = 2697$.
‡ SurgNEC $N = 124$, MedNEC $N = 120$, NoNEC $N = 2699$.

TABLE 2. In-Hospital Treatments and Morbidities of SurgNEC, MedNEC, and NoNEC Follow-up Groups

	SurgNEC	MedNEC	NoNEC	SurgNEC Versus NoNEC	MedNEC Versus NoNEC
Surfactant, *n* (%)	86 (69)	98 (81)	2083 (77)	$P = .062$	NS
PDA, *n* (%)	56 (45)	49 (41)	1138 (42)	NS	NS
Indomethacin sepsis, *n* (%)*	44 (36)	32 (26)	948 (35)	NS	$P = .07$
Early	3 (2)	5 (4)	43 (2)	NS	$P = .08$
Late	83 (67)	70 (58)	939 (35)	$P < .0001$	$P < .0001$
IVH 3/4, *n* (%)†	27 (22)	22 (18)	481 (18)	NS	NS
cPVL, *n* (%)‡	16 (14)	6 (5)	155 (7)	$P = .005$	NS
PNS, *n* (%)	78 (63)	65 (54)	1364 (50)	$P = .009$	NS
BPD, *n* (%)§	70 (57)	62 (51)	1159 (43)	$P = .003$	$P = .09$
Hospital days, mean ± SD	132 ± 54	104 ± 28	90 ± 39	$P < .0001$	$P < .0001$

IVH indicates intraventricular hemorrhage. SurgNEC $N = 124$, MedNEC $N = 121$, NoNEC $N = 2703$. $P > .1$ is reported as NS.
* SurgNEC $N = 122$, MedNEC $N = 121$, NoNEC $N = 2702$.
† SurgNEC $N = 124$, MedNEC $N = 121$, NoNEC $N = 2690$.
‡ SurgNEC $N = 117$, MedNEC $N = 115$, NoNEC $N = 2383$.
§ SurgNEC $N = 123$, MedNEC $N = 121$, NoNEC $N = 269$.

TABLE 3. Growth Failure Rates Among SurgNEC, MedNEC, and NoNEC ELBW Infants at 18 to 22 Months' Adjusted Age

	SurgNEC	MedNEC	NoNEC	SurgNEC Versus NoNEC	MedNEC Versus NoNEC
Weight					
kg, mean ± SD	9.73 ± 1.40	9.93 ± 1.24	10.2 ± 1.50		
<10th, *n* (%)	86 (70)	72 (61)	1434 (54)	$P = .0006$	$P = .17$
N	123	119	2671		
Length					
cm, mean ± SD	78.8 ± 4.3	79.2 ± 4.5	80.1 ± 4.4		
<10th, *n* (%)	59 (48)	48 (40)	920 (35)	$P = .003$	$P = .227$
N	123	119	2666		
HC					
cm, mean ± SD	46.0 ± 2.0	46.4 ± 1.8	46.7 ± 1.9		
<10th, *n* (%)	48 (39)	41 (34)	693 (26)	$P = .002$	$P = .057$
N	123	120	2675		

among the SurgNEC, MedNEC, and NoNEC groups at 18 to 22 months' corrected age are presented in Table 4. Significant differences between the SurgNEC and NoNEC groups were again noted, with SurgNEC infants more likely to receive a diagnosis of CP, deafness, or blindness; however, there were no significant differences in the neuromotor and neurosensory outcomes of the MedNEC and NoNEC groups. It is important to note, however, that the absolute number of patients with deafness or blindness was very small in the NEC treatment groups.

The results of BSID-II testing and the incidence of NDI at 18 to 22 months' adjusted age are shown in

TABLE 4. Neuromotor and Neurosensory Outcomes at 18 to 22 Months Adjusted Age

	SurgNEC	MedNEC	NoNEC	SurgNEC Versus NoNEC	MedNEC Versus NoNEC
CP, *n* (%)	30 (24)	15 (12)	399 (15)	*P* = .006	*P* = NS
N	124	121	2699		
Deaf, *n* (%)	5 (4.1)	1 (0.8)	40 (1.5)	*P* = .045*	*P* = NS*
N	123	121	2686		
Blind, *n* (%)	5 (4.1)	1 (0.8)	26 (1.0)	*P* = .01*	*P* = NS*
N	122	121	2683		

* Statistical analyses by Fisher exact test.

TABLE 5. Bayley-II MDI and PDI and NDI at 18 to 22 Months' Corrected Age

	SurgNEC	MedNEC	No NEC	SurgNEC Versus NoNEC	MedNEC Versus NoNEC
MDI					
Mean ± SD	72.0 ± 18.0	76.9 ± 16.0	79.5 ± 18.4	*P* < .0001	*P* = .14
<70, *n* (%)	52 (44)	41 (37)	772 (31)	*P* = .003	*P* = .20
N	118	112	2533		
PDI					
Mean ± SD	74.0 ± 19.1	82.5 ± 20.7	82.6 ± 18.6	*P* < .0001	*P* = .94
<70, *n* (%)	44 (37)	28 (25)	556 (22)	*P* = .0003	*P* = .53
N	119	111	2500		
NDI, *n* (%)	69 (57)	50 (44)	1014 (40)	*P* = .0003	*P* = .43
N	121	113	2531		

Table 5. Examiners were unable to test successfully 186 children for MDI as a result of illness (12), language barrier (8), severe behavioral problems (60), sensory impairment (28), other issues (68), and no reason given (10). Unsuccessful testing for PDI was reported in 219 as a result of illness (12), language barrier (7), severe behavioral problems (74), sensory impairment (26), other issues (81), and no reason given (20). Significant differences in BSID-II MDI and PDI scores were found between SurgNEC and NoNEC groups but not between MedNEC and NoNEC groups. The proportions of the SurgNEC group with MDI and PDI scores of <70 were significantly higher than the NoNEC group, but there were not significant differences between the MedNEC and NoNEC groups. The incidence of NDI was significantly higher for SurgNEC but not MedNEC compared with NoNEC infants. In light of the potentially substantial impact of PNS on neurodevelopmental outcomes, a subgroup analysis of NDI among infants who were not exposed to PNS was performed. The incidence of NDI was 29.4% for NoNEC (366 of 1243), 31.4% for MedNEC (16 of 51), and 58.7% for SurgNEC (27 of 46). As was the case for the study population overall, the incidence of NDI for the no PNS subgroup was significantly higher for SurgNEC compared with NoNEC infants ($P < .0001$) but not for MedNEC compared with NoNEC infants ($P = .89$).

Regression models estimated the adjusted odds ratios (ORs) of SurgNEC compared with NoNEC and of MedNEC compared with NoNEC for the outcomes of CP, MDI <70, PDI <70, and NDI (Fig 2). Neither SurgNEC nor MedNEC was found to be a significant independent risk factor for CP (SurgNEC OR: 1.31; 95% confidence interval [CI]: 0.80–2.14; MedNEC OR: 0.68; 95% CI: 0.35–1.29). SurgNEC was

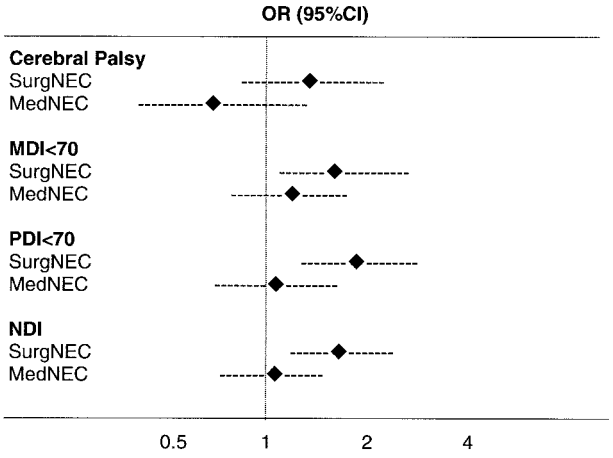

Fig 2. Adjusted ORs for CP, MDI <70, PDI <70 and NDI in SurgNEC and MedNEC compared with NoNEC infants.

an independent risk factor for MDI <70 (OR: 1.61; 95% CI: 1.05–2.50), but MedNEC was not (OR: 1.16; 95% CI: 0.74–1.81). Similarly, SurgNEC was an independent risk factor for PDI <70 (OR: 1.95; 95% CI: 1.25–3.04), but MedNEC was not (OR: 1.08; 95% CI: 0.66–1.80). SurgNEC (OR: 1.78; 95% CI: 1.17–2.73) but not MedNEC (OR: 1.06; 95% CI: 0.69–1.63) was a risk factor for the combined outcome of NDI.

DISCUSSION

This study, the largest to date of the outcome of NEC in ELBW infants, revealed that SurgNEC but not MedNEC was associated with substantial growth delay compared with NoNEC. Furthermore, SurgNEC but not MedNEC was found to be an independent risk factor for MDI <70, PDI <70, and the combined outcome NDI as compared with ELBW

infants who did not have NEC. Multiple factors that are not easily quantified, including perinatal events, the severity of the clinical condition contemporaneous with the NEC episode, complications associated with NEC, and the surgical intervention itself, may contribute to these findings.

The association of SurgNEC with growth failure among ELBW infants in this analysis is concerning. This finding may seem to be inconsistent with the results of previous smaller studies. Abbasi et al[17] reported comparable growth measures at 12 months between NEC and control patients; however, that cohort was not limited to ELBW infants, and included only 4 surgically managed patients among the 22 cases of NEC. Sonntag et al[13] also reported no significant differences in weight, length, or HC between 20 VLBW NEC patients, among whom only 7 had undergone surgery, and 40 VLBW control subjects at 20 months. Although the authors indicated that there were no significant differences in growth parameters between NEC treatment groups, there was a lower median weight at 20 months in the surgically managed group (9.85 kg) as compared with control (10.7 kg). In contrast, Walsh et al[20] reported a significant correlation between severity of NEC and growth delay at 20 months among a VLBW cohort, which is similar to our findings. The Walsh et al study, which examined growth outcomes as a function of NEC staging rather than management, demonstrated substantially greater proportions of stage III NEC compared with control infants with weight (39% vs 24%) and HC (30% vs 13%) >2 SD below the mean. The great majority of infants with stage III NEC had undergone surgery (17 of 23), supporting the notion that the most severely ill NEC patients are more likely to be managed with surgery. Significant growth impairment has also been reported in studies of survivors of surgically treated NEC,[30–32] without contemporaneous control subjects.

The SurgNEC group in the current analysis was also at significantly greater risk for poor neurosensory and neurodevelopmental outcomes than the MedNEC group when compared with NoNEC. This finding is consistent with many previous, smaller reports.[14–16] Major neurodevelopmental impairment was found in 43% of severe NEC survivors compared with 15% of mild to moderate NEC survivors at 20 months by Walsh et al.[20] In follow-up studies of only surgical NEC survivors, significant motor and cognitive delay has been reported in one third to one half.[3,30,31] The current study differs from others in that it focuses specifically on the ELBW population, arguably the highest risk group, and has a much larger sample size. This advantage allows for analysis of NEC management-related adjusted risk for important neurodevelopmental outcomes that, to our knowledge, has not been reported previously for this patient population. Despite the nearly 3000 ELBW infants studied, however, very few in either NEC treatment strategy group had a diagnosis of blindness or deafness. Nonetheless, the outcomes of CP and BSID-II scores <70 were relatively common.

The profound neurodevelopmental impairment observed in the SurgNEC group may be linked closely to significant growth impairment, particularly in HC. Previous studies of VLBW and ELBW infants have demonstrated that subnormal head growth at 8 months[33] and 12 months[34] is associated with poor cognitive ability and academic difficulties at school age. Failure to achieve catch-up head growth to above the fifth percentile by 6 months of age has also been reported to be associated with abnormal motor performance at 12 months among VLBW premature infants.[35] Weight <10th percentile at 2 years' corrected age is also correlated with poor neurodevelopmental and neuromotor outcomes among high-risk ELBW patients, including those with a history of NEC.[36] Although differences in somatic growth in the MedNEC compared with the NoNEC group did not reach statistical significance in the present analysis, growth for this entire ELBW population at 18 to 22 months' adjusted age is disturbing, with >50% of the overall cohort with weights <10th percentile. This is not a novel finding. Connors et al[36] reported that 49% of an ELBW cohort had weights <10th percentile at 2 years' corrected age. Similarly, previous studies have found that as many as half of ELBW and VLBW infants at follow-up had HCs that fell below the 10th percentile at 6 to 8 months.[34,35] In the present study, it may be speculated that prenatal factors or events that predispose certain patients for development of NEC also could have led to the lower mean weight, HC, and length at birth in NEC compared with NoNEC groups. Subsequent morbidities may have differentially affected the NEC treatment groups, resulting in more severe growth delay in SurgNEC at 18 to 22 months. The more pronounced growth impairment observed in the SurgNEC group may also have occurred through a mechanism of persistent nutritional deficits, which might involve the effects of short bowel including malabsorption. Severe short-bowel syndrome has also been linked with subtle visual-spatial impairment at school age.[37] During the study period, no detailed interval nutritional history was gathered at the time of follow-up. This important issue is a crucial area for additional, prospective study, currently ongoing in the NICHD Neonatal Research Network[38]; the current 18- to 22-month follow-up assessment includes questions that address gastrointestinal dysfunction.

Although this study is among the largest to examine the potential association between NEC treatment and neurodevelopmental outcomes using prospectively collected perinatal and neonatal data in ELBW patients, it still does not clarify the specific causes of the increased risk for poorer outcomes in the SurgNEC group. We speculate that this process is likely to be multifactorial. It has been suggested that perinatal events play a potentially important role in the pathogenesis of NEC, with fetal hypoperfusion leading to mucosal vulnerability and gut ischemia.[39,40] The subsequent profound inflammatory response may be associated with release of chemical mediators such as tumor necrosis factor-α, interleukin-6, platelet activating factor, and nitric oxide, purported to contribute to a mechanism that leads to

hemodynamic instability, tissue necrosis, and white matter injury.[40–43] The fetus may also be exposed to such proinflammatory cytokines as a consequence of intrauterine infection. Of note, both ROM >24 hours and diagnosis of cPVL were more likely in the SurgNEC group on univariate comparisons. It therefore is possible that the cascade of events that lead to adverse neurodevelopmental outcomes is programmed in utero. More detailed early neuroimaging studies that focus on subtle white matter changes might help to clarify whether there exists a common fetal determinant for PVL and NEC. Alternatively, the fetal environment may predispose the infant to but not absolutely determine neurodevelopmental consequences unless a specific postnatal milieu is also in place. For example, the severity of the clinical condition contemporaneous with the NEC episode may be an additive or independent determinant of outcome. NEC staging information was not available during the entire study period; thus, outcomes cannot be evaluated on that basis, but it is likely that greater severity of disease does correlate with perceived need for surgery.[16,20] Other in-hospital factors such as late sepsis, BPD, and PNS, which have been linked to adverse neurodevelopmental outcomes, were also significantly more frequent in SurgNEC but not MedNEC compared with NoNEC infants. Whether these morbidities and treatments occurred as a directed consequence of a potentially greater severity of illness in the SurgNEC group is not known. Despite attempts to adjust for differences in these factors through regression modeling, SurgNEC was an independent risk factor for MDI <70, PDI <70, and NDI.

Common postsurgical complications including sepsis, wound infection, strictures, and short-gut syndrome[4] may be a reflection of the severity of the disease process rather than the surgical therapy. Therefore, the "need for surgery" might be considered simply a surrogate for advanced NEC. In the current study, the decision to proceed with surgical intervention for NEC was at the discretion of the surgical teams at each individual network site; no data regarding the specific type of surgical intervention (drain, laparotomy, or both) or the basis for the management approach were collected. Previous reports have suggested that smaller, sicker infants may be more likely to receive drainage in the setting of perforated NEC.[44] Thus, the possibility of a delay to "definitive" treatment in this subgroup cannot be ruled out. A prospective study of surgical treatment for NEC among ELBW infants has recently been completed in the Neonatal Research Network, which will provide detailed assessments of surgical practices, reasons for and types of interventions undertaken, pathologic findings, and complications. These data will be useful in determining the significance of the risk that these factors impart independently on short- and long-term outcomes.

In summary, at 18 to 22 months, ELBW infants who received surgical intervention for management of NEC had significantly reduced weight, length, and HC compared with NoNEC infants, but growth parameters of MedNEC and NoNEC groups were not statistically different. SurgNEC but not MedNEC was also found to be an independent risk factor for BSID MDI <70, PDI <70, and NDI. Numerous factors, including prenatal factors, severity of illness, nutritional deficits, and the surgical intervention and subsequent complications, may have contributed to the poorer outcomes observed in the SurgNEC group. The results of this multicenter, retrospective analysis pose additional crucial questions as to the pathogenesis and natural history of adverse neurodevelopmental consequences of severe NEC among ELBW infants.

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Neurodevelopmental and Growth Outcomes of Extremely Low Birth Weight Infants After Necrotizing Enterocolitis

Susan R. Hintz, Douglas E. Kendrick, Barbara J. Stoll, Betty R. Vohr, Avroy A. Fanaroff, Edward F. Donovan, W. Kenneth Poole, Martin L. Blakely, Linda Wright and Rosemary Higgins

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