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Severe neurodevelopmental disability and healthcare needs among survivors of medical and surgical necrotizing enterocolitis: A prospective cohort study☆

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ABSTRACT

Purpose: This study characterizes neurodevelopmental outcomes and healthcare needs of extremely low birth weight (ELBW) survivors of necrotizing enterocolitis (NEC) compared to ELBW infants without NEC.
Methods: Data were collected prospectively on neonates born 22–27 weeks' gestation or 401–1000 g at 47 Vermont Oxford Network member centers from 1999 to 2012. Detailed neurodevelopmental evaluations were conducted at 18–24 months corrected age. Information regarding rehospitalizations, postdischarge surgeries, and feeding was also collected. "Severe neurodevelopmental disability" was defined as: bilateral blindness, hearing impairment requiring amplification, inability to walk 10 steps with support, cerebral palsy, and/or Bayley Mental or Psychomotor Developmental Index <70. Diagnosis of NEC required both clinical and radiographic findings.
Results: There were 9063 children without NEC, 417 with medical NEC, and 449 with surgical NEC evaluated. Significantly higher rates of morbidity were observed among infants with a history of NEC. Those with surgical NEC were more frequently affected across all outcome measures at 18–24 months corrected age: 38% demonstrated severe neurodevelopmental disability, nearly half underwent postdischarge operations, and a quarter required tube feeding at home.
Conclusion: At 18–24 months, extremely low birth weight survivors of necrotizing enterocolitis were at markedly increased risk ($p < 0.001$) for severe neurodevelopmental disability, postdischarge surgery, and tube feeding.
Level of evidence: II (prospective cohort study with <80% follow-up rate).

Necrotizing enterocolitis (NEC) and spontaneous intestinal perforations (SIP) commonly affect extremely low birth weight (ELBW) neonates and are associated with significant mortality or prolonged and complicated hospital courses [1,2]. In addition, ELBW neonates are known to be at increased risk for long-term developmental disabilities [3,4]. To better characterize morbidity among survivors of NEC, we evaluated neurodevelopmental outcomes and healthcare needs among survivors of medical and surgical NEC, compared to those without a history of NEC, at two year follow-up.

1. Methods

1.1. Study design

This study is a retrospective review of prospectively collected data from the Vermont Oxford Network (VON), a nonprofit voluntary clinical collaborative dedicated to improving the safety and quality of care provided to neonates and their families. VON members prospectively collect data on infants with birth weights 401–1500 g, or gestational age at birth of 22 to 29 completed weeks, who are admitted to a participating center neonatal intensive care unit (NICU) within 28 days of birth. Data are collected by local staff using uniform definitions until neonates are discharged from the hospital, die, or reach one year of age in the hospital. Records are subjected to automated checks and returned for correction if incomplete. Of the 731 North American centers participating in VON, 47 centers participate in the VON ELBW follow-up project and contributed data for this study, on infants born 1999–2012 (Appendix 1, online only). These centers conduct follow-up evaluations with detailed neurodevelopmental assessment on ELBW infants (birth weight 401–1000 g or gestational age at birth 22 to 27 completed weeks) between 18 and 24 months corrected age. For this study, infants with a major congenital anomaly or initial hospital length of stay <72 h were excluded. A clinical diagnosis of NEC required at least one physical finding (bilious gastric aspirate or emesis, abdominal distention, or occult/gross blood in the stool in the absence of anal fissures) and at least one radiographic finding (pneumatosis intestinalis, hepatobiliary gas, or pneumoperitoneum), i.e. minimum Bell's Stage II. Bowel perforation or NEC could also be diagnosed at laparotomy or at postmortem examination [5]. Detailed definition of all data points is as specified in the

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Vermont Oxford Network Manual of Operations [5]. Surgical NEC was defined as that subset of patients who received laparotomy or primary peritoneal drainage.

Follow-up was coordinated by participating institutions, and informed consent for inclusion in the ELBW follow-up project was obtained according to the specifications of each institution's IRB; attempts were made to schedule follow-up with the families/caregivers of all infants who were alive at hospital discharge. Infant status was reported as dead, alive, or unknown. Outcome measures for infants who completed follow-up at 18 to 24 months corrected age included assessment of the home living situation, healthcare needs, and developmental status of the children. Measures were reported using standardized data collection tools; each data item was defined in the ELBW Infant Follow-Up Manual of Operations [6].

The assessment of the home living situation included information regarding with whom the child resided, the type of social support at home, and primary caregiver educational attainment. For infants born after 2005 maternal age at birth was assessed for all infants, and primary language of the caregiver and household income in relation to federal poverty guidelines were collected at US centers. The assessment of healthcare needs included: medical support after hospital discharge (tracheostomy, ventilator, oxygen, gastrostomy, nasogastric feeds, apnea or cardiorespiratory monitor), surgical procedures since discharge, and any medical rehospitalizations requiring an overnight stay. Rehospitalization data do not include rehospitalizations for surgery. Reasons for rehospitalization were categorized as respiratory illness (including apnea), nutrition or failure to thrive, seizure disorder, shunt complications, infections, or other. Infections requiring rehospitalization were further categorized as meningitis, urinary tract infection, gastrointestinal infection, or other. All rehospitalization and surgery write-in codes were reviewed by surgeons at Boston Children's Hospital and appropriately categorized.

The assessment of the developmental outcomes included information from the neurological and developmental evaluations, with definition of severe disability based on the work of Schmidt et al. [4]. The neurological evaluation included assessment of vision (blindness in one or both eyes), hearing (corrective hearing aids for one or both ears), and muscle tone (hypotonia, hypertonia). Whether the infant could walk 10 steps independently or with support was assessed. Cerebral palsy (quadriplegia, hemiplegia, diplegia) was defined as a nonprogressive, nontransient central nervous system disorder characterized by abnormal control of movement and/or posture not owing to mental retardation. The developmental evaluation included Bayley Scales of Infant and Toddler Development (BSID-II or BSID-III); participating centers were given the option to use BSID-III starting in 2004. A score of less than 70 (more than two standard deviations below the mean), using age adjusted for prematurity, was interpreted to represent significantly delayed performance. Severe disability was defined by the presence of one or more of the following: bilateral blindness, hearing impairment requiring amplification, inability to walk 10 steps with support, cerebral palsy, or a BSID Mental Development Index (MDI) or Psychomotor Development Index (PDI) of less than 70.

This study was performed as part of an ongoing collaboration between VON and pediatric surgeons at Boston Children's Hospital. The Committee on Human Research at the University of Vermont approved the use of the VON Research Repository for this analysis (#15-143).

1.2. Statistical methods

Risk ratios are adjusted for gestational age and clustering of infants within hospitals. All analyses were produced using SAS version 9.4 (SAS Institute, Cary, NC).

2. Results

After the exclusion of 2265 infants for congenital anomalies and/or length of stay less than 72 h, and 19 infants for missing data on survival status at hospital discharge, there were 24,018 eligible ELBW infants; 20,762 of these infants survived until hospital discharge. Survival to follow-up was 88% among those without NEC, 74% among those diagnosed with medical NEC, and 62% for those with a history of surgical NEC or bowel perforation. Of 20,565 infants eligible for follow-up, 48% were evaluated: 9063 without NEC, 417 with medical NEC, and 449 with surgical NEC (Fig. 1). The 9929 evaluated infants had a mean gestational age of 26 weeks (± 2 weeks) and a mean birth weight of 803 g (SD ± 169 g). Characteristics associated with risk of disability [3] were similar between survivors with and without follow-up

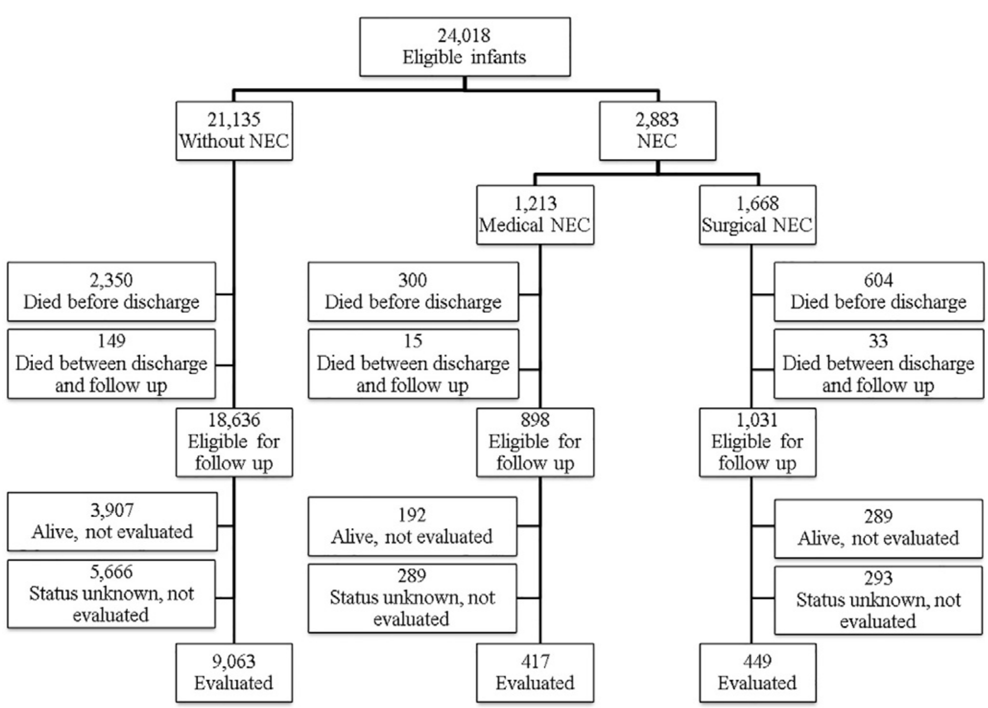

Fig. 1. Infant survival and follow-up.

Table 1
Characteristics of surviving extremely low birth weight infants.

	Surviving Infants		Evaluated Infants		
	Evaluated (N = 9929)	Not evaluated (N = 10,636)	Without NEC (N = 9063)	Medical NEC (N = 417)	Surgical NEC (N = 449)
Obstetric					
Any antenatal steroids	85%	81%	85%	83%	80%
Vaginal delivery	31%	32%	31%	30%	33%
Multiple birth	29%	24%	29%	28%	31%
Inborn	84%	78%	85%	84%	74%
Infant					
Birth weight (g) (mean ± STD)	803 ± 169	861 ± 191	807 ± 169	779 ± 162	752 ± 172
Gestational age (weeks) (mean ± STD)	26.0 ± 2.0	26.0 ± 2.0	26 ± 2	26 ± 2	25 ± 2
Small for gestational age	15%	13%	15%	15%	8%
Male	50%	52%	49%	53%	58%
Nonwhite (maternal race)	41%	49%	41%	47%	39%
Delivery room					
Intubation	78%	74%	78%	78%	84%
Cardiac compressions	6%	7%	6%	7%	10%
Neonatal course					
Treatment for PDA	52%	51%	51%	56%	67%
Early-onset bacterial sepsis	2%	2%	2%	2%	2%
Late-onset bacterial sepsis	27%	25%	25%	39%	53%
Severe IVH or cystic PVL	11%	12%	10%	13%	21%
Severe ROP stage 3–4	17%	15%	16%	21%	32%
Chronic Lung Disease	47%	44%	46%	52%	58%
Total length of stay (median, Q1, Q3)	89 (71, 111)	82 (65, 104)	87 (70, 108)	100 (82, 120)	124 (103, 153)
Necrotizing enterocolitis	6%	7%			

STD: standard deviation. Small for gestational age defined as less than 10th percentile weight for age. PDA: patent ductus arteriosus. Severe IVH: Intraventricular Hemorrhage, grade III or IV. PVL: Periventricular Leukomalacia. ROP: retinopathy of prematurity. Chronic lung disease defined as requiring oxygen at 36 weeks post menstrual age.

(Table 1). Infants with surgical NEC more frequently had neonatal comorbidities associated with increased risk for disability. Infants with a history of NEC had an increased risk of long-term health morbidity as measured by need for rehospitalization, postdischarge surgeries, tube feeding at home, and severe neurodevelopmental disability; those with surgical NEC were consistently the most severely affected group (Fig. 2, Table 2).

2.1. Neurodevelopmental outcomes

For this study 48% of infants were evaluated using the BSID-II, and 52% were evaluated after implementation of the BSID-III. Survivors of NEC had significantly higher rates of neurodevelopmental disability than those without NEC. The risk of severe neurodevelopmental disability among infants with surgical NEC was nearly double that of the reference cohort of ELBW infants without a history of NEC (ARR 1.87, 95% CI 1.58–2.20). At 20 months corrected age (IQR 19, 22) severe disability was diagnosed in 17% of those without NEC, compared to 24% of those with medical NEC, and 38% in the surgical NEC group (Fig. 2). Specific disabilities diagnosed are listed in Table 3. A BSID score more than two standard deviations below the mean (<70) was interpreted as "severe disability." In addition, among the 5212 children evaluated using the BSID-III, an additional 19% met criteria for "moderate disability" with BSID-III cognitive or motor score 70–84 (more than one standard deviation below the mean). The rate of "moderate disability" was 19%

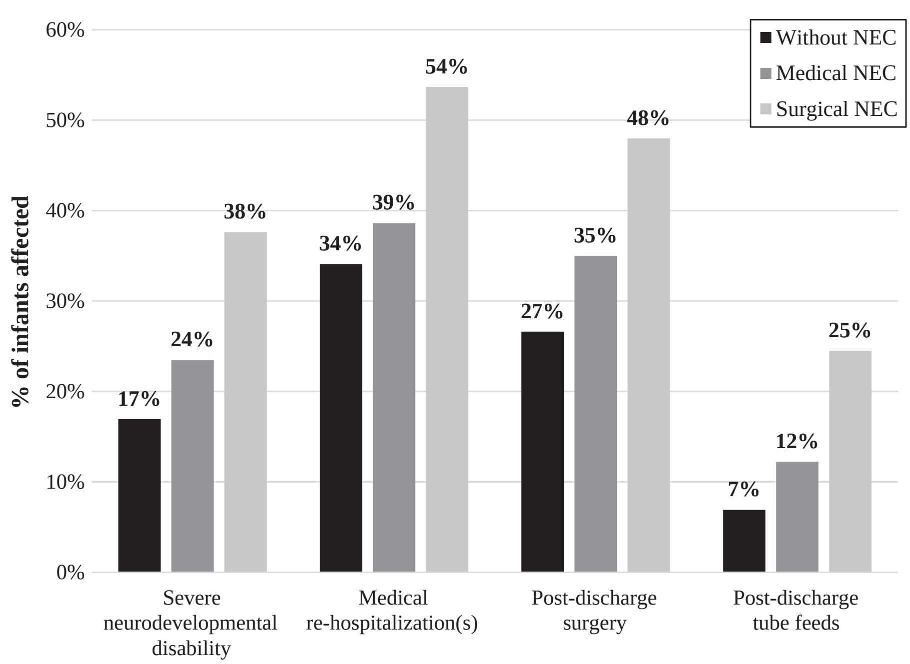

Fig. 2. Extremely low birth weight infants: Morbidity among survivors at 18–24 month corrected age.

Table 2
Adjusted risk ratios (ARR) for morbidity at 18–24 months corrected age, compared to infants without a history of necrotizing enterocolitis.

	Medical NEC		Surgical NEC	
	ARR (95% CI)	p	ARR (95% CI)	P
Severe neurodevelopmental disability	1.32 (1.03–1.69)	0.027	1.87 (1.59–2.20)	<0.001
Medical rehospitalization	1.10 (0.97, 1.26)	0.1454	1.41 (1.27–1.57)	<0.001
Postdischarge surgery	1.29 (1.10–1.50)	0.0013	1.65 (1.41–1.92)	<0.001
Postdischarge tube feeds	1.72 (1.32–2.24)	<0.001	2.66 (2.24–3.16)	<0.001

NEC: necrotizing enterocolitis. ARR: Adjusted risk ratio. CI: confidence interval. Reference group: Infants without NEC.

Table 3
Disability characteristics at 18–24 months corrected age.

	Without NEC (N = 9063)		Medical NEC (N = 417)		Surgical NEC (N = 449)	
	n	%	n	%	n	%
Any Severe Disability	1535	17%	98	24%	169	38%
Bilateral Blindness	57	1%	3	1%	15	3%
Hearing Impairment Requiring Amplification	130	1%	11	3%	16	4%
Inability to Walk 10 Steps with Support	311	3%	22	5%	64	14%
Cerebral Palsy	612	7%	40	10%	93	21%
Bayley Scales of Infant Development (II/III)						
MDI or Cognitive Score < 70	732	8%	51	12%	72	16%
PDI or Motor Score < 70	739	8%	60	14%	92	20%
Too Severely Delayed to Complete BSID	68	1%	3	1%	14	3%

MDI: Mental development index. PDI: Psychomotor development index. BSID: Bayley Scales of Infant Development.

among 4753 children without a history of NEC, 20% among 192 children with a history of medical NEC, and 31% among 267 children with a history of surgical NEC.

2.2. Health care needs after discharge

ELBW infants typically experience prolonged neonatal hospitalizations (Table 1), and also frequently require rehospitalization after their initial discharge. More than half (54%) of infants with a history of surgical NEC had at least one medical rehospitalization, while 39% of those with medical NEC and 34% of infants without a history of NEC were rehospitalized at least once prior to their follow-up evaluation. Reasons for rehospitalization are listed in Table 4; respiratory rehospitalizations were the most common in all groups. In this study medical rehospitalization data were collected separately from data on postdischarge surgeries.

During the initial hospitalization, 18% of the group without a history of NEC and 23% of the group with medical NEC required at least one surgical procedure. After discharge, children with surgical NEC remained the most likely to require further surgery (ARR 1.65, 95% CI 1.41–1.92), with 48% undergoing additional surgery between original hospital discharge and follow-up evaluation (Table 4).

At home, most infants required some form of medical support, with apnea or cardiopulmonary monitors and supplemental oxygen being the most common (Table 4). Infants with a history of surgical NEC had the highest risk of requiring medical support after discharge home

Table 4
Heath care needs between discharge and 18–24 months corrected age follow-up evaluation.

	Without NEC (N = 9063)		Medical NEC (N = 417)		Surgical NEC (N = 449)	
	n	%	n	%	n	%
Any Medical Rehospitalization	3090	34%	161	39%	241	54%
Respiratory Illness	2321	26%	117	28%	146	33%
Nutrition/Failure to Thrive	240	3%	17	4%	36	8%
Seizure Disorder	102	1%	7	2%	8	2%
Shunt Complication	66	1%	5	1%	16	4%
Infection	355	4%	22	5%	50	11%
Meningitis	25	0%	1	0%	2	0%
Urinary Tract Infection	45	0%	4	1%	1	0%
Gastrointestinal Infection	167	2%	12	3%	25	6%
Other Infection	131	1%	6	1%	28	6%
Other Medical Rehospitalization	371	4%	20	5%	49	11%
Any Surgical Procedure	2412	27%	146	35%	213	48%
Gastrostomy Tube Placement	230	3%	12	3%	24	5%
Other Gastrointestinal Surgical Procedures	197	2%	29	7%	89	20%
Inguinal Hernia Repair	670	7%	38	9%	39	9%
Any Medical Support After Discharge	4774	54%	219	53%	291	65%
Tracheostomy	146	2%	7	2%	11	2%
Ventilator	82	1%	6	1%	11	2%
Oxygen	2347	26%	98	24%	148	33%
Apnea or CP Monitor	2718	30%	120	29%	156	35%
Any type of tube feeds	626	7%	51	12%	110	25%
Gastrostomy	465	5%	40	10%	94	21%
Nasogastric Feeds	230	3%	16	4%	25	6%

NEC: necrotizing enterocolitis. CP: cerebral palsy.

Table 5
Sociodemographic characteristics of evaluated infants.

	Without NEC			Medical NEC			Surgical NEC		
	N	n	%	N	n	%	N	n	%
Caregivers									
Single Parent	9056	1222	13%	417	65	16%	448	67	15%
Single Parent Extended Family	9056	627	7%	417	24	6%	448	24	5%
Two Parent	9056	6660	74%	417	303	73%	448	333	74%
Two Parent Extended Family	9056	547	6%	417	25	6%	448	24	5%
Primary Caregiver Education									
High School Graduate or less	8351	2698	32%	373	140	38%	403	150	37%
Some College/University	8351	2320	28%	373	112	30%	403	121	30%
College/University Graduate	8351	3333	40%	373	121	32%	403	132	33%
Child currently in Foster care	9063	180	2%	417	9	2%	449	13	3%
Maternal Age at Birth[a]									
<20 years	4889	347	7%	189	21	11%	294	32	11%
>39 years	4889	223	5%	189	11	6%	294	10	3%
English not the Primary Language[a]	4246	488	11%	168	16	10%	295	26	9%
Income Below HHS Poverty Guidelines[a]	3862	1247	32%	151	56	37%	265	99	37%

[a] Collected since 2006. NEC: necrotizing enterocolitis. HHS Poverty Guidelines: US Department of Health and Human Services Poverty Guidelines [26].

(65%), which was driven in large part by the increased use of tube feeding, which 25% of the surgical NEC survivors received after hospital discharge (ARR 2.66, 95% CI 2.24–3.16).

2.3. Sociodemographic characteristics

Sociodemographic characteristics of evaluated infants and their caregivers are listed in Table 5. Assessment of maternal age, primary language of the caregiver, and household income was added to the data collection in 2006; 5431 of the 9929 children in this study were evaluated since these assessments were added to data collection. Since that time, 99% of participating families chose to provide data on maternal age, 100% on primary language, and 91 on household income. Of the 4278 families in the United States who chose to report income in relation to federal poverty levels, 33% reported living in poverty.

3. Discussion

3.1. Outcomes

Extremely low birth weight infants who develop NEC, particularly when severe enough to warrant surgery, are a population at high risk for mortality and morbidity. While it is difficult to predict outcome for any individual patient, it is incumbent on the healthcare team to guide family expectations through the myriad of difficult decision points that are regularly encountered [7,8]. For this cohort, assuming that the rate of severe disability was similar in the evaluated and nonevaluated group, only 39% of the infants who underwent surgery for NEC were alive and without severe disability at 20 months of age compared to 57% of infants with medical NEC and 73% of infants without NEC.

As ELBW infants increasingly survive, the optimization of neurodevelopmental outcomes remains a key goal in the complex care provided to these patients [9]. Matters of particular interest to the surgical patient include the impact of red blood cell and platelet transfusion practices, the effect of anesthetic and sedative exposure, exposures to other ototoxic drugs including antibiotics, central line associated bloodstream prevention strategies, and optimal nutritional support strategies [10–17]. The question of whether the initial choice of primary peritoneal drainage (PPD) or laparotomy is associated with any difference in long term outcomes remains unanswered by current data. Prior analysis shows that infants who receive PPD are on average higher risk neonates, with higher mortality than those who undergo initial laparotomy [2]. Therefore, a randomized controlled trial would be required assess the effects attributable to the choice of PPD vs. laparotomy.

Postdischarge, the home environment has substantial impacts on the child's health and developmental outcomes; lower educational attainment of the caregiver, nonwhite race, and lower socioeconomic status have previously been demonstrated as independent predictors of impaired cognitive and language development (though motor impairment and cerebral palsy are more directly attributable to focal brain injury including intraventricular hemorrhage and periventricular leukomalacia). Over time the influence of perinatal risk factors diminishes as other social and environmental factors predominate [18–20].

3.2. Impact on health systems and caregivers

In 2011, aggregate hospital costs for the neonatal hospitalizations of infants weighing less than 1500 g at birth was 3.7 billion US dollars, with surviving neonates costing significantly more than those who died prior to discharge [21]; lower birth weight and the presence of comorbidities, including NEC, result in substantial marginal cost increases [22]. As this study demonstrates, the increased utilization of care among survivors of NEC does not stop at hospital discharge. It can be anticipated that many of these children will continue to require various forms of supportive care beyond the first two years of life, with attendant costs within the healthcare system and for their caregivers at home [23]. Families of children with special health care needs contend with challenges that include impact on work for the caregiver, financial strain, social isolation, stress, and unmet care needs [23,24].

In addition to medical and surgical management strategies, social determinants of health impact the outcomes examined at multiple points. Lower socioeconomic status first predisposes women to an increased risk of extremely preterm delivery, is a risk factor for worse neurodevelopmental disability after discharge, and impacts the experience of families caring for medically complex children [19,24,25]. In 2012, 24% of American children less than 6 years old, or 5.8 million children, lived in households with incomes below the US Department of Health and Human Services poverty line ($23,050 for a family of four in 2012) [26,27]. These circumstances must be seriously considered when anticipating the home care logistics for patients with complex medical needs and neurodevelopmental disability, and when designing interventions to optimize post-discharge outcomes.

3.3. Limitations

Loss to follow-up is a common problem in accurately assessing neurodevelopmental outcomes, particularly in the United States [28]. Follow-up bias may result in overestimates or underestimates of true rates of disability; on one hand, parents of children who appear to be developmentally "normal" may not be as likely to engage in follow-up, while on the other hand, the challenges of caring for children with significant disabilities may also result in decreased adherence to follow-up studies [28]. Although patient characteristics known to be associated with severe disability were similar in the evaluated and nonevaluated cohort, leading us to conclude that the infants evaluated were likely a fairly representative sample, the follow-up rate of 49% of infants without NEC, which was higher than the 45% follow up rate of infants with NEC ($P < 0.01$) may result in under- or overestimation of the true prevalence of disability and healthcare needs. The higher proportion of outborn infants with surgical NEC may have contributed to this difference in follow-up rates; when follow-up rate was compared only for inborn infants, there was no difference between infants with and without NEC ($P = 0.33$). Children with socioeconomic disadvantages, including lower caregiver education levels, tend to have more barriers to participating in follow-up and lower follow-up participation [20,28]. Maternal race (reported during initial NICU stay), which in the United States has significant covariance with socioeconomic disadvantage [20], was classified as nonwhite for 49% of the nonevaluated surviving infants compared with 41% of those evaluated at follow-up. Sociodemographic characteristics of infants at follow-up, which are known to impact developmental outcomes, may not be equivalent between evaluated and nonevaluated infants.

It is difficult to know whether these data are generalizable for all infants, or only for those treated and followed at institutions that participate in this multicenter quality improvement collaborative. Participating centers may have more robust neurodevelopmental services, or conversely may see particularly complex patient populations. Socioeconomic and demographic risk factors impact neurodevelopmental outcomes, and these baseline population characteristics vary across centers. The racial and socioeconomic status of children in this cohort may reflect the demographics of populations served by the participating centers, but is also influenced by the higher rate of very preterm and very low birth weight infants born to nonwhite mothers in the United States [29].

In the absence of direct examination of the bowel at laparotomy or postmortem examination, as is the case for infants who undergo primary peritoneal drainage, it is not possible to determine with certainty whether bowel perforation was because of NEC or spontaneous intestinal perforation. While infants with both conditions are known to be at increased risk of mortality and neurodevelopmental morbidity [30] this study does not define any differences in outcomes between these two groups.

The assessment of an individual's neurodevelopmental abilities at 18–24 months corrected age is ultimately not as important as how that individual will function once they reach school age, or as an adult. Critiques of the Bayley Infant Developmental Scales show that while low BSID scores may have insufficient sensitivity to detect subtle disability present by the time the child reaches school age (particularly BSID-III), the specificity for severe disability, still present at school age, approaches 100% for scores <70 (more than two standard deviations below the mean) [31,32]. Therefore, the true rates of disability may be even higher than that detected on the assessment of these individuals as at 18–24 months.

4. Conclusion

Extremely low birth weight survivors of necrotizing enterocolitis were at significantly ($p < 0.001$) increased risk for severe neurodevelopmental disability, postdischarge surgery, and tube feeding at 18–24 months corrected age. Notably, in our cohort 38% of survivors with a history of surgical necrotizing enterocolitis demonstrated severe neurodevelopmental disability, 48% underwent postdischarge operations, more than half required rehospitalizations for medical reasons, and a quarter required tube feeding at home. The social determinants of health are intrinsic to understanding and optimizing outcomes for these children, as various markers of socioeconomic disadvantage result in predisposition to preterm birth, negatively influence neurodevelopmental outcomes, and impact the experience of families providing long term care for medically complex children at home. We hope that these data can help inform the prognosis of infants with medical and surgical necrotizing enterocolitis, drive interventions to improve the quality of survival, and inform discussions of healthcare utilization for these infants.

Role of the authors

Fullerton: Conception/design, analysis and interpretation, participated in drafting, gave final approval

Hong: Conception/design, analysis and interpretation, participated in revision, gave final approval

Velazco: Conception/design, analysis and interpretation, participated in revision, gave final approval

Mercier: Conception/design, analysis and interpretation, participated in revision, gave final approval

Morrow: Conception/design, data acquisition, analysis and interpretation, participated in drafting, gave final approval

Edwards: Conception/Design, data acquisition, analysis and interpretation, participated in revision, gave final approval

Farelli: Conception/Design, data acquisition, analysis and interpretation, participated in revision, gave final approval

Soll: Conception/Design, data acquisition, analysis and interpretation, participated in revision, gave final approval

Modi: Conception/design, analysis and interpretation, participated in revision, gave final approval

Horbar: Conception/Design, data acquisition, analysis and interpretation, participated in revision, gave final approval

Jaksic: Conception/design, analysis and interpretation, participated in revision, gave final approval

Appendix A. Discussions

Brenna Fullerton, Boston MA.

GAIL BESNER (Columbus, OH) Thank you for a lovely presentation. These data are obviously very important apropos of the NECS trial that Marty Blakely is conducting now, and so my question to you is of the patients with surgical NEC did you differentiate those who had a laparotomy versus those who had peritoneal drainage, and was the outcome different in either of those two categories?

BRENNA FULLERTON Unfortunately, in the Vermont Oxford Network data, that differentiation only started to be made halfway through this study collection period, so hopefully going forward there will be more information available on that, but we did not include that distinction in this analysis. We do know from prior analysis that those who receive PPD as their initial choice of treatment are in general a sicker cohort of course, and so it would be difficult to determine whether any difference in outcomes were owing to baseline infant characteristics versus the choice of treatment, but it certainly is something that we will have more data on in years to come.

STEVE STYLIANOS (New York, NY) I think in this day and age people are going to look at anesthesia and wonder about the impact of anesthesia on the surgical cohort. Can you see a way in future studies to tease any information out about that, and did any of the group with medical NEC have say a ductus ligated or have exposure to anesthesia that could be looked at as a subgroup? Thank you.

BRENNA FULLERTON Yes. In the group with medical NEC, about 24% did have some form of surgery within their initial hospitalization. I do not recall the exact percent with ductus ligated, although we do have data on that. I think it is hard to say what the contribution of anesthesia is in particular to these infants because they have so many impacts within their hospital stay on their neurodevelopmental outcomes be it nutritional, transfusion thresholds, oxygen — almost anything that is happening in the field of neonatologist in the care of extremely low birth weight infants seems to impact the neurodevelopmental outcomes, so while anesthesia is a vital component to consider, I think it is really hard to tease out from all of the other morbidities and exposures that these infants have.

HENRI FORD (Los Angeles, CA) So your work clearly corroborates what has been reported by the Neonatal Research Network, from the work Marty Blakely has been doing and others. What do you feel is the incremental improvement in the current literature or our current understanding of this problem that your work brings to the forefront?

BRENNA FULLERTON I think the strength of the work is really the very large number of infants, and I think that it can therefore be seen as somewhat benchmark data for this large cohort of infants with prospectively collected data and standardizes analyses, so I think it is helpful in those regards. In addition, I think one of the strengths of the Vermont Oxford Network's data is the definition of necrotizing enterocolitis. In various follow up studies, the definition for the original cases can vary, but the VON definition is fairly strict requiring at least a Bell's stage II, and we did in more detail examine the medical and surgical group, so I think it is helpful in that regard.

UNIDENTIFIED SPEAKER So you used 1000 g and 1000 g I am sure at risk for neurodevelopmental complications anyway. Did you look at the 1500-g mark, since those patients also develop NEC as an outcome?

BRENNA FULLERTON We did not simply because the follow up study is set to follow up in a standardized fashion just the 1000-g and below infants. We do not have data on the larger infants at least collected in a standardized way.

References

[1] Fitzgibbons SC, Ching Y, Yu D, et al. Mortality of necrotizing enterocolitis expressed by birth weight categories. J Pediatr Surg 2009;44(6):1072–5 [discussion 5-6].

[2] Hull MA, Fisher JG, Gutierrez IM, et al. Mortality and management of surgical necrotizing enterocolitis in very low birth weight neonates: a prospective cohort study. J Am Coll Surg 2014;218(6):1148–55.

[3] Mercier CE, Dunn MS, Ferrelli KR, et al. Neurodevelopmental outcome of extremely low birth weight infants from the Vermont Oxford network: 1998–2003. Neonatology 2010;97(4):329–38.

[4] Schmidt B, Asztalos EV, Roberts RS, et al. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. JAMA 2003;289(9):1124–9.

[5] Manual of operations: part 2 data definitions & infant data forms. 18.018.0 ed. . Burlington, VT: Vermont Oxford Network; 2013.

[6] Vermont Oxford network extremely low birth weight infant follow-up project manual of operations, version 17. Vermont Oxford Network; 2015.

[7] Janvier A, Barrington K, Farlow B. Communication with parents concerning withholding or withdrawing of life-sustaining interventions in neonatology. Semin Perinatol 2014;38(1):38–46.

[8] Kaempf JW, Tomlinson MW, Campbell B, et al. Counseling pregnant women who may deliver extremely premature infants: medical care guidelines, family choices, and neonatal outcomes. Pediatrics 2009;123(6):1509–15.

[9] Stoll BJ, Hansen NI, Bell EF, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. JAMA 2015;314(10):1039–51.

[10] Bell EF, Strauss RG, Widness JA, et al. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. Pediatrics 2005; 115(6):1685–91.

[11] Kirpalani H, Whyte RK, Andersen C, et al. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. J Pediatr 2006; 149(3):301–7.

[12] Sparger KA, Assmann SF, Granger S, et al. Platelet transfusion practices among very-low-birth-weight infants. JAMA Pediatr 2016;170(7):687–94.

[13] Aker J, Block RI, Biddle C. Anesthesia and the developing brain. AANA J 2015;83(2): 139–47.

[14] Davidson AJ, Disma N, de Graaff JC, et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet 2016;387(10015): 239–50.

[15] Zimmerman E, Lahav A. Ototoxicity in preterm infants: effects of genetics, aminoglycosides, and loud environmental noise. J Perinatol 2013;33(1):3–8.

[16] Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004;292(19):2357–65.

[17] Chan SH, Johnson MJ, Leaf AA, et al. Nutrition and neurodevelopmental outcomes in preterm infants: a systematic review. Acta Paediatr 2016;105(6):587–99.

[18] Linsell L, Malouf R, Morris J, et al. Prognostic factors for cerebral palsy and motor impairment in children born very preterm or very low birthweight: a systematic review. Dev Med Child Neurol 2016;58(6):554–69.

[19] Linsell L, Malouf R, Morris J, et al. Prognostic factors for poor cognitive development in children born very preterm or with very low birth weight: a systematic review. JAMA Pediatr 2015;169(12):1162–72.

[20] Brumberg HL, Shah SI. Born early and born poor: an eco-bio-developmental model for poverty and preterm birth. J Neonatal Perinatal Med 2015;8(3):179–87.

[21] Kowlessar NM, Jiang HJ, Steiner C. Hospital stays for newborns, 2011: statistical brief #163. Healthcare Cost and Utilization Project (HCUP) statistical briefs. Rockville (MD); 2006.

[22] Johnson TJ, Patel AL, Jegier BJ, et al. Cost of morbidities in very low birth weight infants. J Pediatr 2013;162(2):243–9 [e1].

[23] Heyman MB, Harmatz P, Acree M, et al. Economic and psychologic costs for maternal caregivers of gastrostomy-dependent children. J Pediatr 2004;145(4):511–6.

[24] Kuo DZ, Cohen E, Agrawal R, et al. A national profile of caregiver challenges among more medically complex children with special health care needs. Arch Pediatr Adolesc Med 2011;165(11):1020–6.

[25] Behrman RE, Butler AS, Institute of Medicine (U.S.). Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Preterm birth : causes, consequences, and prevention. Washington, D.C.: National Academies Press; 2007

[26] Pakarinen MP, Kurvinen A, Koivusalo AI, et al. Long-term controlled outcomes after autologous intestinal reconstruction surgery in treatment of severe short bowel syndrome. J Pediatr Surg 2013;48(2):339–44.

[27] DeNavas-Walt C, Proctor BD, Smith JC. U.S. Census Bureau. Income, poverty, and health insurance coverage in the United States. Washington. D.C.: United States Census Bureau; 2012. p. 2013.

[28] Guillen U, DeMauro S, Ma L, et al. Relationship between attrition and neurodevelopmental impairment rates in extremely preterm infants at 18 to 24 months: a systematic review. Arch Pediatr Adolesc Med 2012;166(2):178–84.

[29] Hamilton BE, Martin JA, Osterman MJ, et al. Births: final data for 2014. Natl Vital Stat Rep 2015;64(12):1–64.

[30] Wadhawan R, Oh W, Hintz SR, et al. Neurodevelopmental outcomes of extremely low birth weight infants with spontaneous intestinal perforation or surgical necrotizing enterocolitis. J Perinatol 2014;34(1):64–70.

[31] Spencer-Smith MM, Spittle AJ, Lee KJ, et al. Bayley-III cognitive and language scales in preterm children. Pediatrics 2015;135(5):e1258-5.

[32] Moore T, Johnson S, Haider S, et al. Relationship between test scores using the second and third editions of the Bayley scales in extremely preterm children. J Pediatr 2012;160(4):553–8.