Rehospitalization Through Childhood and Adolescence: Association with Neonatal Morbidities in Infants of Very Low Birth Weight

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Objective To evaluate the impact of major neonatal morbidities on the risks for rehospitalization in children and adolescents born of very low birth weight.

Study design An observational study was performed on data of the Israel Neonatal Network linked together with the Maccabi Healthcare Services medical records. After discharge from the neonatal intensive care unit, 6385 infants of very low birth weight born from 1995 to 2012 were registered with Maccabi Healthcare Services and formed the study cohort. Multivariable negative binomial regression models were calculated to estimate the adjusted relative risk (aRR) and 95% CI for hospitalization.

Results Up to 18 years following discharge, 3956 infants were hospitalized at least once. The median age of follow-up was 10.7 years with total of follow-up of 67 454 patient years and 10 895 hospitalizations. The risks for rehospitalization were increased significantly for each of the neonatal morbidities: surgical necrotizing enterocolitis (NEC), aRR 2.71 (95% CI 2.08-3.53), intraventricular hemorrhage grades 3-4, 2.13 (1.85-2.46), periventricular leukomalacia (PVL), 1.83 (1.58-2.13), bronchopulmonary dysplasia, 1.94 (1.72-2.17), and retinopathy of prematurity stages 3-4, 1.59 (1.36-1.85). During the first 4 years, children with surgically treated NEC, intraventricular hemorrhage, PVL, or bronchopulmonary dysplasia had 1.5- to 2.5-fold greater risks for hospitalization compared with those without the specific morbidity. In the 11th-14th and 15th-18th years, respectively, surgically treated NEC was associated with a 3.05 (1.32-7.04) and 3.26 (0.99-10.7) aRR for hospitalization, and PVL was associated with a 2.67 (1.79-3.97) and 3.47 (2.03-5.92) aRR for hospitalization.

Conclusions Specific major neonatal morbidities as well as the number of morbidities were associated with excess risks of rehospitalization through childhood and adolescence. *(J Pediatr 2017;188:135-41).*

Infants born preterm and those with very low birth weight (VLBW) are at risk for adverse long-term morbidities with the concomitant increased use of healthcare resources, including an excess risk of rehospitalization through childhood and adolescence.[1] During infancy and early childhood, rehospitalization of infants born preterm after discharge from their initial birth hospitalization has been ascribed to complications of prematurity, especially bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and neurologic disorders.[2,3] In the first year following discharge, 46% of infants born very preterm required readmission, and the risk of rehospitalization was associated with BPD and severe brain injury and was predominantly due to respiratory illness.[2] Ambalavanan et al[3] similarly reported that 45% of infants with extremely low birth weight were rehospitalized by 18-22 months and the predictors for rehospitalization included shunt surgery for hydrocephalus, pulmonary disorders, and NEC.

Hospitalizations of infants born preterm and those with VLBW in late childhood and adolescence predominantly have been due to diagnoses of respiratory disorders,[4] infections,[5] and epilepsy and seizures.[6,7] Walter et al[4] reported that controlling for BPD and cerebral palsy attenuated the risks for respiratory hospitalizations, suggesting that some of the risk was mediated through these diagnoses. However, the long-term impact of specific neonatal morbidities, including BPD, NEC, and neurologic disorders, on the risks for rehospitalization of infants born preterm or those with VLBW through late childhood and adolescence has not been well documented.

This study, linking the Israel national VLBW infant database with the community healthcare provider's database, aimed to determine the impact of specific major neonatal morbidities on the risks for rehospitalization up to 18 years after the birth hospitalization, in a population of children and adolescents born of VLBW.

aRR	Adjusted relative risk	NEC	Necrotizing enterocolitis
BPD	Bronchopulmonary dysplasia	NICU	Neonatal intensive care unit
BW	Birth weight	PVL	Periventricular leukomalacia
GA	Gestational age	PY	Patient years
HMO	Health maintenance organization	ROP	Retinopathy of prematurity
IVH	Intraventricular hemorrhage	SGA	Small for gestational age
MHS	Maccabi Healthcare Services	VLBW	Very low birth weight

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*List of participating centers and neonatal department heads for the Israel Neonatal Network is available at www.jpeds.com (**Appendix**).

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Methods

This observational study was performed on linked data collected by the Israel national VLBW infant database[8] together with the Maccabi Healthcare Services (MHS) health maintenance organization (HMO) electronic patient medical records.[9] Data were collected by the Israel national VLBW infant database on all newborn infants of VLBW (birth weight [BW] ≤1500 g) born in Israel from 1995 through 2012 as previously reported.[8] All 28 neonatal departments in Israel comprising the Israel Neonatal Network participated in the data collection. The data were collected prospectively by the use of standard forms and included demographic details, antenatal and perinatal history, postdelivery status and neonatal diagnosis, treatments, complications, and outcome at discharge. All departments used operating manual and standard definitions, based on those of the Vermont-Oxford Trials Network (https://public.vtoxford.org). All live-born infants in Israel receive a unique identification number at birth. Patient information received by the database coordinator is cross-checked with the national birth registry, and data from any missing infant are requested from the hospital in which the birth occurred. In <1% of births (approximately 10 records per year) the infant could not be traced, possibly reflecting errors in registration or very immature infant delivery room deaths. Interhospital transfers were followed by the database coordinator until final discharge home, and the date of discharge was recorded.

This study was conducted in collaboration with MHS. In Israel, healthcare services are provided by 4 HMOs that by law are obligated to insure every citizen who requests to join them irrespective of age, sex, or medical history.[9] MHS provides comprehensive healthcare for 2 million members, about one-quarter of the Israeli population, approximately one-third of whom are children ages 0-18 years. MHS members are identified by the unique identification number received at birth. The electronic patient record incorporates all health services provided by or funded by MHS. MHS' central databases are updated automatically with each health transaction, including physician visits, diagnostic investigations, hospital admissions, and all medical service provided to the individual through MHS. In Israel, the birth hospitalization of all newborn infants until discharge home is financed through the National Insurance Institute (Jerusalem, Israel). On discharge, all infants are registered with either of their parent's HMOs.

For this study, the identification numbers of all infants with VLBW born from January 1995 through December 2012 and discharged home were crosslinked to the MHS members' database. Only infants who were registered with MHS on their discharge from the neonatal intensive care unit (NICU) following the initial birth hospitalization were included. This process created a new linked file comprising the VLBW infant database record and the MHS electronic patient record. This deidentified secure linked file served as the research file for this study.

This study was approved by the institutional review boards of MHS (MHS 20/2014) and of the Sheba Medical Center (Ramat Gan, Israel; SMC 1587-14). From January 1995 through December 2012, 27 434 infants of VLBW were included in the VLBW infant database, representing >99% of all infants of VLBW born alive in Israel. Of these infants, 5191 died during their initial hospitalization and 22 243 (81%) were discharged home. On discharge from the NICU, 6385 infants, representing 28.7% of all infants of VLBW discharged home, were registered with MHS and formed the study cohort (the remaining 15 858 infants of VLBW were registered with 1 of the 3 other HMOs in Israel). Data were collected until September 30, 2015, or up to 18 years following date of NICU discharge or until leaving MHS or until death, whichever occurred earlier. Fifty-two subjects died after their initial birth hospitalization, and 797 left MHS during this period.

The definitions used have been reported previously in detail.[8] The best estimate of gestational age (GA) in completed weeks was determined by the hierarchy of obstetric measures (last menstrual period, obstetric history and examination, and prenatal ultrasound scans) and a neonatologist's estimate based on early postnatal physical and neurologic examination. Sex-specific BW percentiles were determined according to the intrauterine growth charts of Kramer et al,[10] and small for gestational age (SGA) was defined as a BW below the 10th percentile for GA. Ethnicity was defined according to the mother's ethnic/religious group as reported on the infant's birth certificate, including Jewish, Muslim, Druze, Christian, and other groups. Congenital malformations were recorded according to the list of reportable malformations required in Israel, which includes all major malformations. NEC was diagnosed by the presence of clinical and radiologic characteristics according to the criteria of Bell et al.[11] Only definite NEC (Bell grades 2 and 3) was included. Intraventricular hemorrhage (IVH) and cystic periventricular leukomalacia (PVL) were diagnosed by routine cranial ultrasonography scan, and IVH was graded according to the classification of Papile et al.[12] BPD was diagnosed according to the criteria of Bancalari et al,[13] including clinical and radiologic features together with the requirement of oxygen supplementation at 36 weeks of postmenstrual age.[14]

Retinopathy of prematurity (ROP) was staged according to the international standard classification.[15] Hospitalizations were characterized by admission date, discharge date, and length of hospitalization. Repeat hospitalizations within 2 days were considered as a single hospitalization.

The maternal and infant characteristics and major neonatal morbidities of the hospitalized and nonhospitalized infants were compared with the χ^2 test. All tests were 2-tailed, and results were considered significant at a P value < .05. Hospital admission rates per 100 patient years (PY) of follow-up were calculated for each variable category. PY at risk were calculated from date of discharge from the birth hospitalization until September 30, 2015, or until the date of leaving MHS, or 18 years after discharge, or the date of death, if occurring earlier. The absolute number of hospital admissions was recorded as a count and thus analysis via the negative binomial regression model was selected for this type of response. The initial multivariable negative binomial regression model analyzed the