Antecedents of Neonatal Encephalopathy in the Vermont Oxford Network Encephalopathy Registry

WHAT'S KNOWN ON THIS SUBJECT: Most term and late preterm infants with neonatal encephalopathy have not had recognized asphyxial birth events. Several nonasphyxial risk factors for neonatal encephalopathy have been identified in previous studies.

WHAT THIS STUDY ADDS: In a large sample, we confirm the association of several nonasphyxial factors with neonatal encephalopathy, including markers of intrauterine exposure to infection or inflammation, intrauterine fetal growth restriction, and birth defects. We identify steps that would improve studies of neonatal encephalopathy.

abstract

BACKGROUND: Neonatal encephalopathy (NE) is a major predictor of death and long-term neurologic disability, but there are few studies of antecedents of NE.

OBJECTIVES: To identify antecedents in a large registry of infants who had NE.

METHODS: This was a maternal and infant record review of 4165 singleton neonates, gestational age of ≥36 weeks, meeting criteria for inclusion in the Vermont Oxford Network Neonatal Encephalopathy Registry.

RESULTS: Clinically recognized seizures were the most prevalent condition (60%); 49% had a 5-minute Apgar score of ≤3 and 18% had a reduced level of consciousness. An abnormal maternal or fetal condition predated labor in 46%; maternal hypertension (16%) or small for gestational age (16%) were the most frequent risk factors. In 8%, birth defects were identified. The most prevalent birth complication was elevated maternal temperature in labor of ≥37.5°C in 27% of mothers with documented temperatures compared with 2% to 3.2% in controls in population-based studies. Clinical chorioamnionitis, prolonged membrane rupture, and maternal hypothyroidism exceeded rates in published controls. Acute asphyxial indicators were reported in 15% (in 35% if fetal bradycardia included) and inflammatory indicators in 24%. Almost one-half had neither asphyxial nor inflammatory indicators. Although most infants with NE were observably ill since the first minutes of life, only 54% of placentas were submitted for examination.

CONCLUSIONS: Clinically recognized asphyxial birth events, indicators of intrauterine exposure to inflammation, fetal growth restriction, and birth defects were each observed in term infants with NE, but much of NE in this large registry remained unexplained. *Pediatrics* 2012;130:878–886

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KEY WORDS

asphyxia, encephalopathy, newborn, perinatal factors, registries

ABBREVIATIONS

CNS—central nervous system
CP—cerebral palsy
NE—neonatal encephalopathy
NER—Neonatal Encephalopathy Registry
SGA—small for gestational age
VON—Vermont Oxford Network

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Neonatal encephalopathy (NE) is a syndrome of neurologic dysfunction, often accompanied by seizures, presenting in the early hours of life in term and late preterm infants. Mortality in NE is substantial.[1] Two-thirds of cerebral palsy (CP) arises in infants born at or after 35 weeks' gestational age,[2] with ~30% of CP occurring in survivors of NE.[3]

A majority of births of mature infants occur in facilities without research capabilities. In the past, relatively decentralized care in ill term infants caused our knowledge of neonatal neurologic disorders and their treatment in term infants to lag behind that of our knowledge regarding very preterm infants. With the potential for hypothermia and newer interventions to improve outcome, many more neurologically ill term neonates are now cared for in specialized facilities that provide opportunities to characterize the clinical features of illnesses in such infants, to examine patterns of perinatal care, and to expand our understanding of causes, natural history, and optimal treatment.

Some infants with NE have clinically recognized asphyxial ("sentinel") events at birth. Controlled studies of antecedents of NE in representative populations have found that most infants who have NE did not have recognized asphyxial birth events, however.[4–9] Such studies and others related to them[4,10,11] have identified some additional unsuspected risk factors, pointing to a broader set of causal factors than previously recognized. Still, known risk factors for NE, singly or together, do not account for most cases of NE. Our lack of knowledge about causes of NE seriously impairs the progress of efforts to prevent NE and to treat it optimally.

The Neonatal Encephalopathy Registry (NER), a project of the Vermont Oxford Network (VON),[12] gathers data on infants with NE who were at least 36 weeks' gestational age or who received hypothermia therapy. One of the registry's strengths is its use to examine patterns of perinatal care and to identify changes in those patterns of care. Although the registry is not a representative population and does not have healthy controls, it provides an opportunity to examine selected clinical antecedents of NE. We describe here the frequency with which recognized antecedents of NE occurred in a large sample of encephalopathic term newborns. These findings have implications for future studies of the etiology of NE.

METHODS

Eligibility and Enrollment

VON maintains 2 registries of infants admitted to NICUSs. Any infant born or transferred into a VON member center at ≥36 weeks' gestation who displayed evidence of NE within 3 days of birth was eligible to be enrolled in the NER. NE was defined as presence of seizures and/or altered consciousness (eg, stupor, coma). To capture all infants potentially affected by NE, infants with a 5-minute Apgar score of ≤3 or who received neuromuscular blockade extending through the first 72 hours of life were eligible. Regardless of neurologic status or gestational age, any infant who received hypothermia therapy was eligible. Infants born with central nervous system (CNS) birth defects were excluded from the NER. Because multiple gestations pose special risks for adverse neurologic outcome, only singleton infants were examined in this study.

The registry did not require any interventions or protocols for treatment and only de-identified data were submitted, precluding the necessity for informed consent. The institutional review board at the University of Vermont and the institutional review boards at each participating hospital reviewed and approved registry participation.

Measures

The NER database collected information on obstetric and prenatal history, neurologic indicators, neuroimaging, diagnoses, hypothermia therapy, and discharge status. Acute asphyxial events of birth (sentinel events) were defined as perinatal events capable of interrupting oxygen supply or blood flow to the fetus, such as antepartum hemorrhage including placental abruption, uterine rupture, cord prolapse, tight nuchal cord, or maternal shock or death. Fetal bradycardia was included as a possible asphyxial indicator. Antepartum hemorrhage, cord prolapse, and uterine rupture were routinely recorded. Abruption, tight nuchal cord, and maternal shock or death were not systematically reported but were included as write-ins for other birth traumas. Inflammatory factors were maternal fever in labor of ≥37.5°C, a clinical diagnosis of chorioamnionitis, fetal tachycardia, prolonged rupture of membranes, early bacterial infection in the infant, or toxoplasmosis, other infections, rubella, cytomegalovirus infection, and herpes simplex infection in the infant. Small for gestational age (SGA) was defined as birth weight below the 10th percentile within categories of gender, race, and multiple gestation based on smoothed curves from the US Natality data set, 2001 and 2002.[13] Birth defect included congenital heart defects, gastrointestinal defects, genitourinary defects, chromosomal abnormalities, pulmonary abnormalities, and other defects from the VON Birth Defects Codes List.[14] Other antecedents, including descriptors of maternal and infant conditions, were derived from the VON NER database.[15]

Statistical Analyses

The tables include the number of infants and the number of cases, the

unadjusted percentages for categorical measures, and the mean ± SD for continuous measures. The χ^2 test was used to evaluate the association between SGA and asphyxial events, and SGA and inflammatory events. All analyses were conducted by using SAS version 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS

Between 2006 and 2010, a total of 4165 singleton births were registered in the NER. Clinically recognized seizures, present in 60%, were the most commonly identified criterion for eligibility (Table 1). Reduced level of consciousness was reported in only 18% of infants considered to have NE and was the sole positive criterion in <1%. In 38%, hypothermia was initiated before admission to the NER. Demographic and other characteristics of these mothers and their infants are provided elsewhere in reports that include multiple births.[16]

Maternal conditions predating labor that might be relevant to risk of NE were maternal hypertension, diabetes, hypothyroidism, lack of prenatal care, and assisted reproduction (Table 2). At least 1 of these maternal conditions was noted in 27% of infants. Hypertension (16%) and diabetes (10%) were reported most frequently. Maternal hypothyroidism was reported in 2.5%.

Of conditions intrinsic to the infant, SGA was the most frequently reported, present in 16% (Table 2). Non-CNS birth defects were noted in the newborn period in 8%. One-quarter of infants had ≥1 of these conditions predating the onset of labor.

Mean ± SD birth weight of infants who had NE was 3309 ± 616 g, and mean gestational age was 38.7 ± 1.6 weeks (Table 3). Birth was by spontaneous vaginal delivery in 34% of infants. Surgical delivery, performed in two-thirds of these infants, was without labor in 19% and after failure of vacuum or forceps in 2%. Fetal heart rate monitoring was considered nonreassuring in 60%, and 5% experienced skull or limb fracture or other birth injury (excluding cephalohematoma). Cord blood was sampled in 53% of infants. Of those, 54% had pH levels <7.09 and 46% had a cord blood base deficit >12. Slightly more than half (54%) of placentas were sent for pathologic examination.

In infants with NE, 15% had at least 1 sentinel asphyxial event. The most common was antepartum hemorrhage, including placental abruption (11%) (Table 4). Fetal bradycardia of unknown time of onset, severity, and duration was recorded in 34% of infants. If fetal bradycardia was included as an asphyxial indicator, 35% of infants with NE had at least 1 such indicator. Infants who were SGA (n = 672) were no more likely to experience sentinel asphyxial events than those who were not growth restricted (n = 3492); 15% of each group experienced at least 1 such event.

Maternal temperature in labor was recorded for 37% of infants. Of those recorded, 27% of mothers had a temperature of ≥37.5°C. Overall, 24% of neonates had at least 1 inflammatory indicator. Infants who were SGA were significantly less likely to experience inflammatory indicators than infants who were not growth restricted (19% vs 24%; χ^2 (1, 7.92), $P < .005$).

About one-third of these term infants who had NE had sentinel asphyxial events only (13%), inflammatory indicators only (21%), or both (2%). When bradycardia was included, more than one-half had asphyxial indicators only (29%), inflammatory indicators only (17%), or both (6%).

TABLE 1 Singleton Infants Meeting Eligibility Criteria in the VON NER, 2006–2010

Criterion	*N*	Sole Criterion		One of >1 Criteria		Any	
		Cases	%	Cases	%	Cases	%
Stupor or coma	4131	33	0.8	704	17.0	737	17.8
Apgar score at 5 min ≤3	4107	870	21.2	1159	28.2	2029	49.4
Seizures	4088	1275	31.2	1184	29.0	2459	60.2
Paralysis induced	4150	34	0.8	50	1.2	84	2.0
Hypothermia initiated	4165	298	7.2	1294	31.1	1592	38.2

TABLE 2 Conditions Predating Onset of Labor Among Singleton Infants Eligible for the VON NER, 2006–2010

Condition	*N*	Cases	%
Maternal			
No prenatal care	4135	149	3.6
Assisted reproduction	3784	62	1.6
Hypertension	4018	631	15.7
Diabetes	3967	387	9.8
Hypothyroidism	3941	113	2.9
Any maternal condition	4162	1131	27.2
Infant			
Birth defect	4165	332	8.0
SGA	4164	672	16.1
Congenital neuromuscular defect	4119	25	0.6
Nonvertex presentation (breech or transverse)	3735	238	6.4
Any infant condition	4165	1057	25.4
Any condition	4165	1906	45.8

DISCUSSION

NE is associated with an increased risk of death and is part of an important pathway to long-term neurologic disability.[1–3] Infants who develop CP as a result of asphyxial births regularly experience NE in the newborn period,[17] as do infants with placental infarction[18,19] or intrauterine exposure to inflammation.[20] Sorting out the precursors of NE and NE-associated CP is an important task toward developing more effective strategies for primary prevention of these serious disorders.

Several characteristics reported to be risk factors for NE in previous studies were observed with considerable frequency

TABLE 3 Delivery Characteristics Among Singleton Infants Eligible for the VON NER, 2006–2010

Characteristic	*N*	Cases	Mean
Male	4162	2424	58.2
Mode of delivery			
Spontaneous vaginal	4161	1399	33.6
Vacuum or forceps	4161	444	10.7
Cesarean delivery			
After labor	4161	1400	33.6
After labor with failed vacuum or forceps	4161	97	2.3
No labor	4161	821	19.7
Apgar score ≤3			
1 min	4115	2919	70.9
5 min	4116	2041	49.6
10 min	3212	785	24.4
Fetal heart rate			
Bradycardia	3612	1212	33.6
Tachycardia	3536	267	7.6
Decreased variability	3398	876	25.8
Prolonged decelerations	3479	1237	35.6
Any heart rate abnormality	3728	2234	59.9
Birth injury			
Skull fracture	4138	67	1.6
Limb or clavicle fracture	4138	58	1.4
Brachial plexus injury	4137	91	2.2
Spinal cord injury	4138	4	0.1
Any but cephalohematoma/other trauma	4138	202	4.9
Meconium aspiration syndrome	4160	511	12.3
Placenta to laboratory	2384	1326	55.6
Cord blood sampled	3637	1914	52.6
Worst, pH <7.09	1898	1024	54.0
Worst base deficit >12	1660	767	46.2

in the VON NER: notably, maternal fever in labor in 27% of those recorded, fetal growth restriction in 16%, and birth defects in 8%. The NER did not include within-study controls; we therefore looked for comparisons with the values in control infants from prospective, controlled, population-based studies of NE in term infants in industrialized countries, as included in the studies of Adamson et al,[4] Badawi et al,[5,10] and Blume et al[21] (Table 5). The severity of illness in VON NER infants, one-half of whom had 5-minute Apgar scores of ≤3 and two-thirds with neonatal seizures, was approximately comparable with encephalopathic term infants in these controlled, population-based studies.

Acute Asphyxial Indicators

Of the encephalopathic term singletons in the current study, 15% experienced a clinically recognized sentinel event such as antenatal hemorrhage (presumably, often placental abruption), uterine rupture, or cord prolapse, all of which are capable of compromising oxygen supply. The frequency of hemorrhage and cord prolapse exceeded the frequency in control populations (Table 5), but most infants who had NE did not have clinically recognized asphyxial birth events. Similarly, sentinel events were identified in a fairly small minority of infants with NE in controlled studies in representative populations: 7.9%[5] and 25%.[6] In a referral sample of 500 term infants with NE evaluated for therapeutic hypothermia, 48 (9%) had had a sentinel birth event.[22]

Fetal bradycardia (its onset, severity, and duration unspecified) was recognized in 34% of infants. In the VON NER, a majority of cord bloods tested (54%) were not severely acidotic, and 46% did not have a base deficit >12.

The VON NER did not capture all possible acute asphyxial events or markers. Some infants who had NE may have had undocumented events, such as intermittent occlusions of the umbilical cord in utero, to account for neurologic depression and acidosis. It is not known whether such events were common or rare. Ischemic occlusion, sometimes injurious, can be protective under some circumstances.[23,24]

Maternal Fever and Inflammation

A relatively common intrapartum complication documented in infants who have NE was intrauterine exposure to fever/inflammation. In the NER, 27% of women with data on temperatures recorded in labor had temperatures ≥37.5°C (18% of women had temperatures >38.0°C) compared with 2.2% to 3.2% in infants free of NE in population-based controls (Table 5). Maternal fever was associated with a trebling of risk of NE in both the studies of Badawi et al[5] and Blume et al[21]; it was also associated with an adjusted odds ratio of 4.7 (95% confidence interval: 1.3–17) in a prospective cohort study.[25]

Modest elevation of maternal temperature in labor is, according to a substantial and consistent literature,[20,26,27] robustly related to adverse outcome in term and late preterm infants in the delivery room and newborn nursery, and later. Elevated maternal temperature is associated with low Apgar scores, respiratory depression, neonatal seizures, and with CP. Experimental studies indicate potential interaction of inflammatory and asphyxial risk factors[28] and of those with disorders of coagulation and other potential pathobiologic mechanisms.

Spencer et al[29] found that maternal fever in labor was strongly associated with NE and more predictive of NE than abnormalities of fetal heart rate patterns. Although maternal fever in labor

TABLE 4 Asphyxial and Inflammatory Indicators in NE Among Singleton Infants Eligible for the VON NER, 2006–2010

Indicator	*N*	Cases	%
Sentinel events			
Antepartum hemorrhage or placental abruption	4165	426	10.2
Cord prolapse	4040	120	3.0
Uterine rupture	4070	107	2.6
Tight nuchal cord	4165	14	0.3
Maternal shock or death	4165	2	<0.1
Any	4165	622	14.9
Fetal bradycardia	3612	1212	33.6
Any including bradycardia	4165	1461	35.1
Inflammatory indicators			
Clinical chorioamnionitis	3968	421	10.6
Maternal fever in labor ≥37.5°C	1536	408	26.6
Fetal tachycardia	3536	267	7.6
Rupture of membranes >24 h	3981	212	5.3
Early bacterial infection	4100	69	1.7
TORCH	4001	34	0.8
Any	4164	981	23.6
Combination of indicators excluding fetal bradycardia			
Both asphyxia and inflammatory	4164	76	1.8
Asphyxia only excluding fetal bradycardia	4164	546	13.1
Inflammatory only	4164	905	21.7
Neither asphyxia nor inflammatory	4164	2637	63.3
Combination of indicators including fetal bradycardia			
Both asphyxia and inflammatory	4164	266	6.4
Asphyxia only including fetal bradycardia	4164	1195	28.7
Inflammatory only	4164	715	17.2
Neither asphyxia nor inflammatory	4164	1988	47.7

TORCH, toxoplasmosis, other infections, rubella, cytomegalovirus infection, and herpes simplex.

TABLE 5 Comparison of VON NER Values With Those of Controls in Population-Based Studies of NE

Factor	VON NER	Adamson et al[4]	Badawi et al[5,10]	Blume et al[21]
Inflammatory factors				
Maternal fever in labor	>38°C: 17.8%	–	≥37.5°C: 2.2%	>38°C: 3.2%[a]
Clinical chorioamnionitis	10.6%	–	–	1.3%[a]
Rupture of membranes >24 h	5.3%	2%	–	1.0%[a]
Sentinel event				
Hemorrhage	10.5%	4%[a]	3.6%	–
Cord prolapse	3%	–	0.2%	–
Any	–	–	1.2%	0.9%
Fetal growth restriction	SGA: 16.1%	<3000 g: 13.%	<9th percentile: 8.4%	<2500 g: 3%

[a] Statistically significantly related to NE risk in that study.

can be the result of dehydration and the physical exertion of labor, it is also associated with duration of labor, number of vaginal examinations during labor, and with epidural analgesia.[30] Maternal fever in labor is probably often an indicator of inflammation or infection. Clinically diagnosed chorioamnionitis was documented in 11% of VON NER infants compared with 5.4% of controls in other studies.[31]

Markers of inflammation are consistently associated with adverse neurologic outcome in term and late preterm infants, but few studies from neonatology units have included maternal fever in labor as a predictor of prognosis for NE. The chain of associations of inflammatory placental lesions, microbiologic findings, brain lesions on neuroimaging in the neonatal period, and later neurologic disability have been demonstrated in infants born extremely preterm.[32] No such studies have yet been performed in more mature infants.

Fetal Growth Restriction

In the VON NER, 16% of infants were SGA. In the major controlled study of NE, in which 16% of infants with NE and 1.2% of term infants without NE were growth restricted, growth restriction was the strongest predictor of NE examined, associated with a 30-fold increase in risk.[10] In a regional study of moderate or severe NE in term infants, 17% were SGA.[6] SGA has consistently been associated with risk of CP.[33–35]

Genetic, infectious, and nutritional factors can contribute to growth restriction, and defective placentation and disorders of the placenta also seem to be major factors. Co-occurrence of growth restriction and placental infarction was linked with CP risk in 2 studies[22,23] and was linked with NE-associated CP in 1 study.[23]

Maternal hypertension, associated with growth retardation in many studies, was observed in 16% of the VON NER. Additional studies in human populations are needed to examine differing pathways to growth restriction and to elucidate the relationship of these factors with NE and NE-associated CP.

It is sometimes assumed that infants SGA at term are more vulnerable to asphyxial events of birth than well-grown infants. We found no evidence of such an effect: Among these encephalopathic infants, those who were SGA had no more asphyxial indicators than those who were not growth restricted.

Birth Defects

Infants with non-CNS birth defects recognized in the newborn period comprised 8% of the VON NER and 11.1% of infants with NE in an uncontrolled population-based study.[7] In 1 controlled population-based study, none of 89 controls but 5 of 89 cases (5.6%) had birth defects,[4] whereas in another population-based study, these numbers were 4% and 10%, respectively.[10]

Within each relevant report, birth defects were observed more frequently in infants with NE than without NE. Many significant birth defects are not detected until after the newborn period; in controlled studies that included information ascertained in the first year of life or later, case-control differences were especially large.[36,37]

Because the majority of the infants in the VON NER experienced neonatal seizures, it is relevant to note that in the National Collaborative Perinatal Project, major CNS malformations were observed in the first year of life in 0.5% of controls and in 11.3% of infants with neonatal seizures, non-CNS malformations in 6.9% of controls and 24.7% of infants with neonatal seizures, and any malformation in 14.8% of controls and in 36.5% of infants with neonatal seizures.[37] It is likely that structural malformations contribute to NE. The nature and timing in development of birth defects in children who experienced NE warrant further investigation.

Clinical Hypothyroidism

Associated with heightened risk of NE in 3 previous prospective studies of NE,[4,10,11] clinical hypothyroidism was observed in 3% of mothers in the VON NER. For comparison, a recent review of the literature of overt hypothyroidism during pregnancy cites its prevalence as ≤1.0% in developed countries, and in most studies as 0.2% to 0.3%.[38]

Strengths and Limitations of the NER

The VON NER is a rich repository of information about infants who have NE. It is a registry, however, and did not have standardized definitions, a standardized approach to diagnostic or therapeutic procedures, or a control group. Inferences drawn from the NER are limited by these factors and by the absence of controls and an incomplete range of items included as potential antecedents of NE. This study, like most studies of NE, included infants who had neonatal seizures regardless of whether they had other criteria of NE. Such infants constitute a substantial subgroup of the NER. Because there was no uniform protocol for neuroimaging, or metabolic or genetic disorders, the incidence of perinatal stroke or other etiologies in these infants with seizures is unknown.

Alteration of consciousness is a key feature of encephalopathy, but the most common indication for inclusion of an infant as having NE in the VON NER was clinically recognized neonatal seizures. Depression of consciousness was reported in only 18%, although one-half of the infants in the NER had 5-minute Apgar scores of ≤3 and other markers of serious neonatal illness. These observations suggest underrecognition of depression of consciousness in these newborn infants and a need for training of caregivers in the reliable recognition of neurologic depression and its severity. For future descriptive studies and clinical trials, characteristics such as persistently low Apgar scores (with and without marked acidosis) might be more reliably ascertainable entry criteria.[39]

Although most of these infants showed marked compromise in the delivery room, only about one-half of placentas were submitted for examination, a limitation shared with many other studies of NE. Failure to incorporate information from placental examination is unfortunate, as placental lesions are common in encephalopathic term infants.[40,41] Findings in the placentas of ill neonates can often contribute to an understanding of the underlying pathobiology and can sometimes influence clinical management. Wintermark et al[40] suggest that inflammatory placental pathology reduces the efficacy of therapeutic hypothermia in encephalopathic term newborns, a possibility suggesting that stratification in the analysis for presence, type, and severity of placental lesions should be considered in future trials of therapeutic cooling.

CONCLUSIONS

Observations in the NER support the importance of inflammation, aberrant fetal growth, asphyxial birth events, birth defects, and maternal thyroid disorder in NE. In this study, as in previous studies, most infants who met study criteria for NE did not have recognized asphyxial birth events. Much remains unknown about the antecedents of NE.

Given the importance of neonatal neurologic compromise on the causal pathway to long-term neurologic disability, the etiology of NE is remarkably underresearched. More studies are needed regarding the antecedents of NE to enable better etiologic diagnoses and more rapid and specific treatment.

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APPENDIX Hospitals Registering Infants in the VON NER, 2006–2010

Name	City	State	Country
Cork University Maternity Hospital	Cork	—	Ireland
National Maternity Hospital	Dublin	—	Ireland
Rotunda Hospital	Dublin	—	Ireland
Hospital de S. Joao	Porto	—	Portugal
Hospital Sant Joan de Deu	Barcelona	—	Spain
Latifa Hospital	Dubai	—	United Arab Emirates
Southmead Hospital	Bristol	—	United Kingdom
Arkansas Children's Hospital	Little Rock	AR	United States
UC Irvine Medical Center	Orange	CA	United States
Sharp Mary Birch Hospital for Women & Newborns	San Diego	CA	United States
Santa Clara Valley Medical Center	San Jose	CA	United States
The Children's Hospital	Aurora	CO	United States
Exempla Saint Joseph Hospital	Denver	CO	United States
Poudre Valley Health System	Fort Collins	CO	United States
Yale–New Haven Children's Hospital	New Haven	CT	United States
Christiana Care Health Services	Newark	DE	United States
Children's Hospital of Southwest Florida at Lee Memorial	Fort Myers	FL	United States
Baptist Children's Hospital	Miami	FL	United States
Miami Children's Hospital	Miami	FL	United States
St Joseph's Children's Hospital of Tampa	Tampa	FL	United States
Tampa General Hospital	Tampa	FL	United States
The Medical Center at Columbus Regional	Columbus	GA	United States
St Luke's Regional Medical Center	Boise	ID	United States
Evanston Hospital	Evanston	IL	United States
Edward Hospital and Health Services	Naperville	IL	United States
Advocate Lutheran General Hospital	Park Ridge	IL	United States
Rockford Memorial Hospital	Rockford	IL	United States
St John's Hospital	Springfield	IL	United States
Carle Foundation Hospital	Urbana	IL	United States
Central DuPage Hospital	Winfield	IL	United States
St Luke's Hospital	Cedar Rapids	IA	United States
Blank Children's Hospital	Des Moines	IA	United States
Overland Park Regional Medical Center	Overland Park	KS	United States
Wesley Medical Center	Wichita	KS	United States
Kosair Children's Hospital	Louisville	KY	United States
Woman's Hospital	Baton Rouge	LA	United States
Eastern Maine Medical Center	Bangor	ME	United States
Barbara Bush Children's Hospital at Maine Medical	Portland	ME	United States
University of Maryland Division of Neonatology	Baltimore	MD	United States
Frederick Memorial Hospital	Frederick	MD	United States
Massachusetts General Hospital for Children	Boston	MA	United States
UMass Memorial Health Care	Worcester	MA	United States
University of Michigan CS Mott Children's Hospital	Ann Arbor	MI	United States
Henry Ford Hospital	Detroit	MI	United States
Helen DeVos Children's Hospital, Spectrum Health	Grand Rapids	MI	United States
Sparrow Hospital	Lansing	MI	United States
University of Minnesota Children's Hospital, Fairview	Minneapolis	MN	United States
North Memorial Medical Center	Robbinsdale	MN	United States
St Cloud Hospital	Saint Cloud	MN	United States
St Francis Medical Center, Cape Girardeau	Cape Girardeau	MO	United States
SSM Cardinal Glennon Children's Hospital	St. Louis	MO	United States
St. Louis Children's Hospital	St. Louis	MO	United States
Saint Elizabeth Regional Medical Center	Lincoln	NE	United States
Alegent Health Bergen Mercy Medical Center	Omaha	NE	United States
Nebraska Medical Center	Omaha	NE	United States
Albany Medical Center	Albany	NY	United States

APPENDIX Continued

Name	City	State	Country
Weiler Montefiore Medical Center	Bronx	NY	United States
Winthrop-University Hospital	Mineola	NY	United States
Columbia University Medical Center	New York	NY	United States
Golisano Children's Hospital at Strong	Rochester	NY	United States
Mission Children's Hospital	Asheville	NC	United States
Duke University	Durham	NC	United States
Cape Fear Valley Medical Center	Fayetteville	NC	United States
Women's Hospital of Greensboro	Greensboro	NC	United States
Pitt County Memorial Hospital	Greenville	NC	United States
WakeMed Health & Hospitals	Raleigh	NC	United States
Brenner Children's Hospital at WFUBMC	Winston-Salem	NC	United States
Akron Children's Hospital	Akron	OH	United States
Cincinnati's Children's Hospital Medical Center	Cincinnati	OH	United States
Henry Zarrow Neonatal Intensive Care Unit	Tulsa	OK	United States
Rogue Valley Medical Center	Medford	OR	United States
Providence St Vincent Medical Center	Portland	OR	United States
Randall Children's Hospital at Legacy Emanuel	Portland	OR	United States
Salem Hospital	Salem	OR	United States
Sacred Heart Medical Center	Springfield	OR	United States
St Luke's University Hospital	Bethlehem	PA	United States
Geisinger Medical Center	Danville	PA	United States
Penn State Children's Hospital	Hershey	PA	United States
Thomas Jefferson University Hospital	Philadelphia	PA	United States
Magee Women's Hospital	Pittsburgh	PA	United States
Palmetto Health Richland	Columbia	SC	United States
Children's Hospital of Greenville	Greenville	SC	United States
University of Tennessee Medical Center	Knoxville	TN	United States
Baptist Memorial Hospital for Women	Memphis	TN	United States
Monroe Carell Jr. Children's Hospital at Vanderbilt	Nashville	TN	United States
Cook Children's Medical Center	Fort Worth	TX	United States
CHRISTUS Santa Rosa Health System	San Antonio	TX	United States
Methodist Children's Hospital	San Antonio	TX	United States
Vermont Children's Hospital at Fletcher Allen	Burlington	VT	United States
Carilion Clinic Children's Hospital	Roanoke	VA	United States
Swedish Medical Center	Seattle	WA	United States
West Virginia University School of Medicine	Morgantown	WV	United States
Gundersen Lutheran Medical Center	LaCrosse	WI	United States
St Mary's Hospital Medical Center	Madison	WI	United States
Wheaton Franciscan Healthcare at St Joseph	Milwaukee	WI	United States

WFUBMC, Wake Forest University Baptist Medical Center.