# Neonatal Neurocritical Care

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# Contents

# CLINICS IN PERINATOLOGY

**FORTHCOMING ISSUES**

***September 2025***
**Epidemiology and Genetics of Congenital Heart Disease**
Asaad Beshish and Holly Bauser-Heaton, *Editors*

***December 2025***
**Genetics, Newborn Screening, and Inborn Errors of Metabolism**
Patrick Gallagher and Alex R. Kemper, *Editors*

***March 2026***
**Stillbirth**
Robert M. Silver and Uma M. Reddy, *Editors*

**RECENT ISSUES**

***March 2025***
**Perinatal and Neonatal Infections**
Sagori Mukhopadhyay and Karen M. Puopolo, *Editors*

***December 2024***
**Perinatal HIV**
Ann Chahroudi and Avy Violari, *Editors*

***September 2024***
**Perinatal Asphyxia: Moving the Needle**
Lina Chalak, *Editor*

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# Foreword

# Neonatal Neurocritical Care: The Time Is Now

Lucky Jain, MD, MBA
*Consulting Editor*

Neurocritical care has established itself as an indispensable component of the care paradigm for adults with serious neurologic disorders. The integrated approach involves comprehensive neurologic evaluation, monitoring, and treatment of patients with neurologic and neurosurgical issues requiring intensive care. It requires trained staff and physicians who have cross-training in critical care, neurology, and neurosurgery.[1] This multidisciplinary care allows for development of care paths and guidelines that reduce unnecessary variability in care and improve outcomes. The Society for Neurocritical Care was established in 2002, and in 2007, the Accreditation Council for Graduate Medical Education approved a formal certification program in adult neurocritical care.[2] Since then, neurocritical care units have been established in academic health care systems across the country. Pediatric and neonatal care units with similar capabilities have been slow to come, and there is no formal fellowship training program or certification exam in neonatal neurocritical care to date.

Neonatal intensive care units (NICUs) have historically focused on cardiorespiratory care of the newborn with a focus on improving survival and short-term outcomes. As a result, there have been gains in survival, but long-term neurologic outcomes in surviving infants have lagged, leading to a greater burden of developmentally impaired infants and children.[2] Therapies such as hypothermia for hypoxic ischemic encephalopathy have become integrated into many NICUs across the country; however, there is much room for improvement of neurologic monitoring with inclusion of advanced neuroimaging, amplitude-integrated and continuous video electroencephalography, and more. Ultimately, delivery of high-quality neurocritical care to newborns requires institutional commitment and collaboration between neonatologists, neurologists,

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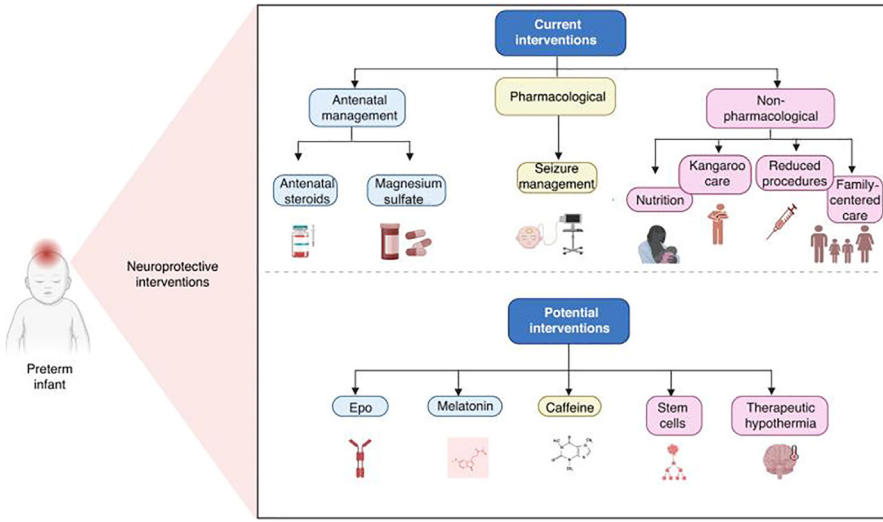


**Fig. 1.** Current and potential therapies to prevent and treat brain injury in the preterm infant. (Molloy, E.J., El-Dib, M., Soul, J. et al. Neuroprotective therapies in the NICU in preterm infants: present and future (Neonatal Neurocritical Care Series). Pediatr Res 95, 1224–1236 (2024). https://doi.org/10.1038/s41390-023-02895-6.)

neurosurgeons, and nursing staff. It also comes with the recognition that no sick neonate requiring intensive care is immune from brain injury, and neuroprotective approaches should be built into the care of the patient just as lung-protective and infection-control approaches are part of the NICU culture now. This includes targeted use of treatments such as erythropoietin, antioxidants, and seizure management (**Fig. 1**).[3] It also includes careful attention to physiologic variables that impact brain function, such as temperature regulation, glucose homeostasis, oxygenation, blood pressure, and intracranial pressure management.

In this issue of the *Clinics in Perinatology*, Drs Pardo, Natarajan, and Vernon have done a phenomenal job of bringing together a wide array of topics and authors related to this important topic. We hope that this collection of excellent articles and access to experts in the field will spur the development of neonatal neurocritical care units in the United States and beyond. As always, I am grateful to the authors for their contributions, and to my publishing partners at Elsevier (Kerry Holland and Nitesh Barthwal) for their help in bringing this valuable resource to you. I hope these timely articles inspire the reader to renew their focus on improving collaboration between neurologists and neonatologists and creation of much-needed training programs for physicians and staff. The delivery of integrated evidence-based care, coupled with a commitment to the development of novel strategies, can help improve long-term outcomes of neurologically challenged neonates for decades to come.

For neonatal neurocritical care, the time is now!

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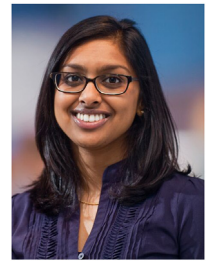
# Preface

# Neonatal Neurocritical Care: Small Patients, Big Advancements



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This issue of *Clinics in Perinatology* delves into the rapidly evolving field of neonatal neurocritical care, a specialized area that has gained increasing recognition for its critical role in improving outcomes for neonates with neurologic conditions.

The content of this issue of *Clinics of Perinatology* focuses on advancements and key topics in neonatal neurocritical care. It starts with critical aspects, such as including delivery planning and the transition to the neonatal intensive care unit, and evolving areas of fetal management. Other topics include neonatal neurocritical care outside of large academic centers, as well as updates on technologies aiding in the evaluation of critically ill neonates from neuromonitoring techniques like electroencephalography and near-infrared spectroscopy, to advances in neuroimaging and genetic testing.

The issue also examines specific conditions and considerations in treatment, including preterm white matter injury, intraventricular hemorrhage, post–hemorrhagic ventricular dilatation, neonatal seizures, and stroke.

Furthermore, it provides insights into hypoxic-ischemic encephalopathy, neonatal encephalopathy, neurocardiac care, and neonatal hypotonia. Ethical considerations in neonatal neurocritical care are also discussed, offering a comprehensive view of current challenges and innovations in the field.

As the field continues to evolve, we hope that this issue provides the latest information on the highest-yield topics of neonatal neurocritical care from leading experts.

The content of this issue collectively underscores the increasing complexity and depth of this specialty, marking significant advancements and providing essential knowledge for health care professionals dedicated to the neurologic well-being of neonates.

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# Fetal Consultation, Delivery Planning, and Perinatal Transition for Congenital Neurologic Disorders

Laura E. Vernon, MD

**KEYWORDS**

• Fetal neurology • Fetal consultation • Prenatal consultation • Fetal imaging
• Prognostication • Neurodevelopmental outcome • Congenital anomalies
• Postnatal care

**KEY POINTS**

- Fetal neurology consultation is a growing field of perinatal medicine, which requires navigating the complex interplay between obstetrics, pediatrics, and neurology using multidisciplinary care.
- Evolution in medical imaging and genetic testing is leading to increased antenatal diagnosis of CNS anomalies, though limitations remain in providing exact neurodevelopmental prognoses.
- Options for fetal intervention in a variety of congenital neurologic conditions are continuing to evolve and will likely increase in the coming years.
- Providers involved in fetal care should tailor information to the individuals involved, work without bias or judgment, and embody compassion and support throughout their practice.

## BACKGROUND

The modern practice of fetal consultation has evolved over decades to support patients and families impacted by congenital disorders. In their ideal format, fetal consultations using multidisciplinary teams can provide care throughout an affected pregnancy and, when needed, progress to orchestrating appropriate postnatal care of affected neonates while also giving ongoing support to family and caregivers. This longitudinal course of care, whether days to years in length, creates a unique opportunity for collaboration between the worlds of obstetrics and pediatrics. For each fetal consultations, there can be a significant range of severity, body system

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| Abbreviations | |
|---|---|
| CNS | central nervous system |
| ISUOG | International Society of Ultrasound in Obstetrics and Gynecology |
| NICU | neonatal intensive care unit |
| US | ultrasound |

involvement, and number of abnormalities present in the developing fetus, which can lead to variable degrees of impact on the management of an individual's pregnancy, delivery planning, and perinatal care.

Congenital disorders (also known as congenital anomalies, congenital abnormalities, congenital malformations, or birth defects[1]) continue to occur at significant rates around the world, ranging between 39.7 and 82 per 1000 births.[2] While neonatal and infant mortality rates are declining, congenital disorders remain a leading cause of death and morbidity in both high-income, middle-income, and low-income countries.[1,3,4] Congenital anomalies of the central nervous system (CNS) are common. Recent prevalence data show CNS abnormalities occurring in 26 per 10,000 live births in one European database (2005–2022),[5] 10 per 10,000 live births in Brazil (2004–2015),[6] 3.3 per 10,000 live births in Kenya (2014–2018) to 98.2 per 10,000 live births in Nigeria (2011–2014),[7,8] and 26.2 per 10,000 live births in India (1960–2013).[9] It is, therefore, not surprising that concern for CNS anomalies is a frequent referral indication for additional perinatal evaluation and management.

During a fetal consultation, the provider's ultimate goals should include delivering an accurate fetal diagnosis, providing appropriate counseling and support to expectant patients, and developing antenatal and postnatal care plans uniquely tailored to each patient and family—all while balancing medical uncertainty, social-emotional complexity, ethical considerations, and holistic care. In this article, we hope to highlight highlight current practice standards, unique challenges in fetal neurology consultation, important considerations for fetal and postnatal care for infants with congenital neurologic conditions, as well as future considerations for the continued growth of perinatal and neonatal medicine.

## CURRENT PRACTICE

### *Consultation Structure*

The practice of fetal neurology consultations is complex and can vary from institution-to-institution.[10,11] There are calls for standardization of consultative training[12,13] and practice as well as work describing the challenges in this field.[14–20] There has also been a blooming body of literature summarizing diagnostic and prognostic information for common nervous system anomalies.[20–25] Access to this information allows providers to give up-to-date, consistent information to expectant patients across consultation settings, even if working outside of a large, multidisciplinary fetal medicine program. The logistics and abilities of each fetal consultant will also depend on access to imaging resources, genetic testing, and the various specialists that can help enrich each consultation, such as genetic counselors, social workers, chaplains, and dedicated fetal consult coordinators.

Some institutions complete their fetal consultations in a single, daylong visit that includes detailed fetal imaging and large meetings with a multidisciplinary team. Others may schedule several meetings with individual providers over many days[10] once appropriate fetal imaging or other additional testing is complete. When utilizing the multidisciplinary team model for CNS abnormalities, there is often a perinatologist, a

neonatologist, a fetal neurologist or neurosurgeon, a social worker, a genetic counselor, and a case coordinator present.

### *Timing Considerations*

Concern for abnormalities of the fetal nervous system often arises during routine ultrasonography conducted between 18 and 20 weeks' gestation. These can be "developmental" in nature, meaning a structural abnormality due to embryologic programming going awry, or "acquired" from a variety of potential fetal insults, including stroke, hemorrhage, infections, teratogens, tumors, or trauma. It is also important to note that CNS anomalies can occur in isolation or in "complex" association with abnormalities in other body systems, such as cardiovascular, limb, gastrointestinal, or genitourinary anomalies.

By the middle of the second trimester, the major structures of the CNS have developed, including the cerebral hemispheres, ventricular system, corpus callosum, cavum septum pellucidum, cerebellum, brainstem, and spine. Absence of these basic structures or significant aberrations in their form can often be detected on ultrasound (US) at this stage. The fetal brain continues to develop and mature throughout the full 9 months of gestation via the complex orchestration of neuronal/glial proliferation, neuronal migration, early synapse formation, and programmed-cell death. This protracted embryologic course can lead to certain significant abnormalities not being detected until the third trimester or after birth.

Early detection of CNS abnormalities allows for timely referral to fetal consultation with a maternal-fetal-medicine provider, a fetal neurologist, and/or a fetal consultation center. Detection of fetal anomalies can prompt discussions about pregnancy management options, including consideration of continuation of pregnancy, changes to delivery location or timing, potentials for palliative "comfort-focused" delivery, or termination of pregnancy. It is, therefore, important for providers to understand the details of local legislation regarding termination of pregnancy, resource access for termination or higher-level neonatal care, and patient/family supports if relocation or prolonged postnatal hospitalization is anticipated—all in the context of gestational age and estimated delivery date at the time of fetal consultation. It is also imperative to be open and understanding as patients and their supporters grapple with these complex and difficult decisions.

### *Consultation Process*

In preparation for consultation, extensive clinical data should be gathered beyond just the current obstetric course and most recent imaging.[11,20] Important clues can be found in prepregnancy medical history, medication lists, prior obstetric history, family history, and social history. Confirmation of any infectious exposures, infectious testing, or genetic testing done prior to consultation will help inform potential next tests offered. Valuable information is also gained by reviewing what the patient has heard or understood of their medical team's concerns leading up to the fetal consultation and if this has sparked specific concerns for family or any considerations about pregnancy management.[11,20]

Fetal imaging plays a significant role in working toward a specific and detailed fetal diagnosis, which will then guide discussions about potential prognosis and future care. US has been the mainstay in fetal imaging around the world given its safety, accessibility, accuracy, and portability. Guidelines from the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) review indications for dedicated neurosonography in cases with concern for or known high-risk for fetal CNS anomalies.[26] Due to recent advances in MRI, fetal MRI has grown to be an important imaging

modality at many centers though access can be limited by availability and cost.[27] A recent review by Tarui and colleagues[28] summarizes the technical considerations, safety, and utility of fetal MRI in current practice.

When comparing fetal US to MRI, the MERIDIAN study[29] was the first multicentered clinical trial to review diagnostic accuracy between the 2 modalities specifically for fetal developmental brain abnormalities. As quoted in the study's report, the overall diagnostic accuracies of ultrasonography and fetal MRI were 67.9% and 92.8%, respectively, meaning that fetal MRI showed an improvement in diagnostic accuracy of 24.9% when using neonatal MRI findings as the confirmed diagnosis.[29] Additionally, the authors state that the results of the fetal MRI provided additional diagnostic information in 49% of cases, caused a documented change in prognosis in 44% of cases, and had major effects on counseling in 15% of cases.[29]

It is important to note that while fetal MRI may improve the diagnostic accuracy of fetal brain abnormalities, US can be equally as accurate or even used to complement the detection of abnormalities in other body systems,[30] particularly when evaluating musculoskeletal anomalies,[31] facial anomalies such as cleft palate,[32,33] bony spine abnormalities,[34] gastrointestinal abnormalities,[35] or cardiovascular anomalies.[36]

Equally essential to the consultation process is the consideration for and review of antenatal genetic testing and family history of congenital disorders. Current practice guidelines recommend that noninvasive screening options (eg, serum analyte screening [eg, alpha-fetoprotein and beta human chorionic gonadotropin], nuchal translucency US, or cell-free DNA screening[37]) and diagnostic testing (chorionic villus sampling or amniocentesis) for chromosomal abnormalities should be discussed and offered to all patients early in pregnancy regardless of maternal age or baseline risk.[38] After review and discussion, every patient should then have the right to pursue or decline noninvasive prenatal genetic screening and diagnostic testing.[38] If not already completed, a similar discussion reviewing options for genetic testing should occur when a genetic disorder is suspected during fetal consultation. Genetic counselors add expert opinion to the next best testing and detailed discussions regarding the risks and benefits of antenatal testing on a case-by-case basis.

Fortin and colleagues[37] recently published a review summarizing the current literature on the yield of genetic testing in the setting of prenatal diagnosis of congenital malformations with multisystem involvement, including the brain and CNS. As one might expect, the reported yield range can be wide depending on the specific anomaly, inclusion/exclusion criteria of the study, and the presence of isolated or complex CNS anomalies (ie, associated with other abnormalities on imaging). Complexities in the interpretation of antenatal testing results will be discussed later.

The bulk of a fetal neurology consultation is spent communicating diagnostic findings from imaging and/or genetic testing as a prelude to reviewing the expected diagnosis, its potential etiology, and its impact on the potential neurodevelopment of a future child. While there have been great improvements in our ability to detect and accurately diagnose these anomalies in utero, limitations in our ability to accurately predict true neurodevelopmental outcomes remain given the complexities of the maternal–placental–fetal triad, impact of environmental and social factors, variability of genotypic–phenotypic correlations, and inconsistencies in current literature reporting developmental outcomes. This lack of "a crystal ball" to make exacting predictions, while inherent to all areas of medicine,[39] can leave pregnant patients and their supporters with a large degree of uncertainty as they start to consider the management of the rest of their pregnancy.

Given these complexities, the tenants of palliative care should be incorporated into the practice of fetal neurology, even when cases may be considered less severe or life-

threatening to the affected fetus.[40,41] As outlined by Rent and colleagues,[41] from the first fetal consultation, providers should work to develop a trusting, supportive, and compassionate relationship between the family and care team. This can facilitate more open discussions of care goals to help tailor plans for both the pregnant patient and the fetus or child along the entire care trajectory. Goals of care can change over the perinatal and neonatal periods as the maternal or fetal/neonatal status evolve, so it is important to revisit these concepts during any follow-up meetings and in the postnatal period.

The patient or family's response to the prognosis or anticipated plans described during a consultation session may be received, interpreted, and responded to very differently by each patient or support person, even when the technical details of a case may be similar. In these scenarios, patience, exploration, and compassion are key.[42] Clinicians should approach each patient as an individual and consider how a family's spiritual, cultural, social, and ethnic beliefs may inform the care they would desire for themselves and their child.[41]

### *Developing Care Plans*

After completing the review of the fetal diagnosis and anticipated prognosis, consultants often shift the focus of their discussions from delivering information to developing plans. Recommendations for care throughout pregnancy or after delivery should be created in collaboration with the patient themselves as well as other providers involved in the pregnant patient's care. Timely communication with outside providers is essential for coordinating and implementing antenatal care recommendations.

Depending on the abnormalities identified during fetal consultation, there can be a wide variety of plans to enact for continued prenatal management. These can include:

- Detailed maternal–fetal monitoring after consultation, for example, creating plans for serial US imaging for monitoring ventriculomegaly or fetal growth.
- Determining whether additional invasive testing such as amniocentesis for genetic/infectious testing is indicated.
- Discussing options and/or timing of potential fetal surgery or other in utero treatment. For example
  - Suitability for and timing of in utero surgery for myelomeningoceles or other spinal dysraphisms.[43–45]
  - Expectant management versus fetoscopic laser photocoagulation versus amnioreduction for the management of twin-twin transfusion syndrome,[46–48] which can have in utero neurologic sequelae.[49]
  - Maternal administration of sirolimus for the management of fetal cardiac rhabdomyomas[50,51] that are often associated with tuberous sclerosis.
  - Maternal intravenous immunoglobulin (IVIG) treatment in cases of suspected neonatal alloimmune thrombocytopenia that can cause fetal intracranial hemorrhage.[52]
  - Options for prenatal or postnatal treatment of suspected congenital infections with CNS involvement.[53]
- Consideration of a delivery planning meeting to review the timing, location, and method of delivery as well as goals of care in the delivery room and anticipated postnatal interventions. This can include discussing options for immediate and full neonatal resuscitation after delivery versus a "palliative delivery" or "comfort-focused delivery" that allows for neonatal-family bonding and memory making.[40,41]

As the family, obstetrician, and birth hospital team prepare for delivery, it is imperative to address postnatal management beyond the delivery room. The details of delivery and postnatal goals should be communicated to obstetrics and

pediatrics team prior to delivery whenever feasible. The delivery team needs to be aware of the family's goals of care. There can also be discussions about which team/teams may need to be present at birth: is a standard postpartum team obstetric (OB)/nursing team adequate, or does a pediatric delivery team or full neonatology resuscitation team need to be present at delivery, versus presence of comfort-focused supports.

There should be thoughtful consideration of how the specific fetal neurologic disorder may impact delivery mode and postnatal transition. For example:

- Consideration of planned C-section in cases of severe ventriculomegaly with significantly enlarged fetal head circumference.[54]
- Indications for ex-utero intrapartum treatment (EXIT) delivery strategy if concurrent obstructive airway anomalies are present.[55]
- Selection of the optimal postnatal care location based on access to appropriate subspecialty providers (eg, need for cardiac intensive care unit if concurrent congenital heart disease, relocation prior to delivery to improve access to a particular facility, or delivery at a local hospital with anticipated neonatal transfer to higher level neonatal intensive care unit [NICU]).
- In discussion with a fetal neurologist, there can also be consideration of whether the congenital neurologic abnormalities are anticipated to manifest in severe neonatal encephalopathy, dysautonomia, or hypotonia that could impact the child's ability to progress through the normal transitions of labor, delivery, and early neonatal period in relation to respiratory and cardiovascular stability.

The neurologist, neonatologist, and/or palliative care teams are essential in addressing the overall goals for and impact of the nursery or NICU stay.[42] This includes reviewing:

- Anticipated testing (imaging, genetics, laboratories, etc.).
- Expected medical interventions (eg, need for invasive respiratory support, nasogastric, or gastrostomy tube) or specific surgeries (eg, shunt for management of hydrocephalus).
- Confirmation of additional subspecialty evaluations and timing after birth (eg, endocrinologic and ophthalmologic evaluations essential in setting of midline CNS anomalies may be deferred to the outpatient setting in a stable newborn).
- Consideration of family life outside the hospital (ie, how to support family if there are other children or dependents, location of nursery/NICU relative to home, length of stay, supports for visiting from afar, supports for necessary absences from work obligations etc.).
- Discussing the goals of care for the nursery/NICU stay (eg, life expectancy with or without medical intervention, using medical technologies to support family goals such as prioritizing time together with infant prior to anticipated early death, getting baby home with or without medical technology, utilization or availability of home nursing or transition facility stays, and anticipated family teaching re: medical technologies).
- Reviewing the expected "cast" of multidisciplinary providers who will support for patient/family/team.

## DISCUSSION

### *Current Challenges*

Even with significant advancements in fetal consultation and medical technology, there are several challenges that must be considered:

- *Access to prenatal care, fetal consultation, and pregnancy management options:* Access to prenatal care, even in healthy, low-risk pregnancies, remains a challenge worldwide.[56–59] Continued investment in provider training, public health advocacy, and care innovations will help access grow to standard prenatal and expert perinatal care.
- *Accuracy of imaging diagnosis and implications on prognosis:* As discussed earlier, recent studies have shown fetal MRI can increase diagnostic accuracy for congenital brain abnormalities and be used to complement fetal US or dedicated neurosonography. However, there remains a variety of limitations in fetal imaging:
  - Gestational age—as an example, a variety of brain cortical malformations are only visible at or after 26 weeks gestational age,[60] so early imaging may miss associated CNS anomalies that can have significant prognostic impact.
  - Imaging can be limited due to fetal movement, sequences utilized, maternal conditions (eg, habitus and medical implants leading to artifact), or access to appropriate imaging modality or sequences.[28,61]
  - Correlation of neurodevelopmental prognosis to imaging findings has mixed outcomes in recent studies.[28,62,63]
  - Inconsistencies in nomenclature (eg, Dandy Walker Malformation vs Dandy Walker Syndrome vs Dandy Walker Spectrum/Continuum or Variant; callosal agenesis, dysgenesis, hypoplasia, and "thinning") can lead to confusion for families or providers and even limit our ability as a medical community to accurately study imaging findings or patient outcomes for specific anomalies.
  - Potential for progressive disorders with evolving imaging findings that may impact prognosis and care plans (eg, worsening ventriculomegaly over a gestation, evolution of injury from a fetal CNS vascular insult, infection, tumor, or environmental exposures).
- *Limitations and potential impacts of antenatal genetic testing:* Lewis and colleagues[64] published a summary on this topic in a recent article of *Prenatal Genetic Counseling* and further highlight the importance of including genetic counselors in prenatal consultations. There is also the evolution of genetic testing availability—most recently the utility and limitations of whole exome sequencing.[65–68] As mentioned earlier, collective summaries of genotype–phenotype outcomes for fetal conditions are increasing,[37] but there are still issues with interpreting probabilities, penetrance, frequency of features, and chances of survival[64,69] in a specific case—particularly for rare or complex conditions.
- *Data pool for neurodevelopmental prognosis:* Data on postnatal outcomes are ever increasing for fetal neurologic conditions, including developmental and acquired abnormalities. Neurodevelopmental data are understandably robust for common conditions, but frequently are based on combined analysis of many small studies, short/variable follow-up, inconsistent developmental evaluation tools used, and confounded by the anomaly nomenclature issues mentioned earlier. Furthermore, information reported in these studies may neither address the specific concerns a family carries nor be easily translated to the "every day" experiences of a future child and their family.[70]
- *Impact of consultations on pregnant people and family unit:* Every family is different—providers throughout the perinatal spectrum need to tailor information to the individuals involved, presenting all options without bias or pressure or judgment.[42] Care should be compassionate and supportive regardless of pregnancy outcome, and supportive care is crucial to those whose journey includes termination.[71,72] As medical providers, we can help moderate the impact of fetal

consultations on parental quality of life that often follow complex discussions, recurrent visits, evolving anticipatory plans, difficult decisions,[73] and inherent uncertainty.[74–77] Neonatologists play a crucial role in providing insight into postnatal care, outcomes, and developmental monitoring during consultation and after birth.[78–80]

- *Impact of fetal consultations and complex postnatal care on the medical team:* As in many areas of medicine, providers participating in fetal care are at risk for compassion fatigue, burnout, and significant discomfort with counseling process. Providers report personal and professional impacts, both positive and negative, from the intense and complex clinical, emotional, and social components of fetal consultations and on-going fetal-perinatal care.[81,82]

### *Future Considerations*

As the field of fetal neurology continues to grow, there are many avenues for augmentation, evolution, innovation, and collaboration:

- Working with families and patients who undergo fetal consultations to better inform specialty care,[83,84] create better educational or information materials for families,[79] and foster collaboration with parent/patient support groups or research organizations.[85]
- Continued advancement of fetal imaging with the goals of not only improving imaging technology itself but also working on updating radiographic fetal norms and clarifying radio-diagnostic nomenclature. It will also be important to work toward consensus statements on "best timing" of imaging given the extended window that CNS anomalies can develop during gestation.
- Continued innovation in fetal surgery[86–89] and other antenatal treatments, such as fetal gene therapy[90] or directed fetal neuroprotection.[91]
- Continued collaboration among providers in creating easily accessible reviews and consensus statements as well as pathways for fetal counseling education for nonperinatal providers to increase accessibility of fetal consults outside of a dedicated fetal center. Formal training in fetal consultation and fetal neurology is important, but providing education and information to other medical professionals can help expand care access to patients.
- Continued collaboration of stakeholder organizations fetal medicine to advance the field, such as the Child Neurology Society Fetal Neurology Special Interest Group (created in June 2022), Newborn Brain Society, American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine, American Academy of Pediatrics, World Health Organization, American Institute for Ultrasound Medicine, ISUOG, and so many more.

## SUMMARY

Fetal consultation is a growing field of medicine that requires navigating the complex interplay between obstetrics and pediatrics using multidisciplinary care. An important subset of perinatal medicine is fetal neurology due to the high frequency of congenital neurologic disorders and their significant impacts on maternal, fetal, and postnatal care. Evolution in medical imaging and genetic testing is leading to increased antenatal diagnosis of CNS anomalies, though limitations remain in providing exact neurodevelopmental prognoses. Options for fetal intervention in a variety of neurologic conditions are continuing to evolve and will likely increase in the coming years. As the field of fetal neurology continues to grow, we must continue to learn from patients and providers to continue moving the field forward while maintaining compassionate and supportive care.

***Best Practices***

### *What is the current practice for fetal neurology consultation?*

In their ideal format, fetal neurology consultations use multidisciplinary teams to provide care throughout an affected pregnancy and, when needed, progress to orchestrating appropriate postnatal care of affected neonates. This requires effective collaboration between obstetrics/perinatology, neonatology, palliative care, neurology, and other allied providers. Consultation involves reviewing and communicating findings from imaging and/or genetic testing to give a diagnosis, the potential etiology, and neurodevelopmental prognosis of a future child. This is followed by developing recommendations for care throughout the pregnancy in collaboration with the patient, support people, and other providers.

### *Care Path Objectives:*

During fetal consultation, the provider's ultimate goals should include

- Delivering an accurate fetal diagnosis
- Providing appropriate prognostic counseling while acknowledging uncertainties
- Support expectant patients through compassionate care
- Developing antenatal and postnatal care plans uniquely tailored to each patient and family
- Navigating the complexities of medical uncertainty, social-emotional complexity, ethical considerations, and holistic care through this journey with a patient or family.
- Understanding the challenges and limitations inherent to fetal neurology consultations, including those in fetal imaging, genetic testing, and fetal treatments.

### *What changes in current practice are likely to improve outcomes?*

- Learning more from patients and families to help evolve the fetal consultation process
- Continued improvements in imaging and genetic testing technologies
- Expansion of fetal therapies for congenital neurologic disorders
- Education, research, and collaboration on local, regional, national, and international levels with prime stakeholders.

### *Pearls/Pitfalls at the point-of-care:*

- Timely referral is essential to ensuring appropriate care.
- Uncertainty is inherent to this field, acknowledging this is essential to developing trust and care connections with expectant patients and families.
- A patient or family's response to prognosis or anticipated plans may be received, interpreted, and responded to very differently, even when the technical details of a case may be similar. Adjust and tailor consultation to match their goals.

### *Major recommendations*

For each fetal consultation, there can be a significant range of severity, body system involvement, and number of abnormalities present in the developing fetus, which can lead to variable degrees of impact on the management of an individual's pregnancy, delivery planning, and perinatal care. Thorough evaluation and thoughtful discussions are essential to providing adequate services during each unique consultation.

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## DISCLOSURE

None.

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# Updates in Neonatal Neuromonitoring

## Electroencephalography, Near-Infrared Spectroscopy, and Transcranial Doppler in the Neonatal Intensive Care Unit

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**KEYWORDS**

• Neonatal seizures • Neonatal encephalopathy • Near-infrared spectroscopy
• Transcranial Doppler ultrasound • Electroencephalography

**KEY POINTS**

- Quantitative EEG (qEEG) can be used as a bedside tool to assess neonatal encephalopathy and detect seizures.
- Machine learning-derived qEEG background categorization predicts acute symptomatic seizures and neurodevelopmental outcomes. While less accurate than neurophysiologist review, it shows promise as a screening tool.
- Near-infrared spectroscopy provides a real-time monitor of neonatal cerebral perfusion, useful for identifying hypoxia and measuring treatment response, the basis of a hemodynamic neuroprotection strategy.
- Transcranial Doppler ultrasound measures cerebral blood flow velocities and estimates brain compliance after neonatal hypoxic-ischemic encephalopathy and correlates with outcomes.

## INTRODUCTION

Brain injury and the risk of subsequent neurodevelopmental impairment are top concerns for parents of infants in the neonatal intensive care unit (NICU).[1] The well-being of these infants is paramount, and significant advancements in neuroprotection have been made over the last 30 years. These include administering steroids to mothers at

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| Abbreviations | |
|---|---|
| ACNS | American Clinical Neurophysiology Society |
| aEEG | amplitude-integrated electroencephalography |
| BP | blood pressure |
| CBFV | cerebral blood flow velocities |
| CI | confidence interval |
| ECMO | extracorporeal membrane oxygenation |
| EEG | electroencephalography |
| HbD | deoxyhemoglobin |
| HbO | oxyhemoglobin |
| HIE | hypoxic-ischemic encephalopathy |
| IVH | intraventricular hemorrhage |
| MAP | mean arterial blood pressure |
| NICU | neonatal intensive care unit |
| NIRS | near-infrared spectroscopy |
| PI | pulsatility index |
| qEEG | Quantitative electroencephalography |
| RI | resistive index |
| $rSO_2$ | regional oxygen saturation |
| TCD | transcranial Doppler |
| TH | therapeutic hypothermia |

risk for preterm delivery,[2] synchronized mechanical ventilation, therapeutic hypothermia (TH),[3] prophylactic indomethacin,[4] and optimized nursing care bundles.[5]

Despite collective efforts to reduce brain injury and neurodevelopmental disability,[6] progress has slowed. Rates of common brain injuries, such as intraventricular hemorrhage,[7] and outcomes like cerebral palsy,[8] have seen little change in the last decade. This stagnation highlights the need for a shift from population-level interventions to personalized strategies based on a patient-specific brain injury profile. This requires continuous and detailed information about the brain's status to recognize unique neurologic risks and evaluate interventions to advance physiology-guided neonatal neurocritical care.

This manuscript describes 3 noninvasive neuromonitoring technologies poised for widespread clinical adoption (**Fig. 1**). Electroencephalography (EEG) measures brain electrical activity, providing continuous data on brain function, seizures, and outcome prediction. Near-infrared spectroscopy (NIRS) monitors cerebral oxygenation and hemodynamics, offering insights into the brain's metabolic state. Transcranial Doppler ultrasound (TCD) measures blood flow velocity in the brain's major arteries, assessing cerebral circulation, brain compliance, and autoregulation. Integrating these techniques into routine care allows clinicians to develop personalized treatment plans, with the ultimate goal of improving outcomes and reducing neurodevelopmental disability.

## ELECTROENCEPHALOGRAPHY AND QUANTITATIVE ELECTROENCEPHALOGRAPHY

### *Overview*

Among various neonatal neuromonitoring techniques, EEG is the most widely adopted. EEG uses scalp electrodes to detect brain electrical activity, measuring the summation of excitatory and inhibitory action potentials (see **Fig. 1**A, **Table 1**). The standard electrode configuration (10–20 system full array or limited neonatal array) provides excellent temporal and spatial resolution, such that EEG remains the gold standard for seizure detection, as greater than 50% of neonatal seizures are

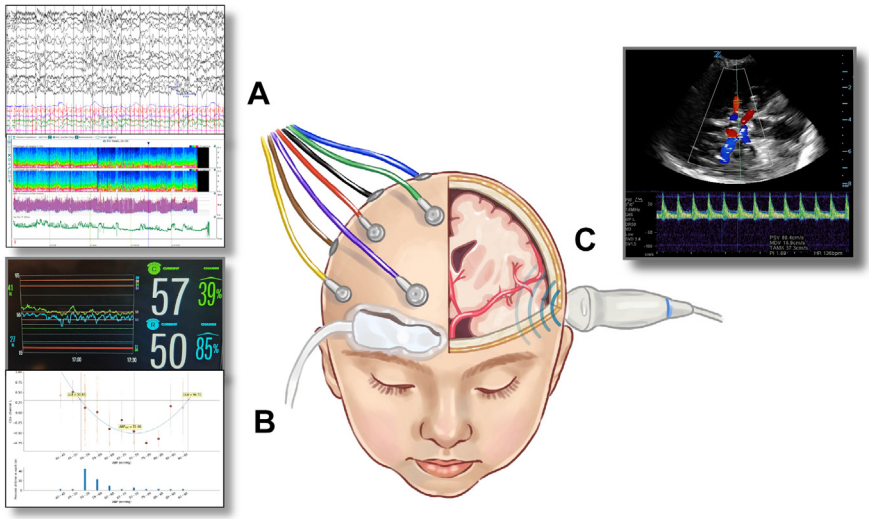


**Fig. 1.** Noninvasive neuromonitoring modalities in critically ill neonates. (*A*) EEG tracing (*top*) and quantitative EEG (*bottom*) including Fast Fourier Color Spectrogram, amplitude-integrate EEG, and heart rate trends. (*B*) NIRS bedside display (*top*) and 4-hour cerebral oximetry index correlation coefficient between NIRS and MAP, identifying optimal MAP (graph nadir) and lower and upper limits of cerebral autoregulation. (*C*) Transcranial Doppler ultrasonography of the major cerebral vessels. Figure manually created by Anika Agarwal. EEG, Electroencephalography; MAP, mean arterial pressure; NIRS, near-infrared spectroscopy; TCD, transcranial Doppler.

subclinical (ie, electrographic-only).[9,10] EEG also assesses background brain activity, predicting risk of acute seizures,[11,12] development of epilepsy including infantile spasms,[13] and long-term neurodevelopmental outcomes.[14]

Quantitative EEG (qEEG) refers to any method of transforming the raw digital EEG waveform into its component parts (eg, amplitude, frequency) and may be displayed at bedside in a time-compressed display. The advanced signal processing underlying qEEG allows objective measurement of brain activity, which can be processed for bedside visualization and used in research. There is a growing body of literature utilizing machine learning and predictive modeling in neonatal qEEG for rapid background categorization which can aid in screening for clinical trial eligibility, predicting seizures, and seizure detection algorithms.[15–17]

### *Electroencephalography and Quantitative Electroencephalography Principles*

EEG detects ion flow from pyramidal neurons, requiring 6 to 20 $cm^2$ of synchronous firing for detection.[18] Seizures involve repetitive excessive depolarization and repolarization with hypersynchronous adjacent neuronal recruitment (**Fig. 2**). Neonatal seizures can be low amplitude with limited spread, and are frequently subclinical, making EEG essential for detection.[9,10]

qEEG harnesses large amounts of continuous EEG data by quantifying EEG waveform features. Amplitude-based trends help classify cerebral dysfunction severity; as brain activity declines, background suppression increases, lowering signal amplitude (**Fig. 3**). While amplitude-integrated EEG (aEEG) has long been used in NICUs for background assessment and seizure detection, interest in other qEEG measures is

**Table 1**
**Neonatal neuromonitoring techniques: electroencephalography, near-infrared spectroscopy, transcranial Doppler**

| Modality | Technical Specifications | Strengths of Monitoring Modality | Disadvantages |
|---|---|---|---|
| EEG | Excitatory and inhibitory postsynaptic potentials resulting in ion flow detectable by scalp electrodes.<br>Neonatal montage is modified from the International 10–20 system to account for smaller head size and will include the following:<br>• 8–11 electrodes<br>• Electrocardiogram (ECG) and respiratory lead<br>• Optional: eye leads, EMG | • Gold-standard for seizure detection<br>• Background assessment is predictive of outcome in neonatal HIE<br>• Can be displayed at bedside for real-time review | • High-cost resource<br>• Requires trained neurophysiologist/ epileptologist for interpretation<br>• Prone to artifact, particularly in the neonatal intensive care unit<br>• Does not detect electrical events in deep structures<br>• Risk of scalp breakdown and infection |
| qEEG | EEG waveform analysis breaks down the EEG signal into component parts and quantifies these features. Displayed in a time-compressed view. Commonly used trends:<br>Time domain tools:<br>• aEEG<br>• Envelope trends<br>• Suppression ration<br>Frequency domain tools:<br>• FFT color spectrogram<br>• Asymmetry spectrogram<br>• Total power<br>• Power by frequency<br>• Frequency ratios (Eg, theta-delta ratio)<br>Automated background categorization<br>Automated seizure detection algorithm | • Eliminates subjectivity, highly reproducible<br>• Does not require trained expert<br>• Automated background classification and seizure detection can reduce burden of monitoring<br>• Time-compressed display allows bedside detection of seizures, background patterns, and gradual trends in brain activity occurring over hours | • Can be influenced by artifact, requires confirmation with raw EEG<br>• Complex measure—more difficult to translate to clinical practice |

| | | | |
|---|---|---|---|
| NIRS | 700–800 nm wavelength light passes from optode, through soft tissue, bone, brain to return to optode. Deoxyhemoglobin and oxyhemoglobin absorb different amounts of NIR light, and the probe provides a ratio oxyhemoglobin to deoxyhemoglobin at a percentage representing regional oxyhemoglobin saturation ($rSO_2$) | • Noninvasive<br>• Requires limited skill to apply probes<br>• Bedside display amenable to real-time interpretation and interventions | • Complex measure—more difficult to translate to clinical practice<br>• Hypoxia threshold not well defined<br>• Interdevice differences are challenging for comparison between centers<br>• Signal can be impacted by melanin content, hair, extracerebral fluid collections (Eg, subdural hematoma), anemia<br>• In other populations, does not correlate consistent with invasive measures of tissue oxygenation |
| TCD | Doppler ultrasound transmits a low-frequency signal through a thin acoustic window to detect cerebral blood flow velocities in major cerebral vessels.<br>Transtemporal window: MCA, ACA, PCA, carotid terminus and siphon.<br>Transorbital window: ophthalmic artery, ICA, optic nerve sheath<br>Suboccipital window: BA, VA<br>Submandibular window: ECA<br>Cerebral blood flow velocity (cm/s):s<br>$V = \frac{\text{Doppler shift x C}}{2 \text{ x Ft x cos } \theta}$<br>Measures of downstream vascular resistance:<br>$RI = \frac{PSV - EDV}{PSV}$ $PI = \frac{PSV - EDV}{mFV}$<br>Autoregulatory Index:<br>$ARI = \frac{\%\Delta eCVR}{\%\Delta eMA}$ (Impaired autoregulation defined as ARI<0.4) | • Portable, performed at bedside<br>• Inexpensive<br>• Real-time monitoring, including continuous monitoring capability<br>• Can be used to assess impact of interventions targeting cerebral blood flow | • Paucity of normative data for healthy neonates, neonates on ventilatory support, neonates on ECMO<br>• Typically performed as a single point in time rather than continuous<br>• Continuous monitoring devices are not widely utilized and are costly. |

*Abbreviations:* ACA, anterior cerebral artery; aEEG, amplitude-integrated EEG; ARI, autoregulatory index; BA, basilar artery; C, speed of sound in soft tissue; CVR, cerebrovascular resistance; ECA, external carotid artery; ECMO, extracorporeal membrane oxygenation; EDV, end diastolic velocity; EEG, electroencephalography; EMG, electromyography; FFT, fast Fourier transform; $F_t$, transmitted frequency; HIE, hypoxic ischemic encephalopathy; ICA, internal carotid artery; ICU, intensive care unit; MCA, middle cerebral artery; mFV, mean flow velocity; NIRS, near-infrared spectroscopy; PCA, posterior cerebral artery; PSV, peak systolic velocity; qEEG, quantitative EEG; TCD, transcranial Doppler ultrasound; VA, vertebral artery.

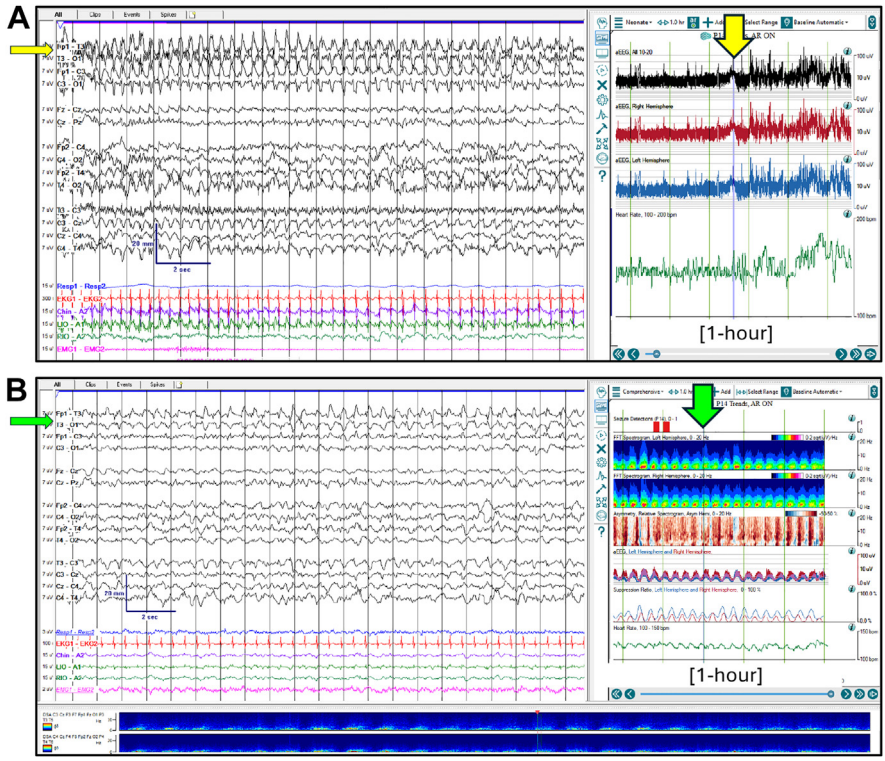


**Fig. 2.** Neonatal seizures on EEG and qEEG. (*A*) A 3-week-old born at 37 5/7 with bilateral subdural hematomas and seizures arising from the left hemisphere. EEG shows left frontocentral (Fp1/C3) seizure. One-hour aEEG panel from top to bottom: aEEG for C3-C4 electrodes, aEEG right/left hemisphere, heart rate trend. During the seizure (*yellow arrow*), there is an arching pattern on aEEG, representing the sudden increase in EEG amplitude during the seizure. (*B*) A 2-week-old born at 40 3/7 who suffered abusive head trauma, experiencing acute seizures and status epilepticus. EEG demonstrates a left temporal (T3) seizure. qEEG panels from top to bottom: seizure detection algorithm, FFT spectrogram left/right hemisphere, asymmetry spectrogram, aEEG, suppression ratio, heart rate trend. During the seizure (*green arrow*), there is a peak of frequency power on the FFT Color Spectrogram, arch pattern on aEEG, and decrease in suppression ratio as the background amplitudes increase >3 μV during the seizure. qEEG demonstrates a background pattern called macroperiodic oscillations, with highly regular peaks and troughs every 2 to 3 mins. Note heart rate oscillations corresponding to qEEG changes. At 2 year, this child has severe neurodevelopmental impairment and medically refractory epilepsy. aEEG, amplitude-integrated electroencephalography; C, central; EEG, electroencephalography; FFT, fast Fourier transform; Fp, frontopolar; qEEG, quantitative electroencephalography; T, temporal.

growing. Frequency analyses summarize the complexity of brain activity and can aid in seizure detection. Coherence and entropy measures discriminate sleep-wake states and such measures decline in severely injured neonatal brains.[19] Keene and colleagues review current neonatal qEEG applications.[20]

### *Reference Values*

A panel of experts appointed by the American Clinical Neurophysiology Society (ACNS) defined normal preterm and term neonatal EEG characteristics.[21] qEEG

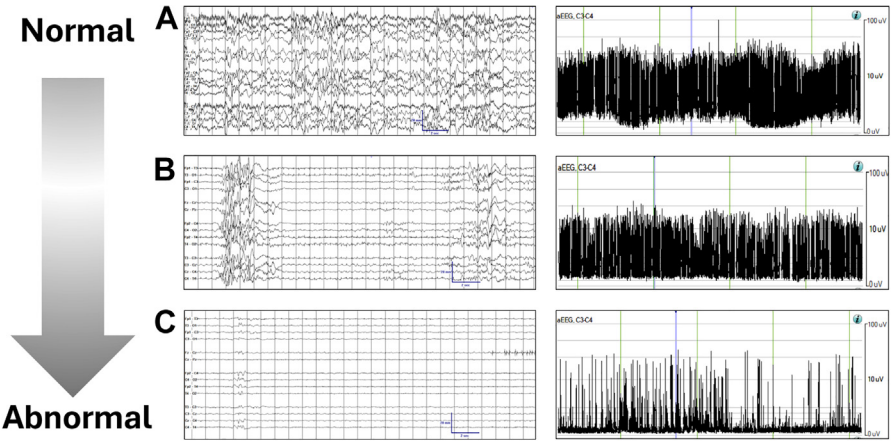


**Fig. 3.** aEEG background patterns. (*A*) Normal EEG and aEEG with preserved sleep-wake cycling. (*B*) Moderately abnormal EEG with excessive discontinuity between symmetric bursts and limited state variability. aEEG shows abnormally low amplitudes and abnormal oscillatory state cycling. (*C*) Severely abnormal EEG with profound background amplitude and frequency suppression, loss of state cycling, and reactivity. aEEG shows a burst-suppressed pattern with amplitudes primarily less than 10 μV and spikes of higher amplitude during electrographic bursts. aEEG, amplitude-integrated electroencephalography; EEG, electroencephalography.

normative standards have largely focused on aEEG patterns,[22] although recent work incorporates more complex qEEG measures, such as frequency power, coherence, and entropy.[19]

### *Electroencephalography in Neonatal Hypoxic-Ischemic Encephalopathy: Background Assessment*

After 6 large randomized controlled trials demonstrated the efficacy of TH in neonatal hypoxic-ischemic encephalopathy (HIE) to improve neurodevelopmental outcomes and reduce mortality, the American Academy of Pediatrics recommends TH for eligible neonates.[3] Hospitals providing TH should have EEG or aEEG monitoring for background assessment and seizure detection, as 40% to 50% of neonates with moderate to severe HIE will seize.[6,16] The World Health Organization and ACNS also endorsed EEG, when available, for background assessment and seizure confirmation.[9,23]

Grading the EEG background incorporates many features including continuity, amplitude, state changes, reactivity, symmetry, synchrony, and presence of age-appropriate graphoelements. One of the earliest changes to a neonatal EEG in the setting of encephalopathy is discontinuity, when the amplitude is less than 25 μV for longer periods of time than expected for age. This can progress to the point of burst suppression or complete suppression. Severe patterns including burst suppression, low voltage, and flat tracings have the highest sensitivity for predicting poor outcome (specificity 0.82, 0.92, 0.99, respectively).[24]

Temporal evolution of the EEG background is an important prognostic indicator as well (**Fig. 4**). The initial background may reflect severity of injury, although that alone may be insufficient to accurately predict outcome. While a severe background that stays poor throughout cooling is highly associated with adverse outcomes, a severe background that improves has far more variable outcomes, with a higher proportion being favorable.[25] In a study of 22 infants with initially severe backgrounds, those

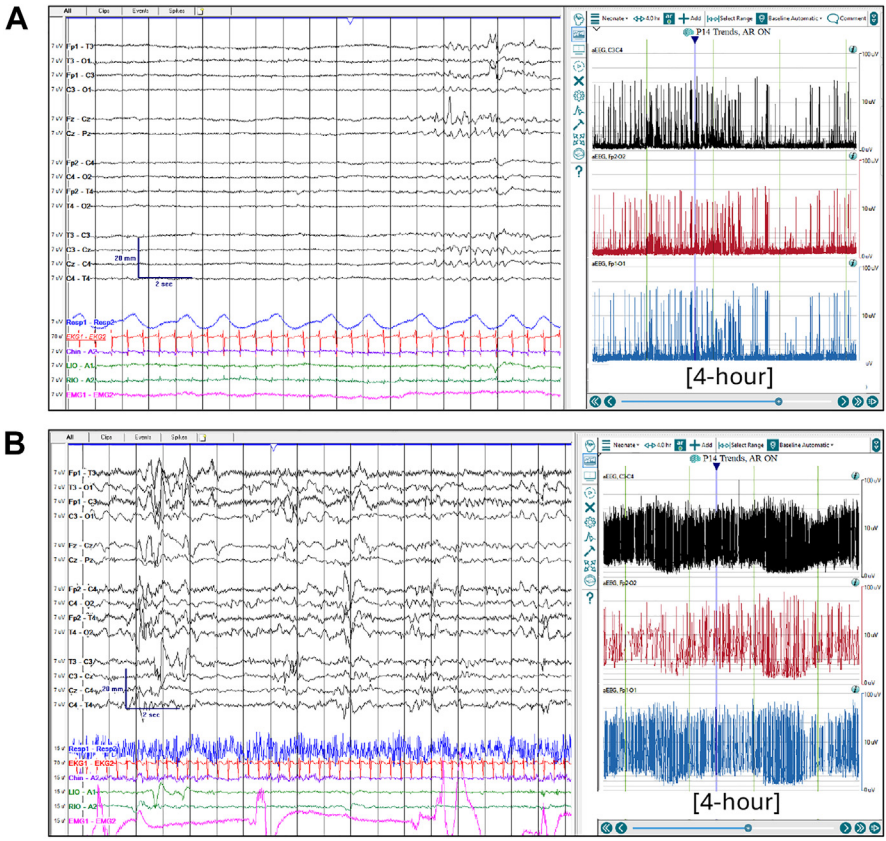


**Fig. 4.** Evolution of brain activity in hypoxic-ischemic encephalopathy. EEG and 4-hour aEEG for a 39-week neonate with severe encephalopathy undergoing therapeutic hypothermia (TH): (*A*) Day 1 EEG shows severe background, including prolonged interburst intervals, low-amplitude bursts, absent state cycling, and reactivity. aEEG demonstrates burst suppression, creating a striped pattern. (*B*) Day 3 EEG mild-to-moderate background abnormalities, with excessive discontinuity and return of sleep-wake cycling. The aEEG shows an oscillatory amplitude pattern indicating sleep-wake cycling.

who had return of sleep-wake cycling had lower incidence of motor and cognitive impairment, while lack of cycling strongly correlated with severe MRI injury.

The most broadly utilized qEEG trend in the NICU is the aEEG. Historically, this involved 2 or 4 electrodes over the right and left vertex (central and parietal electrodes) but can incorporate a full neonatal montage. The aEEG summarizes minimum and maximum amplitude variation of the EEG over time, allowing visualization of normal and abnormal EEG background patterns (see **Fig. 3**). Because of its ability to rapidly categorize background abnormalities, several early TH trials utilized aEEG as eligibility criterion.[26] Conflicting evidence supports the predictive value of aEEG in neonatal HIE. Interrater agreement between aEEG classification and subjective EEG interpretation is only fair to moderate ($\kappa$ 0.34–0.36 compared to 0.45).[27] Adding aEEG to clinical assessment of encephalopathy such as Sarnat score did not improve area under the curve (AUC) or positive predictive valuve (PPV).[26] However, in a study comparing the prognostic value of cranial ultrasound, aEEG, TCD resistive index, and

somatosensory and visual evoked potential, aEEG had the highest PPV and negative predictive value (NPV) for HIE outcomes.[28]

While subjective aEEG background assessment faces challenges with interrater variability and accuracy, other forms of qEEG offer improved classification and better correlation with long-term outcomes. When differentiating encephalopathy grades in 44 infants with clinically mild to moderate encephalopathy, delta (0.5–4 Hz) power and absolute spectral power from the first 3 hours of monitoring accurately distinguished mild from moderate and severe (AUC 0.774 [95% confidence interval (CI), 0.631–0.917] and AUC 0.769 [95% CI, 0.624–0.915], respectively).[29] This and other studies have demonstrated that quantifiable and reproducible EEG features collected within the first 6 hours of life correlate with clinical encephalopathy grade. A qEEG oscillatory pattern seen in neonates with acute brain injury termed macroperiodic oscillations correlated with 18 to 24 month Bayley III score, and outperformed MRI severity in predicting death or disability (see **Fig. 2**B).[30] These studies demonstrate that neonatal qEEG background assessment can feasibly be available during important decision time windows and are promising, reliable biomarkers for encephalopathy severity. These tools may play a future role in patient selection for TH and other neuroprotective interventional trials.

### *Electroencephalography in Neonatal Hypoxic-Ischemic Encephalopathy: Seizure Detection and Treatment*

As previously noted, seizures are common in neonatal HIE, and high seizure burden and status epilepticus are associated with worse neurologic outcomes.[14,31,32] Specifically, an hourly seizure burden greater than 13 minutes was associated with an 8-fold increase in adverse neurodevelopment at 24 to 48 months (OR 8.00; 95% CI: 2.06–31.07).[32] A subsequent study using the same threshold of 13 minutes confirmed that infants in that category had more severe neurodevelopmental impairment and higher risk of death or severe impairment at 2 years.[14]

Of note, early EEG background remains the best predictor of seizures in acutely ill neonates.[11,33] In a cohort of 90 neonates undergoing TH, severe initial EEG background was highly associated with seizures ($P<.00005$), while other variables such as pH less than 6.8, Apgar score $\leq$3 at 10 minutes, and initial examination were not.[11] A seizure prediction model combining EEG background with clinical variables was more predictive of seizures than either feature alone (AUC 0.83 [95% CI 0.776–0.884]).[12] While many centers have adopted the clinical practice of monitoring neonates for 72 hours of TH plus rewarming due to the small risk of late-onset or rebound seizures during rewarming, this strong association between initial EEG background and risk of seizures can be used to identify low-risk patients and guide ideal duration of monitoring. Several studies examined the relationship between early EEG background and timing of seizure onset during hypothermia and rewarming.[33–35] All studies found that when infants have an initially mild EEG background and do not seize in the first 24 hours of monitoring, those infants do not go on to develop late-onset seizures. While exceptions exist, this cohort can likely be safely disconnected from EEG after 24 hours without need for remonitoring during rewarming.

Recently, several groups have derived machine learning algorithms to predict neonatal seizures, achieving AUCs = 0.76 to 0.83, with qEEG variable incorporation consistently out-performing clinical variables or subjective EEG findings alone.[36] Such algorithms utilizing automated background categorization plus clinical features could aid in identifying high-risk neonates and guide EEG monitoring strategies.

While aEEG may be used as a reasonable screening tool for neonatal seizures when full EEG and/or review are not available, seizure identification using aEEG only detects

about 50% of seizures, less for inexperienced users.[37] aEEG often fails to detect short, low- amplitude seizures or seizures occurring far from traditional aEEG centroparietal electrode sites (eg, occipital). Thus, for accurate neonatal seizure detection using aEEG, confirmation with the raw EEG is required. For infants at high risk for seizures, EEG monitoring is preferred.

Another exciting application of qEEG in the NICU is automated seizure detection algorithms, which may improve speed and accuracy of identification and reduce time to treatment. Investigators have used up to 55 unique qEEG features to optimize their models.[38,39] Early pitfalls commonly associated with false negatives included seizures that were short, low amplitude, and without spread to adjacent channels, while causes of false-positive detections included artifact from respirations, cardiac cycle, and sweat.[40] Methods have been employed to remove common artifacts including cardiac[41] and patting artifact.[42] One of the major hindrances to adopting seizure detection algorithms in clinical use is the competing balance between a highly sensitive tool (detecting as many seizures as possible) with a low false- positive rate. Frequent false alarms will fail to improve reader efficiency and may increase workload by requiring frequent verification. Published algorithms detect 50% to 96% of seizures with false-positive detection rates 0.04/h to greater than 2/h[15,43,44]

### *Electroencephalography and Postnatal Epilepsy*

The risk of postnatal epilepsy is dependent upon the etiology of brain insult, ranging from 13% to 30% in HIE, 20% to 25% in bacterial meningitis, up to 80% in cerebral malformations.[31,32] Clinical risk factors after HIE include deep gray or brainstem injury on MRI, abnormal discharge examination, and requirement of multiple antiseizure medications during initial NICU hospitalization.31 EEG and aEEG risk factors include high seizure burden, $\geq$3 days of seizures, and severe EEG background patterns.[31,45] Identifying infants at highest risk of developing postnatal epilepsy should guide surveillance after discharge.

## NEAR-INFRARED SPECTROSCOPY

### *Overview*

Near-infrared spectroscopy (NIRS) is a noninvasive technology that leverages the differential absorption of oxyhemoglobin and deoxyhemoglobin in red and infrared wavelengths of light to measure oxygen saturation in a specific tissue (most commonly the brain) (see **Fig. 1**B, see **Table 1**). It has been widely studied in neonates and used in several large randomized clinical trials.[46,47] The NIRS signal provides valuable insight into cerebral metabolism, cerebrovascular autoregulation, and intermittent cerebral hypoxia—none of which can be quantified through standard monitoring. Indeed, it is the ability of the NIRS monitor to detect occult cerebral hypoxemia that offers the greatest opportunity to avoid intermittent hypoxic events deleterious to brain growth and development.[48,49]

### *Near-Infrared Spectroscopy Principles*

NIRS devices operate on 2 light physics principles: reflectance and absorbance. A typical NIRS optode has an emitter (usually a light emitting diode or LED) emitting light in 2 or more wavelengths in the red and infrared bands and 2 receivers at different distances from the emitter.[50] Light (700–800 nm) penetrates bone and tissue, before scattering, reflecting, and being absorbed in the brain. Photons return to the optode, where their quantity is measured. The interaction of light with blood causes variable absorption of light and reflects tissue oxygen saturation. Deoxyhemoglobin (HbD)

absorbs more red light, less near-infrared (NIR) light; oxyhemoglobin (HbO) absorbs more NIR light, less red light. Tissue oxygen saturation is merely the ratio of HbO to total hemoglobin (HbO + HbD).[50,51] The closer detector measures shallower tissue such as skin (which is ignored), while the further one measures deeper into the cortex, with a common penetration depth of 2.5 cm in neonatal sensors.[52]

NIRS, while somewhat similar in principle to pulse oximetry, is a far more complicated measurement and requires an additional level of interpretation to translate into action. Where pulse oximetry is pulse synchronized and yields an estimation of arterial saturation, NIRS measures absorption in all vascular compartments (venous, arterial, capillary) at once.[50] As it is estimated that 70%, 25%, and 5% of blood is found in the venous, arterial, and capillary beds, respectively, NIRS measurements mostly closely approximate a mixed venous saturation ($SvO_2$) and represent a composite of oxygen delivery and consumption.[53] When NIRS measurements are higher than expected, this could represent either an oversupply of oxygen (eg, too much supplemental oxygen) or under extraction (eg, from injury or sedation). The opposite is true when NIRS measurements are low, too little oxygen is being delivered to the brain, or excessive cerebral metabolic demand (eg, seizures, infection) is not being met by the current oxygen supply.[54]

### *Reference Values*

Large studies of cerebral NIRS have provided reference values for clinical care in delivery rooms, NICU management of preterm infants, and those with HIE. Alderliesten and colleagues conducted the largest study, recording 999 very low birth weight infants over 72 hours post birth,[55] establishing a normative range for cerebral regional oxygen saturation ($rSO_2$) between 55% and 85%. Pichler and colleagues found cerebral $rSO_2$ increases from 40% at 2 minutes to 70% by 9 to 10 minutes, stabilizing thereafter, similar to pulse oximetry patterns during cardiovascular transition.[56] Term infants show a different pattern, with cerebral $rSO_2$ values from 40% to 55% soon after birth, rising to 78% by 24 hours.[57]

Saturation values from NIRS devices vary significantly due to differences in light wavelengths, emitter-receiver spacing, and proprietary algorithms. Kleiser and Hyttel-Sorensen used a blood-lipid phantom model to create linear transformations between different NIRS devices, allowing for equivalent value conversions.[58–60] The widely adopted hypoxia threshold of 55% was obtained using the INVOS 5100c monitor and the small adult sensor. **Table 2** shows equivalent hypoxia thresholds for common NIRS monitors.

**Table 2**
**Cerebral hypoxia thresholds for common near-infrared spectroscopy devices**

| Device | Hypoxia Threshold |
|---|---|
| ForeSight small | 66 |
| ForeSight nonadhesive small | 67 |
| INVOS 5100/7100 neonatal | 63 |
| INVOS 5100/7100 small | 55 |
| NIRO small | 61 |
| NIRO small re-useable | 63 |
| O3 neonatal | 64 |
| SenSmart X-100 pediatric nonadhesive | 66 |

*Adapted from* Hansen et al. 2019.[46]

Neonates present unique challenges for cerebral NIRS monitoring due to variations in head circumference, which changes significantly from 22 to 40 weeks (21 cm to 35 cm).[61] Fixed emitter-detector spacing means the light path traverses different structures at different ages. Kolnik and colleagues used simulations to show brain regions measured at various gestational ages, ranging from ventricular predominance at early gestational age (GA) to cortex and white matter later on.[52]

### *Cerebral Near-Infrared Spectroscopy in Intraventricular Hemorrhage*

Intraventricular hemorrhage (IVH) is a common and consequential form of brain injury in preterm infants, affecting approximately 25% of infants born before 32 weeks.[62] Hypoxia is a major risk factor for IVH[63] and there is increasing recognition of "silent" hypoxia, where cerebral saturations are below hypoxic thresholds while standard clinical monitors (ie, pulse oximeter) are within the normal range.[64] Cerebral NIRS has been used in the evaluation of IVH and evidence supports a biphasic pattern of injury, where cerebral saturations are elevated immediately preceding or during hemorrhage (reflecting reduced extraction in the setting of injury) followed by lower cerebral saturations.[65,66] Cerebral saturations following IVH are lower than expected for weeks to months, reflecting increased metabolism in the setting of injury and deoxygenated blood in the ventricle (which is no longer in circulation).[67,68] This effect scales with severity of injury, with the lowest cerebral saturations found in infants with the highest grades of IVH.[68]

### *Cerebral Near-Infrared Spectroscopy in Hypoxic-Ischemic Encephalopathy*

Hypoxic-ischemic injury to the neonatal brain leads to complex hemodynamic changes in the cerebral circulation. There is an initial drop in cerebral oxygenation in the first 4 to 6 hours following birth, following by recovery at 18 to 20 hours.[57] HIE alters cerebrovascular autoregulation, rendering it less effective in the days following injury, potentially leading to "luxury" perfusion and instigating reperfusion injury.[69] HIE generates significant inflammation, amplifying metabolism and leading to secondary energy failure.[70] Compared to noninjured term infants, many infants with HIE have higher cerebral saturations, reaching a peak of 85% in the first few days of life.[71] This may reflect the twin impact of injury and TH, both of which can decrease cerebral metabolism and oxygen extraction.[72,73] Several studies have identified higher cerebral oxygenation between 24 and 36 hours after birth as a significant predictor for brain injury on MRI and adverse long-term outcomes.[57,73]

### *Cerebral Near-Infrared Spectroscopy in Clinical Management*

Translating NIRS into clinical management is challenging. Although the SafeBoosC and COSGOD phase II trials showed reductions[56,74] in mortality and severe brain injury in the NIRS-guided groups, the phase III trials did not show statistically significant outcome differences.[46,47]

Two significant barriers must be overcome. First, the hypoxia threshold for intervention is crucial. The COSGOD and SafeBoosC trials used thresholds based on the Alderliesten reference study,[55] but these may not match diverse populations. Other investigators have suggested that a much lower threshold of 50%, linked with adverse outcomes, is a better alternative to statistically derived thresholds.[75] Animal studies[76] indicate that both threshold and duration of hypoxia are important, with injury incidence increasing with prolonged exposure. Individual tolerance to hypoxia also plays a role, as shown in studies of adult cardiac surgery patients where cerebral saturations less than 40% for more than 10 minutes were associated with adverse neurologic outcomes.[77]

The second barrier is the choice of appropriate intervention. An out-of-range NIRS value does not directly dictate an intervention and typically requires further investigation. NIRS monitoring is complex due to its mixed nature, representing a composite of oxygen delivery *and* consumption. An example strategy adapted from the SafeBoosC-III trial protocol[46] is shown in **Fig. 5**.

## TRANSCRANIAL DOPPLER ULTRASOUND

### *Overview*

Transcranial Doppler ultrasound (TCD) utilizes principles of Doppler ultrasound to determine cerebral blood flow velocities (CBFV) (see **Fig. 1**C, **Table 1**). Portable machines allow bedside examination, are relatively inexpensive, and provide real-time assessment of neonatal CBFV. TCD has been used to assess cerebrovascular resistance, provide a noninvasive measurement of cerebral autoregulation, monitor vasospasm, and assess vascular malformations.

## PRINCIPLES IN TRANSCRANIAL DOPPLER ULTRASOUND

A low-frequency ultrasound probe with phased array is used for neonatal TCD, utilizing Doppler technology to calculate the velocity and directionality of blood flow within a vessel.[78] Four acoustic windows are used to visualize cerebral blood vessels, detailed in **Table 1**. The resistive index (RI) and pulsatility index (PI) are markers of downstream cerebral vessel resistance. Increased intracranial pressure and poor brain compliance increase RI. In healthy neonates, RI peaks on day 1 before declining on days 2 and 3, likely due to changes in diastolic flow with ductus arteriosus closure.

### *Transcranial Doppler Ultrasound for Neonatal Encephalopathy Stratification and Outcome Prediction*

The standard of care for term and near-term neonates with encephalopathy who meet criteria for TH is to initiate cooling within 6 hours of birth. As noted earlier, rapid bedside assessment with aEEG has been used to screen infants for eligibility. While most TCD research in neonates focused on correlation with long-term outcomes,

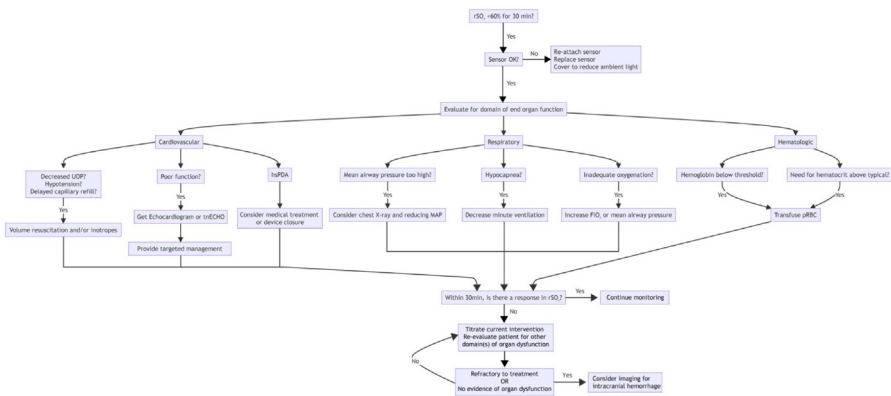


**Fig. 5.** Sample NIRS-guided treatment algorithm. An example NIRS-guided treatment algorithm showing interventions across 3 possible domains of organ dysfunction (cardiovascular, respiratory, and hematologic). Note that infants without low cerebral saturations and no corroborating evidence of disrupted perfusion should undergo evaluation for intracranial hemorrhage.

there is increasing interest in TCD as an adjunctive screening tool in the immediate postnatal period.

RI is of particular interest in neonatal HIE. RI less than 0.55 has been established as an abnormally low value in this context and is thought to correspond to the secondary phase of brain injury.[79] Low RI is associated with more severe encephalopathy and has high specificity for predicting poor long-term outcomes (76%–100%).[28,80] In an investigation of early TCD in 60 infants with HIE (18 mild, 19 moderate or severe, 23 controls), lower RI corresponded to worse severity.[81] Even among those with mild HIE, low RI was associated with confirmed radiographic injury and abnormal aEEG, providing outcome stratification even in lower risk groups.

### *Transcranial Doppler Ultrasound for Detection of Cerebrovascular Disease*

Data are limited regarding the use of TCD for detection of neonatal stroke, vasculopathy, and vascular malformations. In infants 11 to 90 day-old receiving extracorporeal membrane oxygenation (ECMO), PI was significantly elevated in infants later confirmed to have diffused cerebral ischemia compared to those without injury.[82] In a study that included both neonates and older children supported on ECMO, differences between bilateral middle cerebral artery (MCA) velocities were highly associated with arterial ischemic stroke.[83]

### *Transcranial Doppler Ultrasound in Management of Neonatal Infections*

Investigational work identified a common pattern of CBFV in neonatal sepsis. CBFV in the anterior and posterior circulation were compared between 54 preterm and term neonates with sepsis and age-matched controls.[84] Peak systolic and end diastolic velocities were significantly higher in neonates with sepsis; RIs were lower. A similar pattern found in 96 neonates with early-onset sepsis also corresponded with increased cord blood neuron-specific enolase.[85] This combined pattern suggests hyperemia, possibly related to impaired autoregulation during systemic infection.

Beyond systemic infection, central nervous system infections such as bacterial meningitis can cause numerous acute complications which require close neuromonitoring, including hydrocephalus, empyema, cerebritis, seizures, and cerebral vasculopathy. TCD is commonly used to monitor cerebral vasospasm in adults, and while principles of prestenotic and poststenotic waveforms and velocity dynamics likely apply to neonates, TCD for acute vasculopathy monitoring is not yet validated in neonates (**Fig. 6**).

### *Transcranial Doppler Ultrasound for Autoregulation/Cerebrovascular Pressure Reactivity Assessment*

Understanding of neonatal cerebral autoregulation and how this system matures is limited. An exploratory study of 10 healthy term neonates utilized TCDs and tilt table testing to show that autoregulation in 1 to 2 day-old babies was intact when applying an autoregulatory index (see **Table 1**).[86]

For neonates with acute brain injury or congenital heart disease, there is interest in identifying an infant's zone of autoregulation to provide personalized blood pressure (BP) targets. This is accomplished by identifying BP at the upper and lower limits of autoregulation. Numerous surrogate indices have been proposed, typically calculating the correlation between mean arterial blood pressure (MAP) and a noninvasive measure of cerebral perfusion, such as NIRS or TCD velocities. These indices are based on the principle that cerebral vasculature dilates or constricts in response to changes in BP to maintain steady cerebral blood flow. When autoregulation is intact, MAP and

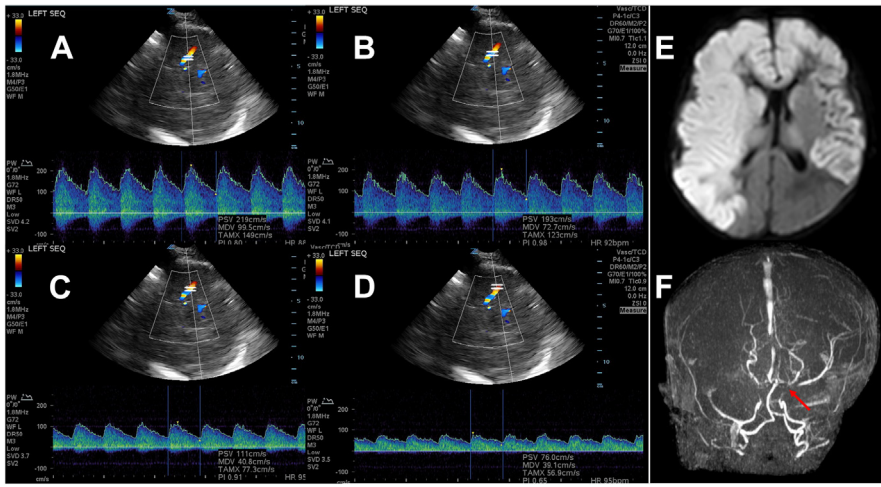


**Fig. 6.** TCD demonstrating severe left middle cerebral artery (MCA) vasculopathy in neonatal bacterial meningitis. (*A–D*) Cerebral blood flow velocities measured sequentially along the left MCA proximal to distal (*white brackets* = TCD gate). Mean flow velocities (TAMx) are greater than 2 standard deviations above age-based norms in A-B, with TAMx 149 cm/s proximally, 123 cm/s at next segment. Poststenotic waveforms (*C*, *D*) with diminished velocities (TAMx 77–56 cm/s) and delayed systolic upstroke, resulting in a blunted appearance. (*E*) Shows acute ischemia on diffuse-weighted MRI involving the right anterior cerebral artery (ACA) and MCA, left ACA, and partial left MCA. (*F*) Magnetic resonance angiogram shows multisegmental vessel narrowing, including the left MCA (*red arrow*), which corresponds with the TCD images.

cerebral blood flow should have minimal correlation, with values less than 0.3 indicating intact autoregulation.[87]

A cohort of 33 preterm neonates less than 33 weeks used continuous 5-minute recordings of BP and CBFV to calculate coherence between these measures during spontaneous increases in BP.[87] Infants with intact autoregulation had return to baseline CBFV within 1 to 2 seconds of a significant BP change. Boylan and colleagues used TCD curves derived from BP increases to determine intact versus impaired autoregulation in 13 term and preterm neonates compared to healthy controls.[88] Further work is needed to validate these measures and determine the impact of interventions to maintain neonates within their optimal zone of autoregulation.

## FUTURE DIRECTIONS

The next frontier in neonatal neurocritical care will be defined by widespread use of many of the devices and techniques described in this manuscript. While the vast amount of real-time data will provide a new dimension to neuroprotective care, it simultaneously adds a significant cognitive burden to providers who must integrate even more information into decision-making. Development and marketing of devices without evidence or consensus-based strategies for use will see limited adoption and variable benefits. It is essential that clinical trials pairing devices and interventions be supported by researchers who understand the pathophysiology of acute neonatal brain injury and the strengths and limitations of these devices. The use of high performance, automated software algorithms, as is beginning to happen with

qEEG, has the potential to identify neurologic emergencies faster, with the goal of identifying decompensation in time for effective interventions.

Potential clinical scenarios warranting further investigation include (1) timely identification and treatment of neonatal seizures, (2) reducing early cerebral hypoxia burden in preterm infants, (2) NIRS-based transfusion management, (3) guided respiratory weaning to avoid occult hypoxia, (4) early warning of cardiorespiratory decompensation in critical illness (eg, respiratory failure, sepsis, ECMO), (5) early risk stratification of infants with suspected brain injury to provide targeted intervention to those likely to benefit, and (6) noninvasive measures of intracranial pressure.

## SUMMARY

Noninvasive neuromonitoring techniques including EEG, NIRS, and TCD have proven effective and in some cases are highly accurate in predicting long-term neuroprognosis. However, the true impact of these tools lies in their ability to identify and quantify the severity of brain injury in neonates, which may support rapid identification of candidates most likely to benefit from validated neuroprotective measures, enhance subject selection in future interventional trials, and detect neurologic emergencies in time to intervene, with the ultimate goal of using these tools to improve survival and neurodevelopmental outcomes.

***Best Practices***

### *What is the current practice for critical care neonatal neuromonitoring?*

Neonates with the following conditions should be monitored on continuous video electroencephalogram:
- Neonatal encephalopathy
- Seizure screening for high-risk neonates
- Diagnostic evaluation of paroxysmal events concerning seizures.

NIRS monitoring and NIRS-directed care should be considered for the following:
- Neonates at risk for impaired cerebral oxygenation (eg, congenital heart disease, respiratory failure, sepsis) or abnormal cerebral metabolism.

Transcranial Doppler should be considered for the following:
- Prognostic value in early assessment of neonatal HIE severity, but is not yet standard care.

### *Best Practice/Guideline/Care Path Objective(s):*

EEG

Neonates undergoing therapeutic hypothermia for hypoxic-ischemic encephalopathy should be monitored for background assessment and seizure screening.
- When seizures are identified, EEG should be used to assess treatment response and continued until 24 hour seizure free in most cases.
- Typically, 24 hours of monitoring is needed to rule out subclinical seizures but may be discontinued if the clinical event is recorded.

Near-infrared spectroscopy
- See **Fig. 2** for a proposed NIRS-guided treatment algorithm.

Transcranial Doppler
- Not typically part of guidelines but used at some institutions for assessing neonatal HIE severity.

### *What changes in current practice are likely to improve outcomes?*

- Incorporating neuromonitoring tools into clinical care and research will lead to innovations through individualized, brain-directed care with the ultimate goal of improving neurodevelopmental outcomes in critically ill neonates.

***Is there a Clinical Algorithm?***

The ACNS provides clinical guidelines for the use of neonatal EEG. Fig. 2 provides a proposed NIRS-directed care algorithm.

***Pearls/Pitfalls at the point-of-care:***

- EEG is resource-intensive and requires expert review; not available at every institution.
- NIRS thresholds for intervention are not well established and vary by individual.
- TCD lacks rigorous validation in neonates for various measures of brain pathology.

***Major recommendations***

- EEG should be used to screen for seizures in high-risk neonates with acute brain injury, to diagnose paroxysmal clinical events, and assess background for cerebral dysfunction.
- qEEG holds promise for predictive modeling for seizures and neurodevelopmental outcomes.
- NIRS should be used for early identification of cerebral hypoxia in infants at risk for impaired cerebral blood flow and to assess treatment.
- Additional work is needed to better understand postnatal cerebral blood flow physiology, response to acute brain injury, neonatal cerebral autoregulation, and the accuracy of this modality for bedside detection of cerebral pathology including vasospasm, increased intracranial pressure, and stroke.

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# Advances in Neonatal Neuroimaging

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**KEYWORDS**

• Neuroimaging • Neonates • Infants • Ultrasound • MRI
• Neurodevelopmental outcomes

**KEY POINTS**

- Head ultrasound is the ideal first-line imaging modality in neonates; however, MRI is the most informative and can be safely obtained without sedation.
- Clinical guidelines and collaboration with local neuroradiology teams are important for framing decisions on timing of imaging studies and optimizing imaging sequences.
- Neuroimaging continues to guide long-term risk stratification for neurodevelopmental outcomes across both the clinical and research domains.

## INTRODUCTION

Neuroimaging has an integral role in the diagnosis and management of neurologic pathology in both preterm and term neonates. It allows clinicians and researchers to visualize the dynamic evolution of brain maturation and response to injury. In this article, an overview of current neuroimaging modalities (**Table 1**) and their application to clinical practice is followed by a discussion of advanced neuroimaging techniques and future directions for this field in neonatal populations.

## NEUROIMAGING MODALITIES

### *Head Ultrasound*

Ultrasound imaging is based on the transmission and reflection of acoustic energy of a structure using a hand-held transducer that serves as both transmitter and receiver. Ultrasound waves are reflected by boundaries where materials of different acoustic impedance meet. In the case of the brain, these boundaries are present where tissues

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| Abbreviations | |
|---|---|
| CT | computed tomography |
| CSF | cerebrospinal fluid |
| DOT | diffuse optical tomography |
| DTI | diffusion tensor imaging |
| DWI | diffusion-weighted imaging |
| EEG | electrocardiogram |
| fMRI | functional MRI |
| HII | hypoxic-ischemic injury |
| HUS | head ultrasound |
| IVH | intraventricular hemorrhage |
| LF | low field |
| MRA | MR angiography |
| MRS | MR spectroscopy |
| NAA | *N*-acetyl aspartate |
| PAIS | perinatal arterial ischemic stroke |
| PC | phase contrast |
| PHVD | posthemorrhagic ventricular dilatation |
| PVL | periventricular leukomalacia |
| SNR | signal-to-noise ratio |
| SWI | susceptibility-weighted image |
| T1WI | $T_1$-weighted images |
| T2WI | $T_2$-weighted images |
| ULF | ultralow field |

abut water (eg, ventricular margins) and the borders between red blood cell membranes and adjacent fluid. Consequently, ultrasound excels at demonstrating ventricular/brain outline and hemorrhage. However, little contrast is present between gray and white matter or even normal and nonhemorrhagic injured tissue. As a result, a "normal" ultrasound does not always rule out nonhemorrhagic brain injury.

Portability, tolerability, ease of evaluation, and affordability make ultrasound an appealing first-line neuroimaging option in neonates and it is done without sedation.[1] The cerebral hemispheres are evaluated through the anterior and posterior fontanelles (**Fig. 1**), while the posterior fossa can be further evaluated through the mastoid fontanelle.[2] Doppler techniques provide additional information on blood flow and vascular resistive indices. Comparatively, ultrasound is more technique- and technician-dependent than computed tomography (CT) or MRI and can be confounded by limitations due to fontanelle size, poor gray/white contrast, and poor sensitivity to nonhemorrhagic brain injury.

### *Clinical use*

Standard protocols are often implemented for neonates at high risk for brain injury and posthemorrhagic ventricular dilatation (PHVD). At our institution, we obtain ultrasound studies on days 1 to 3, 10, and 28 for infants born less than 29 weeks' gestation, and days 10 and 28 for infants born at 29 to 32 weeks' gestation. Additional studies may be obtained based on findings.

## *Computed Tomography*

CT produces cross-sectional images from a rotating series of X-rays. This modality has limited utility in the neonatal population due to its use of ionizing radiation,[3] though recent advances in scanner technology, such as photon counting CT, have improved image quality and artifact rejection while lowering radiation dosing.[4] Like ultrasound, CT provides information on ventricular size and shape, as well as presence/absence

**Table 1**
**Comparison of neuroimaging modalities**

| | Modality | | |
|---|---|---|---|
| | **Ultrasound** | **Computed Tomography** | **MRI** |
| Advantages | • Performed at the bedside with minimal disruption of patient or medical care<br>• Excellent for showing ventricular configuration and hemorrhage | • Shows hemorrhage and ventricular size well<br>• Some contrast for nonhemorrhagic brain injury<br>• Excellent angiography (requires contrast)<br>• More sensitive for intracranial calcifications than MRI | • Outstanding gray/white contrast with excellent sensitivity for brain malformations and heterotopias<br>• Excellent contrast for injury (hemorrhagic/nonhemorrhagic)<br>• Sensitive for hemorrhage<br>• Provides angiography (without contrast requirement) |
| Disadvantages | • Operator dependent<br>• Incomplete brain coverage<br>• Poor contrast for nonhemorrhagic brain injury | • Radiation exposure<br>• May require transport out of NICU<br>• Less sensitivity for nonhemorrhagic injury than MRI | • Expensive<br>• Requires transport out of NICU<br>• Patient less accessible during the study |

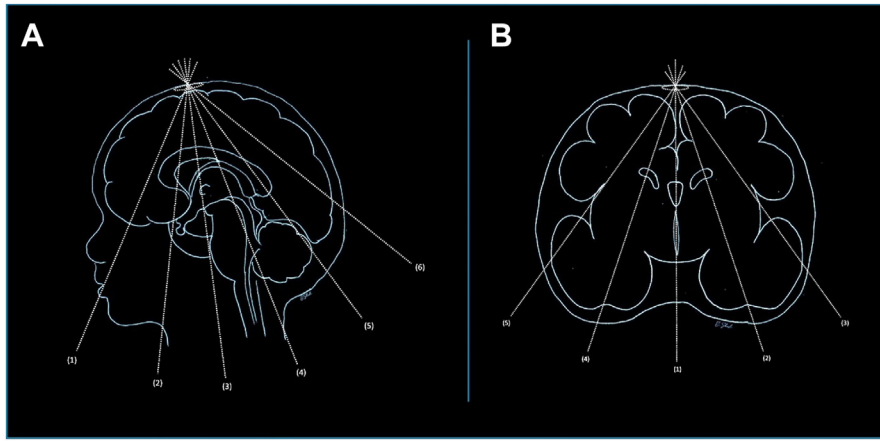


**Fig. 1.** Head ultrasound technique. Standard images when using head ultrasound are obtained through the anterior fontanelle.[2] Six coronal imaging planes (*A*) encompass (1) frontal lobe, (2) frontal horns of the lateral ventricles, (3) third ventricle, (4) cerebellum and quadrigeminal cistern, (5) trigone of the lateral ventricle, and (6) occipital lobes. Five sagittal imaging planes (*B*) encompass (1) midline, (2) left lateral ventricle, (3) left Sylvian fissure, (4) right lateral ventricle, and (5) right Sylvian fissure.

of hemorrhage. Unlike ultrasound, it provides some contrast between normal and nonhemorrhagic injured brain, though offers less sensitivity than MRI. CT also offers excellent angiography when used with intravenous contrast. CT imaging typically requires the patient to be taken to the scanner, and therefore, clinical instability can be a limiting factor unless a portable scanner is available. Compared to MRI, CT scans are shorter in duration. In addition, CT scanners have a more open configuration, allowing faster patient access in the event of an emergency. Like MRI, CT is prone to degradation by subject motion.

### *Clinical use*

Ultrasound and MRI are the preferred modalities in neonates, but in specific critical and noncritical situations (eg, acute hemorrhage, hypoxic-ischemic injury (HII), focal ischemic infarction, mass, hydrocephalus, calcification, and skull abnormality), or if MRI is not available, CT imaging may be useful.[1,5]

## *MRI*

MRI is based on the detection of signal from $^{1}H$ atoms in $^{1}H_2O$. The means by which these signals are detected and localized are beyond the scope of this review; however, several basic concepts should be considered. First, use of signal from water protons is advantageous because their concentration in the brain is on the order of 80 M, as compared with brain metabolites that have concentrations at millimolar levels. Second, the radiofrequency coil used for signal detection has a marked effect on image signal-to-noise ratio (SNR). Thus, the coil should be chosen judiciously, as SNR provides a currency that can be "spent" to obtain images faster and/or at higher spatial resolution.

A wide variety of image sequences are available through MRI, which increase its tissue contrast and clarity. For example, water protons in different chemical environments, such as gray and white matter, have different $T_1$ and $T_2$ relaxation time constants.

Images weighted by these time constants ($T_1$-weighted images [T1WI] and $T_2$-weighted images [T2WI]) provide excellent gray/white/cerebrospinal fluid (CSF) contrast. From a clinical standpoint, T1WI and T2WI are used to identify macroscopic anatomy and abnormalities. They are sensitive to injury, with signal intensity in areas of edema or glial scars differing from adjacent normal tissue. However, it usually takes days for injury to appear on conventional images.

Image contrast can also be based on water motion; either microscopic (diffusion) or macroscopic (angiography), aiding in the visualization of ischemia or vasculature, respectively. For detection of acute injury, diffusion-weighted imaging (DWI) is most helpful. The microscopic displacements of tissue water decrease within minutes of injury, providing a sensitive and early indicator of injury. This reduction in water displacements reverses after a period of days,[6,7] making DWI no longer sensitive to injury. Thus, DWI is best for detecting acute and subacute injury, whereas conventional imaging is sensitive for older injury.

In neonates, a few additional sequences are routinely incorporated. Images can be sensitized to the magnetic field distortions caused by the presence of the reduced iron in deoxyhemoglobin, creating susceptibility-weighted images (SWI) sensitive to hemorrhage. Finally, it is possible to detect resonances of various metabolites through MR spectroscopy (MRS), albeit at lower SNR than conventional imaging. Comparison of these modalities (eg, T1W1, T2WI, DWI, SWI, MRS) can serve as a rough indicator of injury age.

#### *Additional practical considerations*

We typically scan neonates at our institution while they sleep after being fed and swaddled tightly, allowing scanning without sedation. As always, safety is important, and monitoring with pulse oximetry, ECG leads, and video is often utilized. Special consideration is needed for critically ill neonates who have invasive respiratory support, intravenous lines, drains, electrocardiogram (EEG) leads, and/or shunts, as these need to be MR compatible.

Most centers use scanners with field strengths of 1.5 or 3 T. While higher magnetic field strength provides better SNR, excellent images can be obtained at either field strength. Coordination with neuroradiology teams at local institutions is important to optimize image acquisition protocols, radiofrequency coils, and postprocessing tools for neonates to minimize time in the scanner, reduce motion artifact, and improve spatial resolution.

## CURRENT CLINICAL APPLICATION OF NEUROIMAGING

Neuroimaging is utilized in many clinical contexts. In addition to the common scenarios described below, neuroimaging can also aid in the evaluation of neonatal patients with encephalopathy, seizures, abnormal tone, microcephaly and macrocephaly, congenital heart disease, and in neonates who require extracorporeal membrane oxygenation. Ultrasound is often chosen initially followed by MRI (or CT in specific circumstances) if clinically warranted. Timing of neuroimaging often depends on the clinical concern and time course of pathology.

### *The Developing Brain*

Brain MRI is useful in assessment of sulcation (**Fig. 2**), myelination, and overall brain growth in critically ill neonates. Cortical sulcation and gyrification are accompanied by neuronal differentiation, proliferation, migration, and dynamic changes in water and lipid content in a complex and structured process in the developing brain.[8–11] Understanding the normal progression of brain development and its effects on

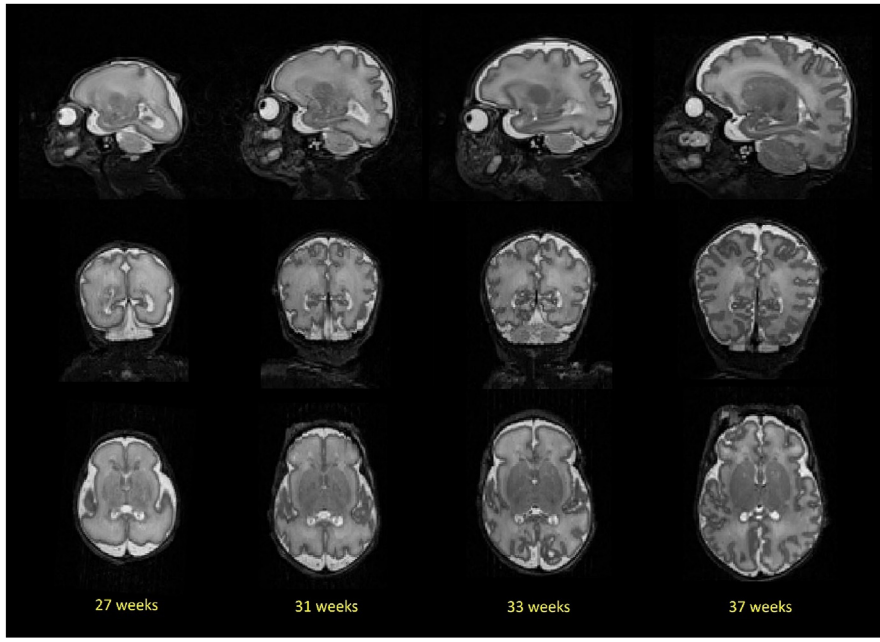


**Fig. 2.** Development of cortical folding and myelination. Prior to the fifth gestational month, the brain is largely lissencephalic. Over the following months, sulci develop in a temporally ordered manner. Longitudinal MRI in a preterm neonate shows the macroscopic changes of cortical sulcation and gyrification during the third trimester.

neuroimaging is important to the interpretation of neonatal MRIs. As white matter myelinates, its signal characteristics on T1WI and T2WI change. Myelinated white matter appears brighter than unmyelinated on T1WI and darker than unmyelinated on T2WI. In contrast, gray matter signal characteristics stay constant. Thus, changes in white matter signal intensity due to myelination lead to an inversion of gray/white contrast during development, with comparatively poor gray/white contrast at age 4 to 6 months, when their signal intensities are similar. Corticospinal tracts are myelinating at birth and are easily detected as bright on T1WI of term infants.

The impact of prematurity and/or early critical illness on brain development is also important to recognize. Brain volumes are reduced in preterm neonates at term-equivalent compared to term-born control infants, including total brain, cortical and subcortical gray matter, white matter, and regional volumes within sensorimotor, parieto-occipital, orbito-frontal, temporal, and prefrontal areas.[12–18] Term-equivalent preterm neonates additionally have reduced cortical surface area proportional to their degree of prematurity.[16–18] These differences are influenced by clinical factors, including brain injury, critical illness, bronchopulmonary dysplasia, and medications. Importantly, these volumetric and surface area reductions have been associated with adverse neurodevelopmental outcomes in children born prematurely.[13,19–22]

### *Hypoxic-Ischemic Injury*

HII occurs in the setting of inadequate oxygen and substrate delivery from maternal, fetal, neonatal, and/or placental etiologies, contributing to biphasic energy failure. Patterns of injury with HII are age-specific and duration/severity dependent.

Mild-to-moderate HII in preterm infants can affect vulnerable oligodendrocytes, resulting in periventricular leukomalacia (PVL) or deep white matter injury.[23–27] Profound insults can additionally affect the brainstem, thalami, and basal ganglia.[23] PVL (Fig. 3) is unique to premature neonates. It is usually detected initially by HUS showing increased echogenicity or cystic change in the white matter superolateral to the lateral ventricles. In some cases, increased echogenicity evolves to cystic change overtime. On MRI, white matter scarring from PVL may appear hyperintense on T1WI and hypointense on T2WI. In addition, if the periventricular cysts fuse with the ventricular wall, PVL may take the appearance of ventriculomegaly with white matter volume loss or irregular contours of the ventricular walls. PVL is associated with neuronal/axonal dysfunction and adverse long-term neurodevelopmental outcomes, notably spastic diplegia.[26,28,29]

In term-born infants, MRI is the optimal study for detection of HII. In the acute period, DWI is the most sensitive for this type of injury. In the first 24 hours, DWI may not show milder injury in neonates (unlike in adults, where the incidence of "diffusion negative" injury is lower), and the maximum sensitivity of DWI for detection of injury is 2 to 3 days after injury for normothermic infants and 2 to 4 days for neonates who undergo therapeutic hypothermia.[7,23] Thereafter, DWI becomes less sensitive for detecting injury due to pseudonormalization, which occurs approximately 6 to 8 days after injury in normothermic infants and approximately 11 to 12 days after injury in infants who undergo therapeutic hypothermia.[7] Among conventional MRI sequences, T1WI and T2WI are sensitive for injury by the end of the first week. At our institution, we obtain imaging on day 4 in infants treated with therapeutic hypothermia, detecting injury on DWI. We often also obtain follow-up imaging at 10 days, at which time injury is visible on T1WI and T2WI.

Mild-to-moderate HII in a term infant (Figs. 4 and 5) can result in injury to watershed zones and subcortical and periventricular white matter. Profound insults can affect the dorsal brainstem, anterior cerebellar vermis, thalami, basal ganglia, hippocampi, and perirolandic areas with relative sparing of the cerebral cortex.[23] In cases where clinical instability or contraindications interfere with MRI capabilities, CT has been used to demonstrate decreased attenuation within affected regions with blurring of the gray–white junction in severe cases. It is typical for neonates to have low attenuation in frontal and parieto-occipital regions[23]; therefore, images need to be interpreted by specialists. Overall, these patterns of injury commonly have prognostic significance, with basal ganglia injury associated with motor deficits and watershed injury associated with epilepsy and cognitive deficits.[30–35]

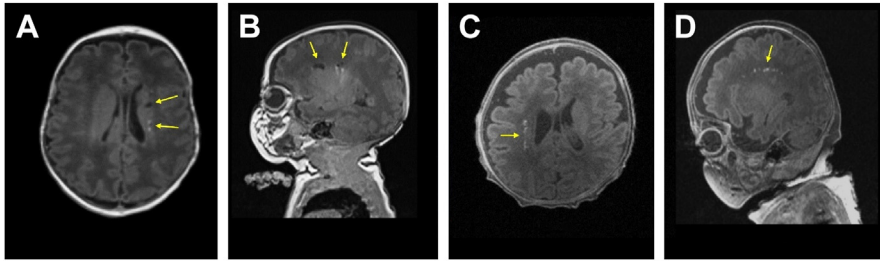


**Fig. 3.** Periventricular leukomalacia in preterm neonates. Axial (*A*) and sagittal (*B*) T1WI in a preterm neonate demonstrate left periventricular leukomalacia with cystic changes (*arrows*). Axial (*C*) and sagittal T1WI (*D*) in another preterm neonate demonstrate periventricular leukomalacia without cystic changes (*arrows*).

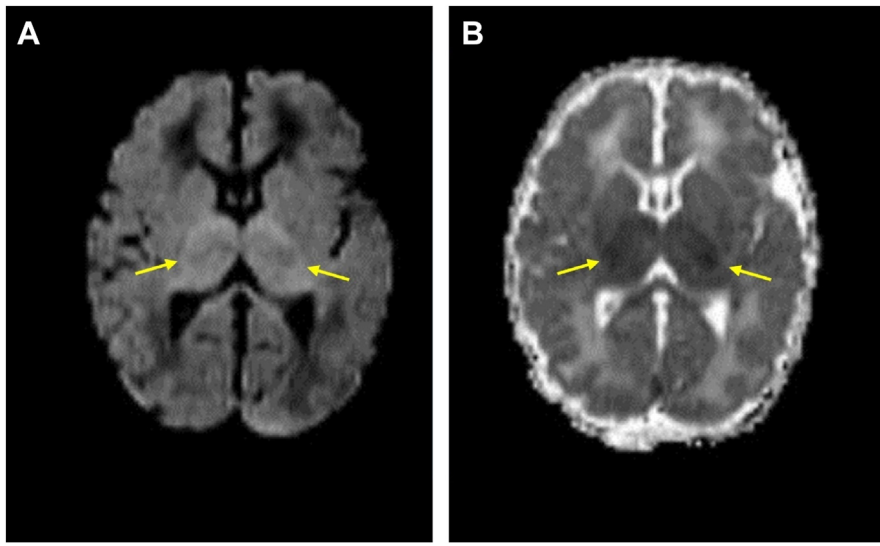


**Fig. 4.** Hypoxic-ischemic injury of deep gray matter structures in a term neonate. Diffusion-weighted axial image (DWI) in which areas of reduced water diffusion appear bright (*A, arrows*) and corresponding apparent diffusion coefficient (ADC) map (*B*) in which areas of reduced diffusion appear dark (*arrows*) in a term neonate at 2 days of life demonstrating hypoxic-ischemic injury with restricted diffusion of bilateral thalami and punctuate area in the left periventricular white matter abutting the atrium of the lateral ventricle.

MRS can provide additional prognostic value with HII, but this varies based on brain regions evaluated, age at measurement, and technical differences. Lactate levels rise and peak in the acute period after an insult followed by a reduction in *N*-acetyl aspartate (NAA).[23,36] Among metabolites, lower NAA levels have the most consistent association with adverse outcomes.[37–39]

### *Perinatal Arterial Ischemic Stroke*

Perinatal arterial ischemic stroke (PAIS) can manifest clinically with acute symptomatic seizures or neonatal encephalopathy within the first days of life, though a considerable number of insults are diagnosed later when patients present with focal symptoms.[40,41] Infarctions in both premature and term neonates have a predilection for the middle cerebral artery territory within the left hemisphere.[41–43] Main branch occlusions are seen similarly between premature and term neonates; however, premature neonates tend to have occlusions within lenticulostriate vessels, while term neonates tend to have occlusions within cortical branches.[43,44]

Neuroimaging in PAIS shows similarities to HII. MRI is again the most useful modality (**Fig. 6**) with consideration of MR angiography (MRA) for evaluation of intracranial and neck vasculature. MRA can be obtained without contrast administration using time-of-flight techniques. For improved evaluation of distal vessels and small malformations, a contrast study can be considered. Long-term outcomes after PAIS depend on the location and extent of injury. Poor motor outcomes are recognized with concomitant injury within the basal ganglia, corpus callosum, and posterior limb of the internal capsule, while seizures, cognitive difficulties, and visual deficits are recognized with cortical injury.[41,45–47]

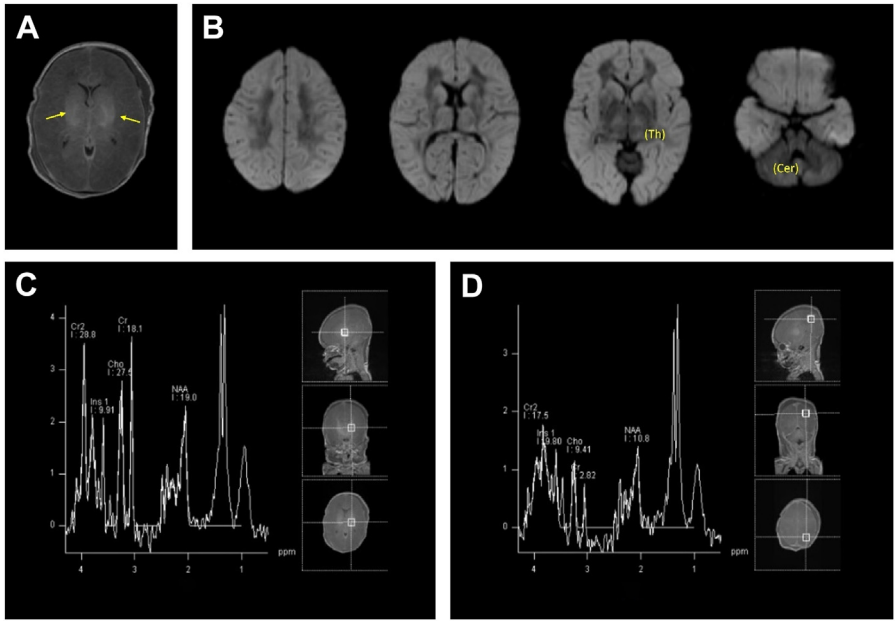


**Fig. 5.** Diffuse hypoxic-ischemic injury in a term neonate. Axial T1WI (*A*) and DWI (*B*) in a term neonate at 4 days of life demonstrate severe diffuse injury. Increased T1 signal (*arrows*) in the deep gray matter structures with sulcal effacement is indicative of global cerebral edema. DWI shows diffusely increased signal, corresponding to reduced water diffusion, with relative sparing of the cerebellum (Cer) and thalamus (Th). MR spectroscopy demonstrates marked elevation of the lactate peak in the left thalamus (*C*) and left parietal white matter (*D*).

### *Intracranial Hemorrhage*

As with other types of pathology, patterns of intracranial hemorrhage (ICH) tend to be age specific. Preterm neonates are more likely to have ICH within germinal zones due to vulnerability of their immature vessels to hemodynamic instability and systemic stressors.[48] The ventricular/subventricular zone is the region most often implicated for contributing to intraventricular hemorrhage (IVH). Incidence of IVH has been decreasing,[48,49] but the severity continues to be linked to degree of prematurity and

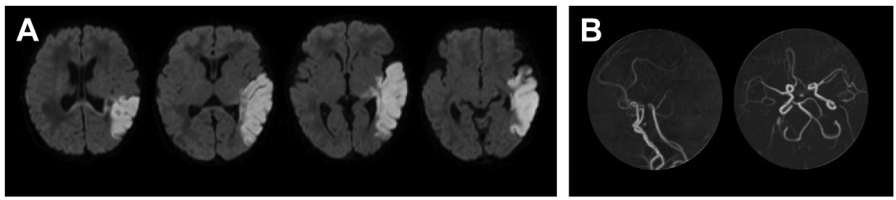


**Fig. 6.** Perinatal arterial ischemic stroke in a term neonate. Axial DWI (*A*) of a term neonate at 4 days of life demonstrates increased signal (reduced water diffusion) within the left temporo-parietal region and posterior thalamus, consistent with infarction of the inferior division of the left middle cerebral artery. Wallerian degeneration is additionally demonstrated within the splenium of the corpus callosum and corticospinal tract. Time-of-flight MRA (*B*) on the same day of life was negative for occlusions or irregularities.

**Table 2**
**Classification of intraventricular hemorrhage in a neonate**

| Papile et al,[52] 1978 | Severity | Volpe et al,[53] 2024 |
|---|---|---|
| Isolated subependymal germinal matrix | Grade I | Germinal matrix with no or <10% IVH |
| Subependymal germinal matrix + intraventricular *without* ventricular dilation | Grade II | Germinal matrix + 10%–50% IVH |
| Subependymal germinal matrix + intraventricular *with* ventricular dilation | Grade III | Germinal matrix + >50% IVH |
| Subependymal germinal matrix + intraventricular with ventricular dilation + parenchymal hemorrhage | Grade IV | Periventricular echodensity or periventricular hemorrhagic infarction |

*Abbreviation:* IVH, intraventricular hemorrhage.

superimposed intravascular, extravascular, and vascular factors.[48,50,51] Clinical grading systems[52,53] (**Table 2**) are based on degree of hemorrhage within the endothelial-lined vessels of the subependymal germinal matrix and its impact on the ventricular system and surrounding parenchyma from venous congestion (**Fig. 7**). Parenchymal injury from venous infarction, referred to as periventricular hemorrhagic infarction, has a predilection for posterior frontal and parietal regions followed by anterior frontal, occipital, and, finally, temporal areas.[54] Increased IVH severity, degree of parenchymal involvement, and development of PHVD contribute to increased long-term neurodevelopmental differences across domains.[54–58]

Cerebellar hemorrhagic injury is also commonly recognized in preterm neonates and can be either unilateral or bilateral.[59] Vulnerable regions include the internal granular layer of the cerebellum along with other germinal zones, such as the subependymal

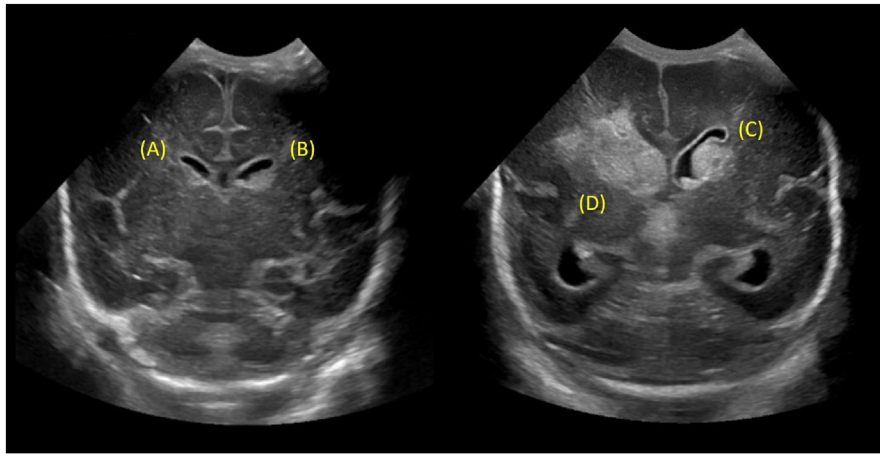


**Fig. 7.** Intraventricular hemorrhage in preterm neonates. Head ultrasound images in the coronal plane demonstrating variable grades of intraventricular hemorrhage (IVH) in 2 different preterm neonates. Using the scoring system of Papille and colleagues, grade I (A) is hemorrhage isolated to the subependymal germinal matrix region, grade II (B) is IVH without ventricular dilatation, grade III (C) is IVH with ventricular dilatation, and grade IV (D) is IVH with parenchymal hemorrhage.

region around the fourth ventricle and external granular layer.[59] In the acute period, serial imaging is considered through hemorrhage stabilization. Over time, atrophy of the affected cerebellar region often occurs.

Term infants, in contrast, are more likely to have epidural, subdural, subpial, and parenchymal hemorrhages (**Fig. 8**).[60] Certain types of hemorrhage have regional predispositions. Subdural hemorrhages tend toward posterior quadrants and are associated with vaginal delivery.[61] Subpial hemorrhages (**Fig. 9**) have predilection for the temporal lobe with accompanying venous thrombosis and IVH and/or intraparenchymal hemorrhage.[62]

Neuroimaging findings with ICH are dependent on the stage of evolution and demonstrate similar trajectories to adults, though porencephaly may develop over weeks in infants, which is quicker than adults. Additional complications from hemorrhagic insults should be evaluated with neuroimaging, including PHVD, white matter injury, and parenchymal injury.

Ultrasound is usually chosen for acute evaluation. Through the subacute period, hyperechoic signal is appreciated within the region of concern. In the chronic period, atrophy or cystic changes within the affected tissue can be seen. Ultrasound is additionally used for evaluation of PHVD. Serial scans can gauge progression of pathology and need for neurosurgical intervention.

MRI and CT scans have greater sensitivity to detect the full extent of hemorrhage, and the former is preferentially chosen due to lack of ionizing radiation and improved evaluation of parenchyma. SWI is notably sensitive to even small hemorrhages. T1WI and T2WI, though not as sensitive, can be used for gauging evolution of hemorrhage[63] (**Table 3**). When there is concern for ICH, a clinician should consider obtaining MR venography (MRV) to evaluate for venous sinus thrombosis as described later.

### *Cerebral Venous Sinus Thrombosis*

The deep and superficial venous systems are susceptible to occlusion from predisposing maternal, fetal, neonatal, and/or placental factors causing venous congestion and outflow obstruction. Superficial venous structures are more commonly involved, and complications occur secondary to increased intravenous pressure, contributing to infarction and/or white matter injury.[43,64–66]

Head ultrasound can be used initially in these cases, and color Doppler can evaluate venous flow; however, ultrasound is associated with false negatives. In clinical situations where CT is necessary, increased signal with venous dilation can be seen in noncontrasted studies and a filling defect can be seen in contrasted studies. In neonates,

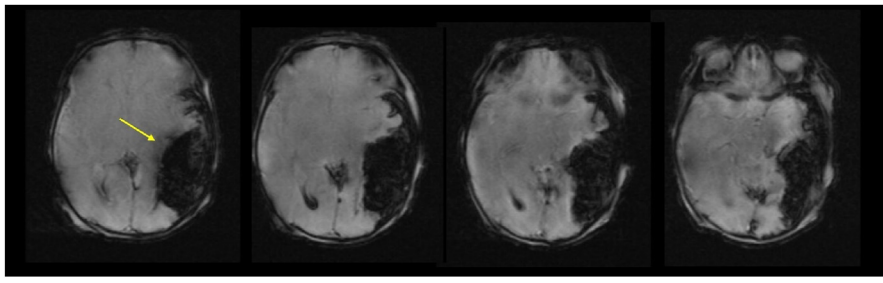

**Fig. 8.** Intraparenchymal hemorrhage (*arrows*) in a term neonate. Axial SWI in a term neonate at 1 day of life demonstrates intraparenchymal hemorrhage primarily involving the left temporal, parietal, occipital lobes.

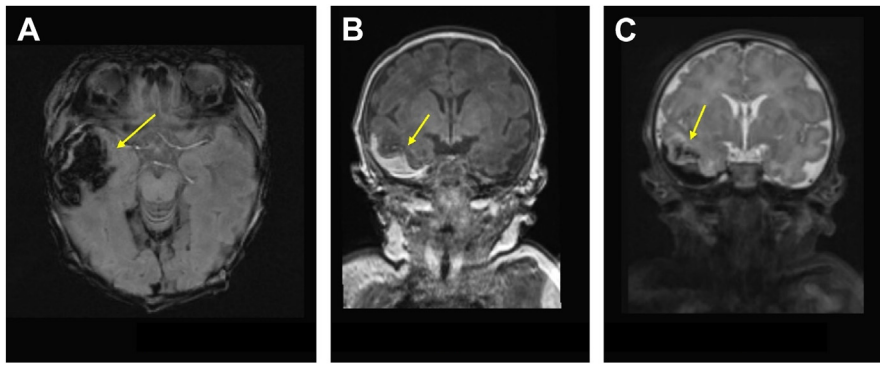


**Fig. 9.** Subpial hemorrhage in a term neonate. Axial SWI (*A*), coronal T1WI (*B*), and coronal T2WI (*C*) in a term neonate at 4 days of life demonstrating subpial hemorrhage and associated venous infarction (*arrows*) within the right temporal lobe.

higher hematocrit levels and slower venous flow can falsely increase signal within the venous system. Additionally, clinically insignificant subdural hemorrhages along the tentorium and posterior fossa from delivery can mimic signal changes seen with a thrombus.[67]

MRI is the most useful modality for identification of cerebral venous sinus thrombosis (CVST) and associated brain injury (**Fig. 10**). Protocols typically include conventional MRI with diffusion-weighted sequences supplemented with MRV. Time-of-flight MRV in this period could be confounded by T1 properties emulating a patent vessel, so phase-contrast studies may be needed for comprehensive evaluation. A follow-up MRI can be considered in the short term for thrombus characterization and evaluation of clot propagation to assist with management and risk stratification for long-term neurodevelopmental differences.[64,65,68]

**Table 3**
**Evolution of parenchymal and extracerebral hemorrhage in neonates**

| Period After Injury | Conventional T1 MRI | Conventional T2 MRI |
|---|---|---|
| Evolution of parenchymal hemorrhage in neonates | | |
| <3 d | Isointense/hyperintense rim | Hypointense |
| 3–10 d | Isointense/hyperintense | Hypointense (hyperintense periphery) |
| 10–21 d | Hyperintense | Hyperintense |
| 3–6 wk | Hyperintense | Hyperintense (hypointense periphery) |
| 6 wk–10 mo | Isointense/mildly hyperintense | Isointense/hypointense |
| Evolution of extracerebral hemorrhage in neonates | | |
| <3 d | Hyperintense | Isointense/hypointense |
| 3–10 d | Hyperintense | Hypointense (LL: mildly hyperintense) |
| 10–21 d | Hyperintense | Hypointense (LL: mildly hyperintense) |
| 3–6 wk | Isointense/mildly hyperintense | Hypointense |
| 6 wk–10 mo | Isointense | Isointense/hypointense |

Evolution of MRI changes in neonates with intracranial hemorrhage.
*Abbreviation:* LL, large lesions.
*Adapted from* Ref.[63]

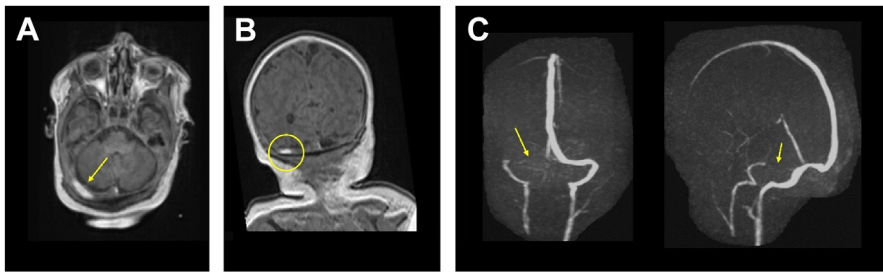


**Fig. 10.** Venous sinus thrombosis in a term neonate. Axial (*A*) and coronal (*B*) T1WI of a term neonate demonstrate *Arrow* in (*A*) and circle in (*B*) pointing to the increased signal along the right transverse sinus due to a thrombus. MR venography (*C*) subsequently confirms a *Arrows* in (*C*) pointing to the filling defect in the right transverse venous sinus with partial sigmoid reconstitution, consistent with a dural venous sinus thrombosis.

## *Antenatal Abnormalities*

### *Antenatal insults*

The sequelae from antenatal hypoxia, ischemia, and/or inflammation depend on the gestational age at which the insult occurs. The immature brain is susceptible to excitotoxicity and free radical species and is limited in mounting an astrocytic response compared to adult brains. Focal lesions before the beginning of the third trimester tend to form a porencephalic cyst.[23] Lesions affecting the entire anterior circulation can evolve to hydranencephaly.[23] Focal lesions from the third trimester through the neonatal period often result in compensatory astrocytic proliferation and gliosis.[69]

### *Congenital malformations*

Congenital malformations are best evaluated using MRI due to optimal tissue contrast and spatial resolution. Head ultrasound and CT can, however, still provide some insight; these modalities are useful for evaluation of ventricular contour and size, gyral development, and larger cortical malformations. Posterior fossa malformations are best evaluated with MRI; head ultrasound is challenging due to the small size of the mastoid fontanelle, and CT is hindered by the density of bone at the base of the skull.

Ventriculomegaly is the most common prenatal sonographic finding and can be accompanied by other neurologic malformations.[70,71] When the ventricular system is under pressure, hydrocephalus develops. Stenosis of the aqueduct of Sylvius (**Fig. 11**)

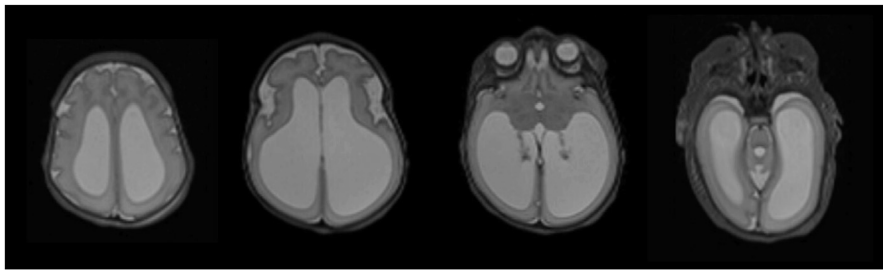

**Fig. 11.** Congenital aqueductal stenosis. Axial T2WI in a preterm neonate with congenital hydrocephalus secondary to aqueductal stenosis demonstrate marked dilation of the lateral and third ventricles, thinning of the corpus callosum, and a simplified cortical gyral pattern.

is a common cause of obstructive hydrocephalus, resulting in compensatory, progressive lateral and third ventricle dilation, corpus callosum deformation, and cortical mantle compression. Though all modalities can evaluate the ventricular system, MRI will be the most useful to screen for coexisting brain abnormalities and assess risk for long-term neurodevelopmental differences.

Midline defects are a heterogeneous category that include neural tube defects, cephaloceles (**Fig. 12**), or anomalies of the prosencephalon affecting the corpus callosum (**Fig. 13**), anterior commissure, or hippocampal commissure.[72] Holoprosencephaly (**Fig. 14**) and septo-optic dysplasia also fall within this class. When a midline defect is identified, structural evaluation of other malformations and a midline workup evaluating for pituitary, ophthalmologic, cardiac, and abdominal comorbidities are often indicated.

Posterior fossa malformations include cystic and non-cystic malformations and the 3 types of Chiari malformations[73,74] (**Table 4**, **Figs. 15–17**). The cystic subtype can be difficult to differentiate due to the course of posterior fossa development[75] but can be subdivided into anterior and posterior defects.[73]

Congenital malformations of the cortex can be divided into disorders of neuronal and glial proliferation, neuronal migration, cortical organization, and other malformations[72] (**Table 5**, **Fig. 18**). Detection of these malformations with neuroimaging warrants infectious, metabolic, and/or genetic evaluation to help uncover the underlying etiology.

Defects of meninx primitiva include lipomas and arachnoid cysts. Lipomas are cavities of abnormal fatty tissue often found along the midline, usually within the subarachnoid space. On MRI, they are hyperintense on T1WI and hypointense on T2WI. Arachnoid cysts (**Fig. 19**) are CSF-filled cavities commonly found within the Sylvian fissure or posterior fossa (see **Table 4**). They are iso-intense to CSF on MRI and can be associated with mass effect on the parenchyma and/or skull.[72]

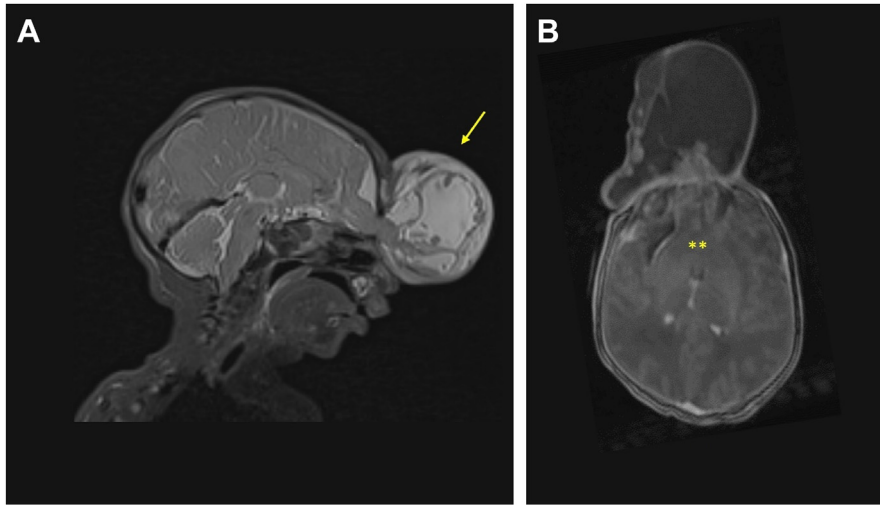


**Fig. 12.** Frontal encephalocele. Sagittal T2WI (*A*) and axial T1WI (*B*) in a term neonate demonstrate a large frontal encephalocele (*arrows*) with extension of the gyri recti into the encephalocele sac and fusion of the basal ganglia demarcated with (*double asterisks*) consistent with septopreoptic holoprosencephaly.

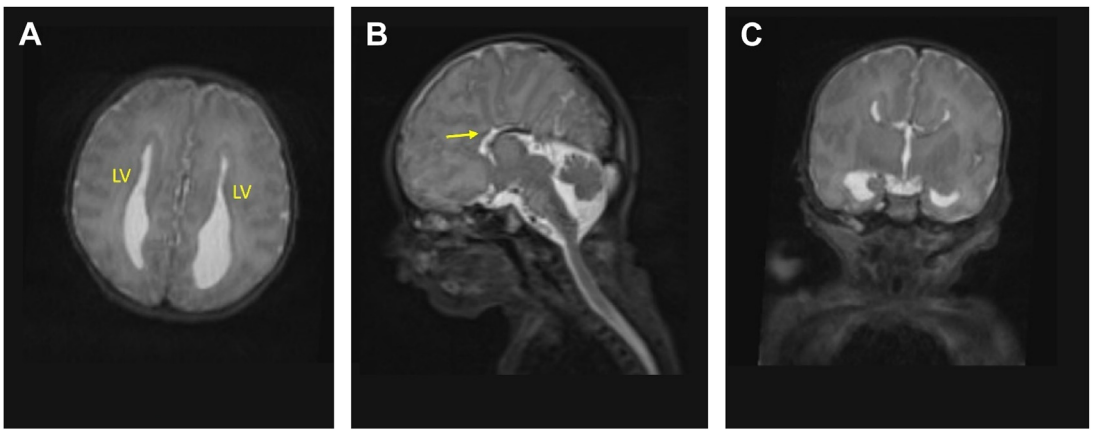


**Fig. 13.** Corpus callosal agenesis. T2WI **in the axial (*A*), sagittal (*B*), and coronal (*C*) planes** from an infant with agenesis of the corpus callosum. Note: The parallel configuration of the lateral ventricles (LV) and colpocephaly characterized by widening of the posterior portion of the lateral ventricles (*A*). Note: The absence of a cingulate gyrus (*arrow*), with sulci extending to the inferior margin of the cerebral hemisphere (*B*).

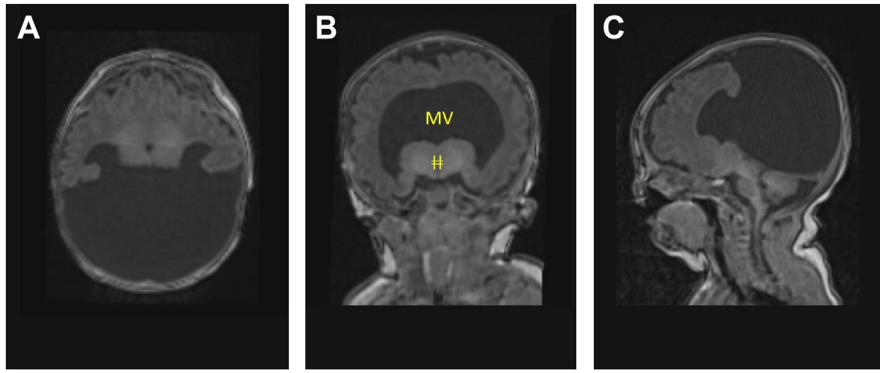


**Fig. 14.** Alobar holoprosencephaly axial (*A*), coronal (*B*), and sagittal (*C*) T1WI in a term neonate demonstrate alobar holoprosencephaly. Note: The single midline monoventricle (MV) that communicates with a dorsal cyst and is accompanied by fused thalami (≠) and absence of the corpus callosum, septum pellucidum, and falx cerebri.

### *Infection*

The developing brain is susceptible to neurotropic congenital and acquired infections. Brain structure and development can be variably affected by these pathogens depending on the trimester at the time of infection. Across modalities, neuroimaging has a role in elucidating these changes and deciphering the underlying etiology.

Neuroimaging findings with congenital infections (**Table 6**) include intracranial calcifications, ventricular abnormalities, structural changes, and white matter differences.[77,78] Imaging modalities have variable sensitivities to these pathologies. Ultrasound is often chosen initially. Its sensitivity to calcifications, ventricular size, and white matter changes can be helpful in assessing need for supplemental studies. MRI is typically the most effective, but CT can be useful.

Acquired neonatal infections from bacterial or fungal pathogens can be complicated by abscess, empyema, vasculitis, infarction, CVST, ventriculitis, leptomeningeal fibrosis, arachnoiditis, and white matter injury[79] (**Fig. 21**). Contrast administration and vessel imaging should be considered to evaluate complications and inform need for intervention and antibiotic duration.

### *Neurometabolic Disorders*

Neurometabolic disorders are a heterogenous group of pathologies that affect metabolic pathways including synthesis, processing, storage, and/or transport of substrates and byproducts. Clinically, these disorders can be challenging to diagnose due to nonspecific signs and symptoms. Among modalities, MRS, DWI, and conventional MRI are most informative for evaluation and differentiation of these disorders.[80,81] Imaging changes range from nonspecific to pathognomonic findings and are based on pattern recognition due to selective vulnerability of the gray and/or white matter (**Table 7**).

## ADDITIONAL MODALITIES

a. *Arterial spin labeling (ASL) MRI:* In this technique, water in arterial blood is labeled with RF pulses as it passes through the neck, and its arrival in parenchyma can be detected to create a perfusion map.[84] ASL's ability to evaluate cerebral perfusion

**Table 4**
**Posterior fossa abnormalities**

| | |
|---|---|
| *Cystic defects* | |
| Anterior defect | |
| Dandy–Walker malformation | Hypoplastic, elevated, and rotated vermis, cystic dilatation of fourth ventricle with posterior extension and communication with enlarged posterior fossa and supratentorial hydrocephalus (Fig. 15). |
| Posterior defect | |
| Blake's pouch cyst | Enlargement of fourth ventricle, which communicates with infravermian cystic compartment corresponding to the Blake pouch cyst, normal vermis/cerebellum, and hydrocephalus. |
| Mega cisterna magna | Large cisterna magna with normal cerebellum and fourth ventricle; no hydrocephalus (Fig. 16). |
| *Non-cystic defects* | |
| Joubert syndrome | Molar tooth sign, hypoplasia of vermis with dysplasia of vermian remnants, shortening of ponto-mesencephalic isthmus, and enlargement of fourth ventricle with upward displacement of fastigium. |
| Rhombencephalosynapsis | Partial or total agenesis of the cerebellar vermis with midline fusion of cerebellar hemispheres. |
| *Malformations of the cranial vault* | |
| Chiari malformations | Inferior displacement of the cerebellar tonsils through the foramen magnum.<br>Chiari I: Defect of mesoderm development with underdevelopment of occipital somites; cervical syringomyelia can be seen.<br>Chiari II: Defects of neuroectodermal development with additional inferior displacements of cerebellar vermis, medulla, and/or fourth ventricle; often associated with myelomeningocele (Fig. 17).<br>Chiari III: Like Chiari II malformations; associated with occipital/cervical encephalocele. |
| *Other* | |
| Arachnoid cyst | CSF isointense cyst with posterior fossa enlargement, mass effect (may include occipital bone scalloping), normal-appearing vermis/cerebellum, normal fourth ventricle, and hydrocephalus. |

Types of posterior fossa abnormalities, including structural differences unique to each abnormality.[73,74,76]

has been valuable in assessment of brain maturation and vascular lesions, as well as outcomes following PAIS or HII.[85–89] Though physiologic differences in regional blood volume in the developing brain must be considered in interpretation.[90] Limitations include low SNR, challenges with labeling efficiency, and arterial transit effects.[91,92]

b. *Phase contrast (PC)-MRI:* This technique measures the phase shift of mobile protons passing through magnetic field gradient pulses, which is related to flow velocity and, therefore, provides information on cerebral blood flow.[93] In neonates, PC-MRI has been used to evaluate cerebral blood flow properties, energy consumption, and oxygen metabolism.[94–97] Additionally, though PC-MRI has low

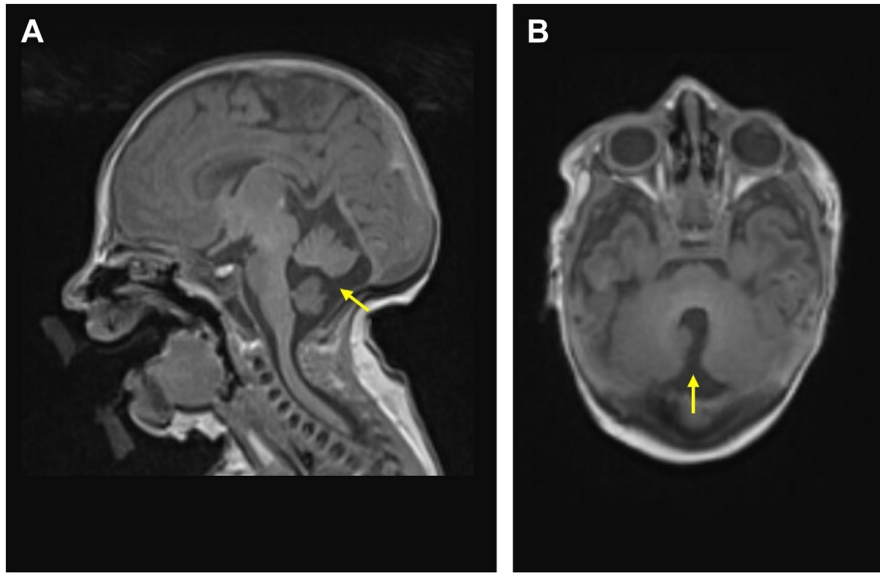


**Fig. 15.** Dandy–Walker malformation. Sagittal (*A*) and axial (*B*) T1WI in term neonate demonstrate vermian hypoplasia with wide communication of the subarachnoid space with the fourth ventricle (*arrows*), consistent with Dandy–Walker malformation.

SNR, it has faster acquisition times and complements ASL in its ability to assist with signal calibration.[93,94]

c. *Diffuse optical tomography (DOT):* DOT is a modality sensitive to oxyhemoglobin and deoxyhemoglobin concentration. This method uses an array of optodes applied to the scalp as sources of near-infrared light and detectors of its scatter.

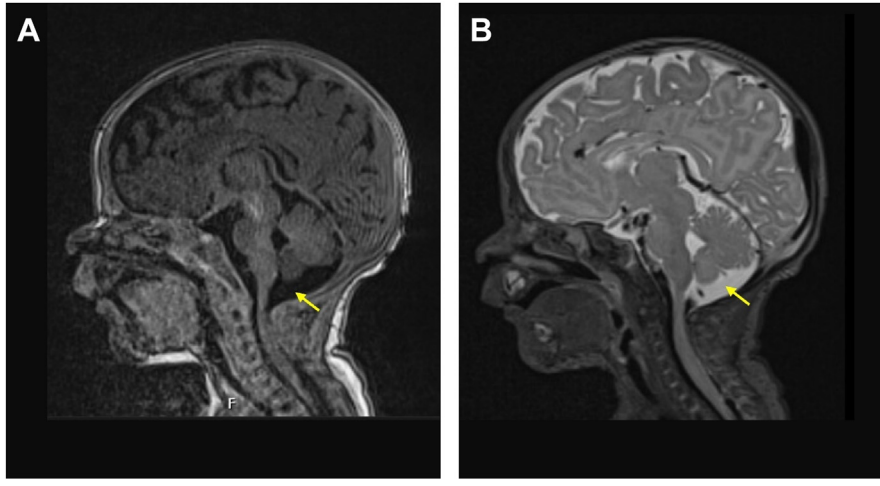


**Fig. 16.** Mega cisterna magna. Sagittal T1WI (*A*) and T2WI (*B*) in term neonate demonstrate enlargement of the basal cistern (cisterna magna) (*arrows*) with otherwise normal posterior fossa anatomy, consistent with mega cisterna magna.

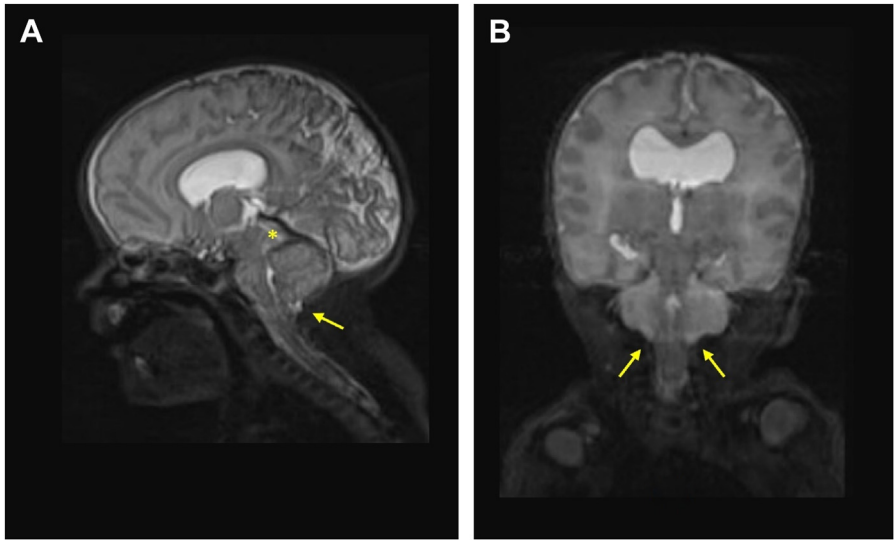


**Fig. 17.** Chiari II malformation. Sagittal (*A*) and coronal (*B*) T2WI in preterm neonate with a lumbar myelomeningocele demonstrate tectal beaking (*asterisk*) with crowding at foramen magnum and cerebellar tonsillar ectopia (*arrows*), consistent with Chiari II malformation.

**Table 5**
**Malformations of cortical development**

| | |
|---|---|
| Abnormal neuronal and glial proliferation | 1. Abnormal brain size<br>a. Microcephaly with normal to thin cortex, lissencephaly, or extensive polymicrogyria<br>b. Macrocephaly<br>2. Abnormal proliferation, nonneoplastic<br>a. Cortical hamartomas of tuberous sclerosis complex<br>b. FCD type II<br>c. Hemimegalencephaly<br>3. Abnormal proliferation, neoplastic<br>a. Dysembryoplastic neuroepithelial tumor<br>b. Ganglioma<br>c. Gangliocytoma |
| Abnormal neuronal migration | 1. Lissencephaly/pachygyria spectrum (Fig. 18)<br>2. Cobblestone complex/pial limiting membrane anomalies/congenital muscular dystrophy syndromes<br>3. Heterotopia<br>a. Subependymal (periventricular)<br>b. Subcortical<br>c. Marginal glioneuronal |
| Abnormal cortical organization | 1. Polymicrogyria and schizencephaly<br>2. FCD type I, FCD type III<br>3. Microdysgenesis |
| Malformations of cortical development, not otherwise specified | 1. Malformations secondary to inborn errors of metabolism<br>2. Other unclassified malformations |

Malformations of cortical development can be divided into abnormal neuronal and glial proliferation, abnormal neuronal migration, abnormal cortical organization, and miscellaneous subtypes.[72]
*Abbreviation:* FCD, focal cortical dysplasia.

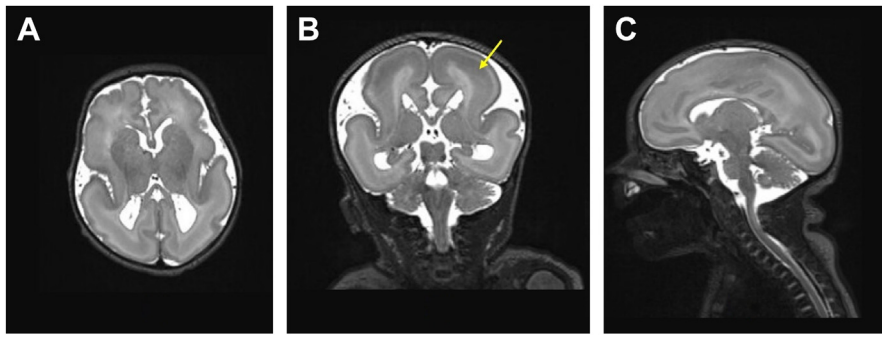


**Fig. 18.** Lissencephaly. T2WI in axial (*A*), coronal (*B*), and sagittal (*C*) planes in term infant demonstrate diffuse under gyration, subcortical band heterotopia (*arrow*), and a dysmorphic ventricular system, consistent with lissencephaly/subcortical band heterotopia spectrum.

Multichannel acquisition creates a 3 dimensional image showing regional variation in blood oxygenation.[98,99] DOT is portable and can be performed at the bedside. It has been used in neonates for functional mapping of motor, visual, and auditory stimuli, as well as in HII and PAIS.[99,100]

d. *Spinal imaging:* Spinal imaging is used for evaluation of spinal lesions and dysraphisms. Ultrasound is performed as first-line imaging; however, MR imaging can provide better tissue differentiation. Spin echo sequences are routinely used with the addition of short tau inversion recovery to improve detection of acute injury (eg, marrow edema).[101] For optimal spatial resolution, thin slices are ideal to discriminate between neural and nonneural components.[102]

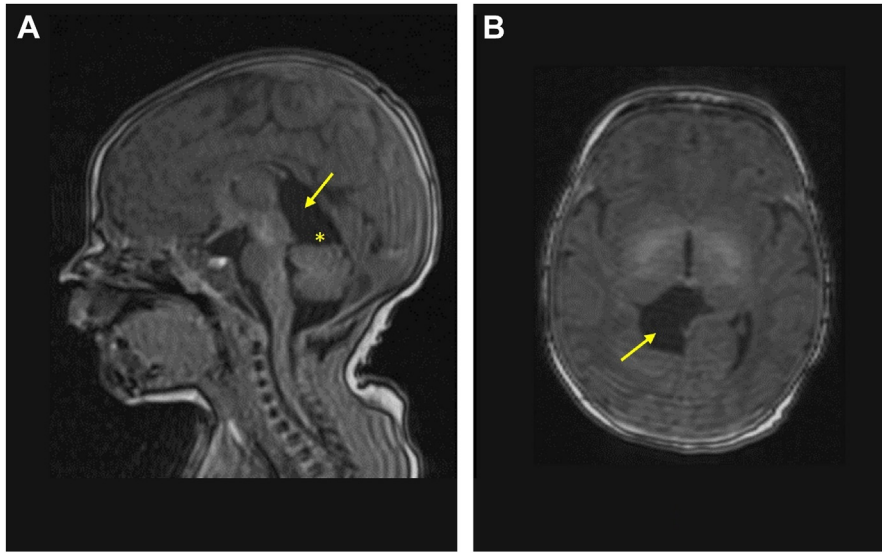


**Fig. 19.** Arachnoid cyst. Sagittal (*A*) and axial (*B*) T1WI in a term neonate demonstrate a cystic lesion in the right ambient/quadrigeminal plate cistern with mass effect on surrounding structures [note flattening of the superior portion of the cerebellar hemisphere (*asterisk*) in (*A*)], consistent with an arachnoid cyst (*arrows*).

**Table 6**
**Congenital infections**

| Congenital Infection | Calcifications | Ventricular Changes | Structural Changes | White Matter Changes | Miscellaneous |
|---|---|---|---|---|---|
| Syphilis | - | Ventriculomegaly | Diffuse atrophy | - | - |
| Toxoplasmosis | Extensive basal ganglia, thalami, cerebral cortex, periventricular | Hydranencephaly, progressive hydrocephalus | Macrocephaly, porencephaly | Myelination delay | Chorioretinitis |
| Rubella | Periventricular, basal ganglia | Hydranencephaly, ventriculomegaly | Microcephaly, PMG, diffuse or cerebellar atrophy | Myelination delay, multifocal WM injury | Microangiopathy, AIS |
| Cytomegalovirus (Fig. 20) | Periventricular, basal ganglia | Ventriculomegaly | Microcephaly, lissencephaly, schizencephaly, PMG, cerebellar hypoplasia, cisterna magna anomalies | Myelination delay, WM hypoplasia | Subependymal cysts |
| Herpes simplex virus | - | Hydranencephaly, ventriculomegaly | Microcephaly, porencephaly, multifocal cystic encephalomalacia | - | Deep GM and WM hemorrhage, microphthalmia, cataracts |
| Varicella zoster virus | - | Hydranencephaly, ventriculomegaly | Microcephaly, porencephaly, lissencephaly, PMG, cerebellar hypoplasia | - | Microphthalmia, chorioretinitis, cataracts, segmental spinal cord necrosis |
| SARS-COVID-19 virus | - | - | - | PVL | IVH, IPH, CVST, AIS |

Overview of intracranial findings with common congenital infections.

*Abbreviations:* AIS, arterial ischemic stroke; CVST, cerebral venous sinus thrombosis; GM, gray matter; IPH, intraparenchymal hemorrhage; IVH, intraventricular hemorrhage; PMG, polymicrogyria; PVL, periventricular leukomalacia; WM, white matter.

*Adapted from* Refs.[77,78]

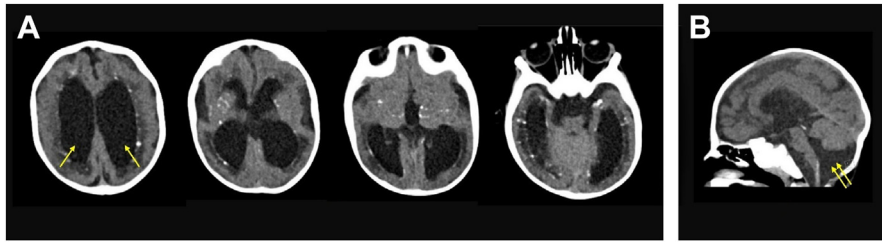


**Fig. 20.** Congenital CMV infection. Axial (*A*) and sagittal (*B*) CT images demonstrate marked dilation of ventricular system (*single arrows*) and cisterna magna (*double arrows*), periventricular and basal ganglia calcifications, and diffuse white matter hypoattenuation, consistent with congenital cytomegalovirus.

## FUTURE DIRECTIONS

Investigators continue to explore the utility of other MRI techniques in neonates to improve our understanding of brain growth and development across the antenatal and neonatal periods. Currently, these modalities remain limited in the clinical arena and are primarily used in research.

a. *Low field (LF) and ultralow field (ULF) MRI:* Current clinical imaging utilizes magnetic field strengths between 1.5 and 3 T. Higher magnet strengths improve SNR and image quality but are costly and require substantive infrastructure, limiting accessibility for critically ill patients and in resource-limited locations. Magnetic field strengths between 10 mT and 100 mT are classified as LF-MRI; magnetic field strengths less than 10 mT are classified as ULF-MRI.[103] Though imaging at these field strengths provides lower image resolution and limited sequence capabilities, it can be a practical and cost-effective means of assessing brain maturation, injury, and ventricular size in neonates.[103,104] Additionally, by virtue of its design, LF-MRI and ULF-MRI are portable and designed for use at the bedside, improving access, particularly for critically ill patients.

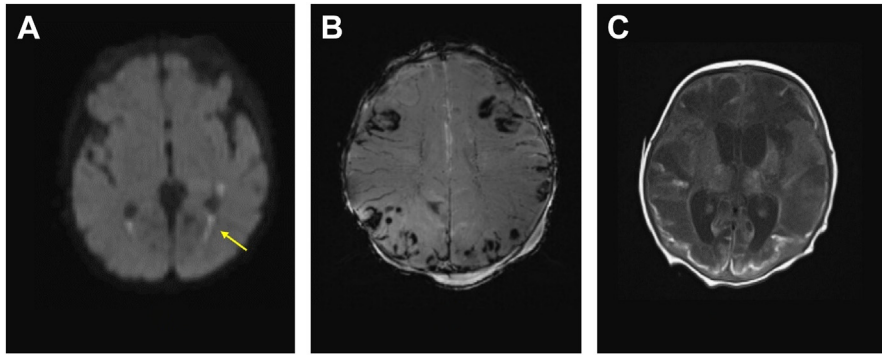


**Fig. 21.** Meningitis complications. Group B streptococcal meningitis can be associated with diverse types and severities of brain injury in neonates. Axial DWI (*A*) demonstrates increased signal within the lateral ventricles, consistent with ventriculitis (*arrow*). Axial SWI (*B*) demonstrates multifocal areas of intracranial hemorrhage (hypodense areas). Axial T1WI (*C*) demonstrates bihemispheric cystic encephalomalacia, cortical laminar necrosis (hyperintense signal), and ex vacuo dilatation of the lateral ventricles.

**Table 7**
**Neonatal neurometabolic disorders**

| Disorder | Diffusion-Weighted MRI | Conventional MRI | MRS |
|---|---|---|---|
| Neurotoxic metabolite accumulation | | | |
| Urea cycle disorders | Scalloped ribbon of restricted diffusion of affected cortex | ↓T1 and ↑T2 of deep GM structures, perirolandic, and insular cortex | ↑ glutamine, lactate doublet |
| Maple syrup urine disease (MSUD) | Restricted diffusion of affected WM ("MSUD edema") | ↑T2 myelinated structures (thalamus, CST, cerebellum, brainstem), myelination delay, white matter atrophy | BCKA (0.9 ppm) |
| Phenylketonuria | Restricted diffusion of affected WM | ↑T2 periventricular WM (posterior > anterior) | Phenylalanine (7.3 ppm) |
| Isovaleric acidemia | - | Intracranial hemorrhage, mild ↑T2 WM | ↑ lactate, alanine (1.5 ppm), isovalerate (0.9 ppm) |
| Propionic acidemia | Restricted diffusion of BG | ↑T2 putamen/caudate, myelination delay, lobar infarcts, cerebellar hemorrhage | ↓NAA and myo-inositol in BG, ↑ lactate |
| Methylmalonic acidemia | Restricted diffusion of GP | ↑T2 cerebellar WM, myelination delay | ↓NAA, ↑ lactate |
| Glutaric aciduria type I | Restricted diffusion of putamen + caudate | ↑T2 putamen/caudate, enlarged Sylvian fissures, large cavum septum pellucidum | ↑WM lactate |
| Energy production disorders | | | |
| Pyruvate dehydrogenase (PDH) complex deficiency | Restricted diffusion of BG and WM | ↑T2 BG and WM (posterior limb of internal capsule, occipital lobe, cerebellum).<br>Callosal dysgenesis, subependymal cysts, subcortical heterotopia, pachygyria, cortical atrophy, mega cisterna magna | Lactate doublet |
| Mitochondrial oxidative phosphorylation disorders | Complex I: Restricted diffusion of cortex, CST, or thalamus | Complex I: Diffuse cerebral atrophy, WM abnormalities (subcortical, midbrain, and brainstem)<br>Complex III and IV: ↑T2 dorsal midbrain and brainstem, could present as "Leigh pattern" of injury | Complex I: Lactate doublet in affected areas |

(*continued on next page*)

**Table 7**
**(*continued*)**

| Disorder | Diffusion-Weighted MRI | Conventional MRI | MRS |
|---|---|---|---|
| Sulfite oxidase deficiency | Restricted diffusion of affected regions can be diffuse | ↑T2 of caudate and WM; chronic changes of cystic degeneration, laminar necrosis, cortical atrophy | ↑ lactate, ↑ choline, ↑ glutamate + glutamine, ↓ NAA<br>Taurine (3.42 and 3.24 ppm), S-sulfocysteine (3.61 ppm), cysteine (2.92 and 2.97 ppm) |
| Disorders of biosynthesis and byproduct degradation | | | |
| Zellweger syndrome | - | Cortical malformations (PMG, pachygyria, PV heterotopia), subependymal cysts, diffuse ↑T2 of WM; hypomyelination, global atrophy | ↓NAA, ↑ lactate |
| Neonatal adrenoleukodystrophy | - | Diffuse WM abnormalities, hypomyelination | - |
| Congenital disorder of glycosylation | - | Preferential pontocerebellar hypoplasia | - |
| Smith-Lemli-Opitz syndrome | - | Ventriculomegaly, corpus callosal hypo/aplasia, frontal lobe hypoplasia, cerebellar hypoplasia, pituitary lipoma, abnormal myelination | ↑choline/NAA ratio, lipid peak (0.8–1.5 ppm) |
| Krabbe disease or globoid-cell leukodystrophy | Can have restricted diffusion of WM | Can be normal or have ↑T2 in lateral thalami, deep WM, and dentate nuclei, abnormal WM development, enlarged optic chiasm | ↑ myo-inositol, ↑ choline, ↓ NAA |
| Neurotransmitter defects and related disorders | | | |
| Nonketotic hyperglycinemia | Restricted diffusion of myelinated white matter | ↑T2 of myelinated WM and cortex, corpus callosal agenesis, vermian hypoplasia | Glycine (3.55 ppm) |
| Pyridoxine-dependent epilepsy | - | Can be normal or have corpus callosal dysgenesis, heterotopia, ventriculomegaly, PVL, cerebellar hypoplasia, mega cisterna magna | - |

| | | | |
|---|---|---|---|
| Creatine deficiency syndromes | - | Usually, normal | ↓/absent creatine (3.0 ppm) |
| Other | | | |
| Neonatal hypoglycemia (Fig. 22) | Restricted diffusion within affected area | Variable; ↑T2 within parietal/occipital region and subcortical WM, intracranial hemorrhage, infarcts, or deep GM abnormalities | Lactate peak |
| Kernicterus (Fig. 23) | - | Symmetric ↑T1 (acute) and ↑T2 (subacute/chronic) in bilateral GP | ↑ glutamate + glutamine, ↓ choline ↓ NAA |

Neurometabolic disorders that present in neonates range from nonspecific to pathognomonic findings helpful for clinical care and prognostication.

*Abbreviations:* BCKA, branched-chain keto acid; BG, basal ganglia; CST, corticospinal tract; GM, gray matter; GP, globus pallidus; NAA, N-acetyl aspartate; PMG, polymicrogyria; PVL, periventricular leukomalacia; Restricted diffusion, reduced water diffusion; WM, white matter.

*Adapted from* Refs.[80–83]

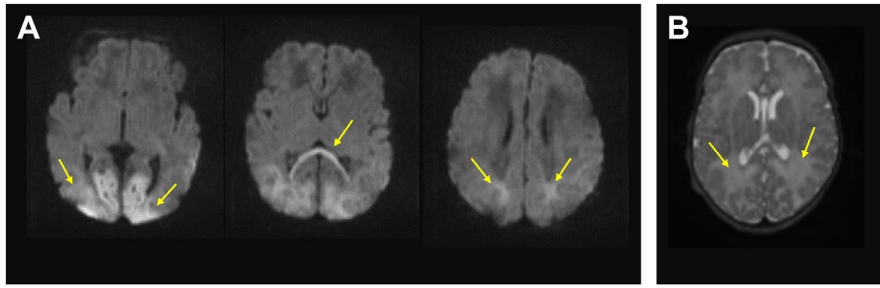


**Fig. 22.** Neonatal hypoglycemia. Axial DWI (*A*) in term infant at 4 days of life with profound hypoglycemia demonstrates symmetric areas of restricted diffusion (*arrows*) within the bilateral parieto-occipital lobes, splenium of the corpus callosum, and bilateral posterior optic radiations. Follow-up axial T2WI in the chronic period (*B*) demonstrate increased white matter signal (*arrows*) in the posterior fossa with atrophy of the cortical gray matter, consistent with evolution of occipital injury.

b. *Functional MRI (fMRI):* This modality is based on MRI's ability to detect changes in deoxyhemoglobin. In a variant of the approach used for SWI, MRI is sensitized to changes in blood flow and local deoxyhemoglobin.[105] Though task-based fMRI is infrequently used in infants, fMRI can detect spontaneous, infraslow (0.01-0.1 Hz) fluctuations in blood oxygenation dependent signal independent of task (eg, resting state fMRI), identifying networks demonstrating synchronous neuronal activity throughout the brain. A growing number of studies suggest early disruption of these networks may be an indicator of future neurologic impairment.[106–108]
c. *Diffusion tensor imaging (DTI):* The primary clinical use for diffusion imaging is early detection of injury. However, displacements of water also contain information on tissue microstructure, particularly with respect to the fact that water displacements

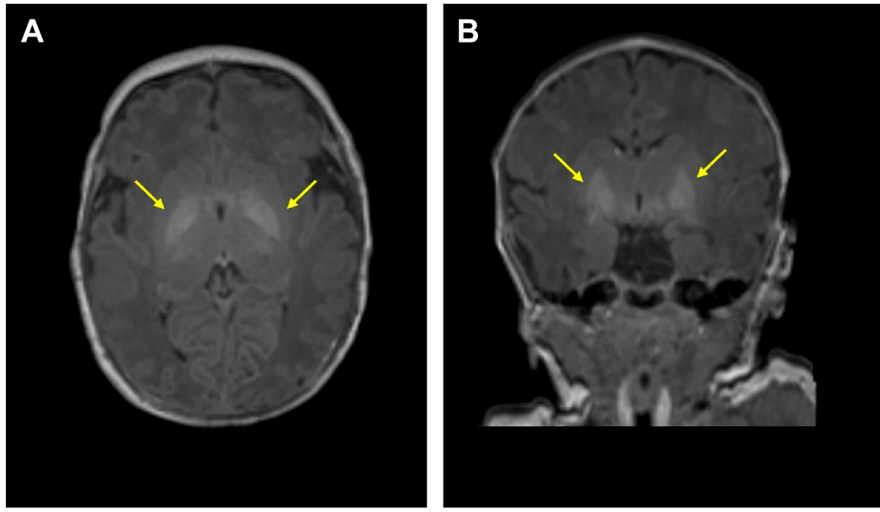


**Fig. 23.** Kernicterus. Axial (*A*) and coronal (*B*) T1WI in term infant at 7 days of life with bilirubin encephalopathy demonstrate symmetric, increased signal in the globus pallidi (*arrows*), consistent with acute phase of kernicterus.

in tissue are not necessarily the same in all orientations (diffusion anisotropy). For example, displacements are greater when measured parallel to a bundle of axons as compared to perpendicular to it, and this effect is strongly affected by the addition of myelin, which further reduces water displacements perpendicular to axons and thereby increases anisotropy. Thus, diffusion anisotropy is useful for characterizing myelination. Multiple studies employing DTI have shown an association between DTI measures and neurodevelopmental outcomes in preterm and term populations.[109–112]

## SUMMARY

Neuroimaging has proven useful for diagnosis, management, and prognostication for long-term neurodevelopmental risks in the neonatal population. Tissue characteristics are age dependent due to rapid tissue growth and maturation, and knowledge of this process is important to image interpretation. Ongoing research with improved computational techniques across modalities is an exciting direction for this field, enabling a refined understanding of brain maturation, development, and plasticity in this unique population.

***Best Practices***

***What is the current practice for neuroimaging evaluation of neonates?***

Neuroimaging evaluation is driven by local clinical guidelines. Head ultrasound is first line in neonates. It has screening and diagnostic utility and can be helpful in assessing the need for supplemental studies. When clinically safe to obtain, MRI remains the most informative among neuroimaging modalities in evaluating brain growth, maturation, congenital malformations, and injury and can be helpful in stratifying risk for long-term neurodevelopmental differences with longitudinal clinical evaluation.

***Best practice/guideline/care path objective(s):***

Pearls/pitfalls at the point-of-care:

- MRI scans can be performed without sedation with good success in neonates if feeding and swaddling techniques are applied.
- Timing of neuroimaging is important for accurate assessment of pathology.
- Collaboration with the neuroradiology teams prior to scans can be helpful in obtaining necessary sequences in complex cases.

## DISCLOSURES

The authors have nothing to disclose.

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# Advances in Genetic Testing of Neurologically Abnormal Neonates in the Neonatal Intensive Care Unit

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**KEYWORDS**

• Neonatal neurology • Neurocritical care • Rapid genome sequencing

**KEY POINTS**

- Genome sequencing is increasingly available with rapid turnaround time.
- Rapid genome sequencing is the recommended first line for most unexplained neurologic presentations in the neonatal intensive care unit.
- Accurate and updated phenotyping is essential for meaningful interpretation of genetic testing results.
- Concurrent biochemical testing should be ordered with molecular testing, based on clinical suspicion, to avoid delays in diagnosis of treatable disorders.
- When genome sequencing is nondiagnostic but suspicion for genetic etiology remains, consider conditions and mechanisms not covered by genome sequencing and/or reinterpreting genomic data at regular intervals.

## INTRODUCTION

By definition, rare diseases affect a small number of individuals (<200,000 Americans or <1/2000 in any World Health Organization region); yet, with more than 10,000 rare diseases, the cumulative burden is significant.[1] Worldwide, approximately 300 million

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| Abbreviations | |
|---|---|
| ACP | acylcarnitine profile |
| CCHS | central congenital hypoventilation syndrome |
| CDG | congenital disorders of glycosylation |
| CMAs | chromosomal microarrays |
| ES | exome sequencing |
| FAOD | fatty acid oxidation disorders |
| FISH | fluorescent in situ hybridization |
| GS | genome sequencing |
| HIE | hypoxic ischemic encephalopathy |
| IEM | inborn errors of metabolism |
| IVH | intraventricular hemorrhage |
| LP | lumbar punctures |
| MOCD-A | molybdenum cofactor deficiency type A |
| NBS | newborn screening |
| NE | neonatal encephalopathy |
| NGS | next-generation sequencing |
| NICU | neonatal intensive care unit |
| PDE | pyridoxine-dependent epilepsy |
| rES | rapid exome sequencing |
| rGS | rapid genome sequencing |
| SMA | spinal muscular atrophy |
| TAT | turnaround time |
| UCD | urea cycle defects |

people live with rare diseases. Around 80% of rare diseases have a genetic cause, most present in childhood, and very few have approved treatments. The average time to an accurate diagnosis is 4.8 years and about 30% of children with rare diseases die before age 5 years.[2] Ninety percent of rare childhood disorders have major neurologic components.[3] Achieving precise and early diagnosis poses challenges because of the low likelihood of any given disease and poor knowledge among patients and health care workers of typical signs and symptoms.

Specific to the neonatal intensive care unit (NICU), signs and symptoms are often nonspecific with neurologic dysfunction potentially representing infection, structural central nervous system lesions, functional defects like channelopathies, neuromuscular disorders, neurometabolic disorders, intoxicating inborn errors of metabolism (IEM), hypoxic ischemic encephalopathy (HIE), hypoglycemia or electrolyte disturbances, and withdrawal syndromes, amongst other etiologies.

Recently, substantial diagnostic advances have been made using exome and genome sequencing (ES and GS), not only because of increased analytical sensitivity[4] but also because of improved turnaround time (TAT).[5] Because of this, early and aggressive rapid GS (rGS) has become an integral part of the care of the neurologically abnormal neonate in well-resourced settings.[6] This, in turn, has changed the roles of previous diagnostic strategies (other cytogenetic and molecular genetic tests, biochemical testing, and muscle biopsy) for rare genetic diseases in the NICU. In this article, we will first discuss the relative merits of different genetic testing approaches in contemporary neonatal neurocritical care with an emphasis on identifying approaches that inform care and expedite access to targeted therapies. We then discuss "*can't miss*" treatable disorders and the limitations of relying on newborn screening (NBS) to identify treatable disorders in this population. Finally, we provide practical guidance on the genetic evaluation of common neurologic presentations in the NICU based on published evidence, when available, and our local practices developed through consensus between experts in neonatology, neurology, medical and

biochemical genetics, including specific expertise in neonatal genomics and neonatal neurology. As an aid to the reader, a list of abbreviations used is provided in the Abbreviations box.

## EVOLVING TECHNOLOGIES

### *Cytogenetic and Molecular Genetic Testing*

Almost all clinicians are familiar with classical karyotyping and fluorescent in situ hybridization (FISH), while neurologists and neonatologists are typically also quite familiar with chromosomal microarrays (CMAs) and even next-generation sequencing (NGS). However, many nongeneticists are often unaware of the specific limitations or technical properties of these tests. These knowledge gaps are worse when considering ES/GS because over half of practicing neonatologists graduated from medical school before 2001 and so received little or no formal education on contemporary genetic testing methods.[7] We assume the reader has a foundational knowledge in molecular genetics and the central dogma of molecular biology. Those in need of a clinically oriented refresher are directed to Thompson & Thompson[8] (**Table 1**).

A high-level overview of the cytogenetic and molecular genetic testing modalities typically available in Level III and IV NICUs in the United States, as well as relative strengths and weaknesses, are highlighted in **Table 2**. Rather than review these in chronologic order of development and availability, given the high burden of genetic disease in this population and the central role of correct diagnosis in optimal management, we begin with rGS and then discuss the complementary roles of other testing modalities.

Readers are referred to the Medical Genome Initiative's work reviewing technical and analytical aspects of GS.[4,9] In practice, there are few, if any, differences between GS and rGS in terms of what variants are detectable or reported. The main difference is the time frame in which results are ascertained and communicated.[5,6] While a key

**Table 1**
**Resources**

| | |
|---|---|
| Thompson & Thompson | ISBN: 9780323547628 |
| Recommended textbook for readers seeking foundational knowledge of genetics and genomics in clinical medicine | |
| UNIQUE | https://Rarechromo.org |
| Authoritative summaries of clinical characteristics and patient-reported outcomes for many rare chromosomal deletions and duplications | |
| *GeneReviews* | https://genereviews.org |
| Expert prepared summaries of diagnosis, natural history, and management of thousands of rare genetic conditions. Mostly represents single gene disorders, in contrast to UNIQUE. Also includes disease agnostic "Resource Materials" to understand technical limitations of assays | |
| ACMG ACT Sheets | https://www.acmg.net/ACMG/Medical-Genetics-PracticeResources/ACT_Sheets_and_Algorithms.aspx |
| Information about conditions screened by state newborn screening programs and algorithms for follow-up of abnormal screens | |
| Baby's First Test | https://www.babysfirsttest.org/ |
| Resources for parents and clinicians about newborn screening with links out to state specific information and resources | |
| Knowledge Nuggets | https://nccrcg.org/knowledge-nugget-series/ |
| Five to 10 min videos on selected conditions detected by state newborn screening programs. Intended to complement but not replace ACMG ACT Sheets | |

**Table 2**
**Molecular and cytogenetic testing modalities in neonatal intensive care unit**

| Test | Scale of Variants Detected | Turn Around Time | Primary Use Case in Neurologically Abnormal Neonate | Comments & Special Consideration |
|---|---|---|---|---|
| Karyotype | Mb+ | 2–3 d | 1. Suspected aneuploidy<br>2. Suspected structural rearrangement | Limited diagnostic utility as a first-line test outside of suspected aneuploidy. |
| Chromosomal microarray | Kb to Mb | 10–14 d | Detection of copy number variants (CNVs)when detection by next-generation sequencing (NGS) unavailable | The diagnostic yield of microarray in neonatal intensive care unit (NICU) (all comers) is ~10% |
| Fluorescent in situ hybridization (FISH) | Kb to Mb | Days to week | Suspected aneuploidy when rapid karyotype unavailable. | No need to order FISH after normal microarray. |
| NGS panel | 1 to ~1000 bp, >10 kb | 2–6 wk | 1. Strongly suspected phenotype, patient can wait a week.<br>2. Genes exome sequencing (ES)/ genome sequencing (GS) cannot resolve. | Panel content and performance is highly variable and should be reviewed with a geneticist or genetic counselor prior to use in place of ES/GS.<br>Large panels often produce VUSs (variants of uncertain significance) requiring follow-up parental studies. |
| Rapid exome sequencing | 1 to ~1000 bp, multiexon CNVs | 1–2 wk | Rapid genome sequencing (rGS) not available | Limited to analysis of coding and flanking regions.<br>Limited resolution of CNVs.<br>Limited in regions of homology, repeats.<br>Fewer VUS than large panels.<br>Best with parental samples. |
| rGS | ~Scale invariant | 3 d–2 wk | Preferred first- line genetic test | Assay-specific limitation related to homology repeats may exist.<br>Fewer VUS than large panels.<br>Best with parental samples. |

technical benefit of GS over ES is better resolution of copy number and structural variation,[4] clinicians involved in selecting a laboratory for their hospital should understand the limits of resolution claimed by the laboratory in question. Furthermore, while structural variation and repeat expansion disorders are theoretically assayable, laboratories differ greatly in their claims in these rapidly evolving areas. A given laboratory's GS assay may or may not include mitochondrial DNA, though we note that the vast majority of mitochondrial disease presenting in the NICU is encoded by the nuclear genome,[10] so the significance of this when choosing a testing laboratory in this setting is of unclear importance. One should also note that neuro-genetic disorders presenting in the NICU may be due to mosaicism.[11] While technical advances have improved our ability to distinguish low-level mosaicism from sequencing artifact, the typical depth of sequencing in genome sequencing (30–60 $\times$ for most clinically available assays) limits what can be done computationally.[12] Additionally, our discussion here is limited to short-read genome sequencing. While long read sequencing is increasingly clinically available, rapid turnaround options are only available in research settings.[13] Finally, while our focus here is on the initial genetic evaluation of the neurologically abnormal neonate in a NICU, a substantial fraction of such patients will have nondiagnostic GS and may benefit from periodic reanalysis[14] (**Fig. 1**).

At the outset, it is important to acknowledge that there is not a standard definition of how quickly GS must be available before it is considered rGS, though lab TATs of 7 to 10 days or less are commonly cited and advertised. Similarly, some commercial labs may advertise GS with shorter TATs as "ultra-rapid" (3 day TAT). Clinicians should recognize that these are largely marketing labels and that they focus on time from lab receipt of samples to issuing a preliminary report. Multiple studies have demonstrated that it takes many days after admission or onset of symptoms, sometimes almost as many as the sequencing itself, to get samples to the reference lab.[15–17] Reasons for this include delayed recognition of the value of GS to a child's care, delays in connecting geneticists and genetic counselors to the family to provide pretest counseling and obtain consent for testing, challenges collecting samples from parents who may not yet be present at the NICU, and finally logistical barriers related to shipping samples across the country. Thus, centers should think of genetic testing in neonatal neurocritical care as an integrated service with considerations far beyond picking the "best" lab. We highlight the key stakeholders in such an integrated service and the expertise they bring in **Box 1**. We underscore the importance of providing the laboratory with an accurate phenotype to best inform variant interpretation and call out the role of parents as partners in the provision of genomic medicine services.

Allowing for these caveats, multiple studies have shown high clinical and personal utility of GS if offered with rapid TAT, early in an intensive care unit course.[6] Fewer studies have specifically looked at neurologic presentations in NICUs, but these benefits have been shown in selected neurologically abnormal neonates[18] as well as those with new-onset infantile epilepsies.[19,20]

Due to economies of scale, many laboratories are phasing out ES in favor of GS. However, because ES covers only 2% of the genome, rapid ES (rES) may be available at lower cost than rGS. In our experience, reimbursement within the NICU is no better (and sometimes worse) for rES compared to rGS.[21] Given the economic realities and the balance of many benefits against minimal limitations described earlier, we recommend that programs implementing rapid genetic testing start with rGS when possible.

With the fastest rGS options returning results in 3 to 5 days, there are few testing options with shorter TATs. Cytogenetics remains the exception. Given the widespread availability of stat karyotype and/or FISH analysis for common aneuploidies, when aneuploidy is suspected, cytogenetics should be used in place of rGS.

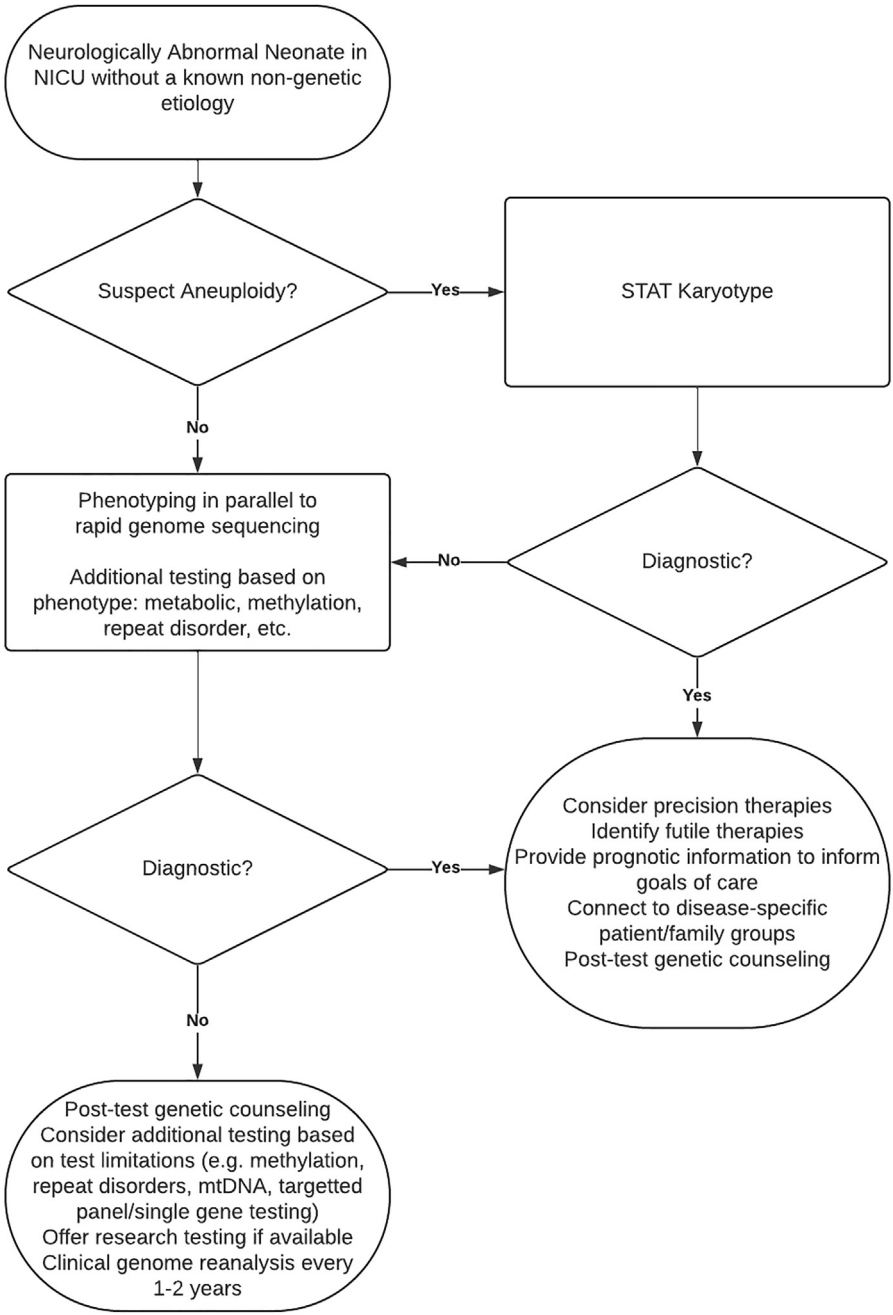


**Fig. 1.** Suggested approach to genetic evaluation of the neurologically abnormal neonate in neonatal intensive care unit.

CMA for genome-wide, sub-microscopic copy number variation revolutionized genetic testing in the NICU when first made available. However, particularly in the neurologically abnormal but nondysmorphic neonate, its utility is increasingly limited. Commercially available rGS has copy number resolution far exceeding that of

**Box 1**
**Stakeholder contributions to an effective neonatal intensive care unit neuro-genomics program**

Parents
- Provide accurate family & pregnancy history
- Provide parental samples for rapid genome sequencing (rGS) in a timely manner

Medical Geneticist & Genetic Counselor
- Technical understanding of test limitations
- Psychosocial expertise in pretest counseling
- Identifies potentially treatable disorders
- Phenotyping (dysmorphology)

Neonatologist
- Contextualizes neurogenetic concerns within the provision of critical care services to other stakeholders
- Phenotyping (Distinguishes explained versus unexplained features of critical illness)

Neurologist
- Characterizes nature and degree of neurologic dysfunction
- Identifies potential treatment implications of genetic testing
- Phenotyping (Selection and interpretation of diagnostics such as MRI and electroencephalography)

CMAs. The main potential advantage of CMA over genome sequencing is highly technical and relates to resolution of copy number variants (CNVs) in regions of homology[22] [see GeneReviews (see **Table 1**) for a list of such loci and a fuller description of the issue].

Before the advent of rGS, NGS panels were a mainstay of genetic testing in NICUs. Such panels suffer from 2 key disadvantages which render them less efficacious than rGS. The first is speed. The fastest panels can theoretically produce results in around 2 weeks. Additionally, most panels do not concurrently sequence parents which is typical of GS (when parents are available). While this reduces costs, it means panels frequently require follow-up testing when results are uncertain.[23] Second, the content of a panel is typically fixed in advance and updated idiosyncratically. It is very easy to identify the correct phenotype to test for with a panel and still get a negative result because the diagnostic gene was not on the panel.[24] Some panels may be designed in ways that provide distinct advantages over rGS. Specifically, they may employ much higher sequencing depth, allowing improved resolution of mosaicism and/or CNVs. They may also represent a bundle of assays combining sequencing with a dedicated repeat disorder assay (to cover myotonic dystrophy, for example). Panels with these advantages invariably have TATs on the order of weeks or months, rendering them less useful as first-line genetic tests in the NICU. Instead, their new role is as a second-line test when rGS or metabolic testing suggests a diagnosis that is not molecularly confirmed or as an adjunct obtained in parallel to, but not instead of, rGS (see **Fig. 1**).

### *Metabolic Testing*

In the setting of neonatal neurologic disorders, biochemical testing is recommended to rule out common IEMs. While individually rare, IEMs are collectively a common cause of disease.[25] Neurologic presentations are common. When considering IEMs, it is helpful to consider readily available testing to be directed by the NICU in addition to specialized metabolic testing. Specific biochemical tests are described in **Table 3**. The purpose of the readily available tests is to identify neonates at risk for IEMs and

**Table 3**
**Initial biochemical testing for suspected conditions in a neurologically abnormal neonate**

| Suspected Condition | Common Disorders | Presentation | Test |
|---|---|---|---|
| Congenital disorders of glycosylation (CDG) | Phosphomannomutase 2 (PMM2)-CDG<br>glycosylphosphatidylinositol (GPI) anchor disorders (eg, phosphatidylinositol glycan anchor [PIGA]-CDG)<br>mannose phosphate isomerase (MPI)-CDG | *High variable:*<br>Seizures<br>Congenital anomalies<br>Multisystemic | Transferrins<br>N-glycan profile |
| Peroxisomal disorder | Zellweger Spectrum | Atypical features<br>Cholestasis<br>Encephalopathy or seizures | Very long chain fatty acids |
| Urea cycle defects | Ornithine transcarbamylase deficiency<br>Citrullinemia N-acetylglutamate synthase (NAGS) deficiency | Encephalopathy<br>Respiratory alkalosis | Plasma amino acids (PAA)<br>Orotic acid (U)<br>Urine organic acids (UOA) (U) |
| Aminoacidopathy | Maple syrup urine disease | Encephalopathy | PAA<br>UOA |
| Organic acidemia | Propionic acidemia<br>Methylmalonic acidemia<br>Isovaleric acidemia | Seizures or encephalopathy<br>Anion gap metabolic acidosis<br>Ketosis | PAA<br>Acylcarnitine profile (ACP)<br>UOA (U) |
| Fatty acid oxidation disorders | Long-chain hydroxyacyl-CoA dehydrogrenase deficiency<br>Carnitine palmitoyltransferase 2 deficiency | Seizures<br>Hypoketosis<br>Hypoglycemia<br>Hepatomegaly possible | ACP<br>UOA (U) |
| Mitochondrial | - | Seizures or encephalopathy<br>Elevated lactate<br>Multisystemic | Lactate<br>ACP<br>UOA (U)<br>PAA |
| Lysosomal storage disorder | Mucopolysaccharidosis (MPS) type 1<br>Pompe<br>Krabbe | Disease-specific presentations | *Disorder Dependent:*<br>Glycosaminoglycans for MPS (B/U)<br>Hex4 for Pompe (U)<br>Psychosine for Krabbe<br>Enzyme analysis |
| Purine and pyrimidine disorders | Molybdenum cofactor deficiency type A (MOCD-A)<br>Sulfite oxidase deficiency | Encephalopathy<br>Lens ectopia<br>Atypical facial features | Homocysteine<br>Uric acid (B/U)<br>Purine and pyrimidine panel (U) |

(U) denotes tests on urine; (B/U) denotes tests run on either blood or urine; tests listed run on blood unless otherwise indicated.

provide some direction for more specialized testing. Early diagnosis in many IEMs can improve long-term outcomes due to initiation of disease-targeted management.

Initial testing for suspected IEMs includes a combination of general and specialized testing. Of widely available labs, the most useful include blood gases, basic chemistries with or without hepatic function, ammonia, lactate, glucose, total homocysteine, and uric acid. Total homocysteine may not be available in all facilities. These tests can help guide follow-up biochemical and molecular testing. For example, hyperammonemia may suggest urea cycle defects (UCD), organic acidemias (OA), or fatty acid oxidation disorders (FAOD) depending on presence of ketones or acidosis.

The specialized biochemical tests needed vary by IEM and some have no specific biomarkers available. Therefore, testing recommendations are based on a patient's specific presentation. IEMs leading to neonatal neurologic disease fall into several categories including intoxicating syndromes, congenital disorders of glycosylation (CDG), storage disorders, and peroxisomal disorders. Despite the ubiquity of the lactate:pyruvate ratio in the literature, we do not recommend routinely checking pyruvate, even when lactate is elevated, due to prolonged TAT and unreliable results. In limited circumstances, we recommend sending a sample to a laboratory which will specifically report the ratio from a single sample.

Intoxicating syndromes and storage disease are caused by abnormal buildup of toxic metabolites (eg, hyperammonemia) or accumulation of normal metabolites (eg, leucine in maple syrup urine disease [MSUD]). Intoxicating disorders include UCDs, OAs, amino acidopathies, and disorders of purine and pyrimidine metabolism. Lysosomal storage disorders (LSDs) may present with neonatal symptoms. Peroxisomal disorders disrupt very long chain fat metabolism which frequently causes neonatal neurologic symptoms. Similarly, CDGs disrupt glycosylation of proteins leading to abnormal localization or dysfunction of multiple proteins.

Intoxicating disorders are amongst the most common IEMs with neonatal neurologic presentations. Examples include MSUD, UCDs, and OAs. Many are screened at birth in the United States, but symptoms may precede NBS results and often mimic sepsis. Common metabolic testing includes plasma amino acids, plasma acylcarnitine profile (ACP), and urine organic acids. These tests can identify disorders involving amino acid metabolism, OAs, UCDs, and FAOD. If UCD is suspected, urine orotic acid should also be obtained. Free and total carnitine analysis should accompany an ACP for interpretation but may need a separate order. In specific cases, urine and cerebrospinal fluid amino acid analysis can be clinically indicated. Disorders of purines and pyrimidines often present as a mimic of HIE and have specific biomarkers requiring additional testing on urine. If these are being considered, plasma uric acid and total homocysteine may be used as initial screening tests.

Many of the greater than 150 CDGs affect the central and/or peripheral nervous system; each is attributable to different single gene defect leading to a different biochemical defect.[26] There are limitations of biochemical testing for CDGs. CDG testing includes serum transferrin or total N-linked glycans, which can identify some N-linked and O-linked CDGs. For many CDGs, gene sequencing is required for diagnosis as they cannot be identified with biochemical profiles. Additionally, transferrins and N-linked glycan studies indicate patterns of glycosylation which may encompass more than 1 disorder. For this reason, even when CDGs are considered, NGS is advised.

In contrast to the nonspecific patterns seen in CDGs, storage disorders frequently have specific biomarkers (see **Table 3**), like glycosaminoglycans in mucopolysaccharidoses or psychosine in Krabbe disease. Enzyme analysis is available either as a stand-alone diagnostic, or, more likely, as an adjunct to NGS. In the United States, an increasing number of storage disorders are being included on NBS. There are a

limited number of LSDs with neonatal presentations, including Pompe disease, Krabbe disease presenting as encephalopathy, and severe Hurler syndrome which may present with neonatal hypotonia.

Peroxisomal disorders with neonatal presentations include peroxisome biogenesis disorders and acyl-CoA oxidase deficiency. Symptoms of these disorders (seizures, dysmorphic features, abnormal central nervous system imaging, and/or renal cysts) are caused by abnormal buildup of very long chain fatty acids (VLCFAs) and disrupted metabolism of key metabolites, such as plasmalogens and bile acids. Testing includes VLCFAs, plasmalogens, bile acids, and pristanic and phytanic acid. Diagnosis is made based on specific pattern present, often complemented by NGS.

### *Practical approach to metabolic testing*

Technologic advances have altered the way IEMs are diagnosed. In the past, the initial workup for suspected IEMs was phenotypic-driven biochemical testing. Molecular testing was limited to genes related to a patient's biochemical profile. NGS has lowered costs, reduced TATs, and increased availability, allowing concurrent molecular and biochemical testing. In centers with rGS, sequencing TAT may be equivalent to or faster than biochemical testing. For critically ill patients, a suspected or confirmed molecular diagnosis of an IEM may be made prior to biochemical markers being available. In these cases, metabolic testing serves to clarify or support molecular findings.

However, the importance of biochemical testing should not be dismissed. In many disorders, there are individuals with biochemical features who lack an identifiable molecular variant in known genes. This discrepancy may be due to unidentified genes in a specific pathway or limitations of the testing modality. Additionally, biochemical testing can confirm a diagnosis when sequencing reveals a variant of uncertain significance. Thus, in all clinical cases where an IEM is suspected, metabolic testing should be obtained regardless of molecular testing. Further testing may be obtained afterward based on these results. In centers without rapid ES/GS, metabolic testing should be a first-line approach in cases of suspected IEMs. Molecular testing in such centers may include large commercial panels or targeted sequencing based on biochemical results.

Historically, lumbar punctures (LP) were frequently recommended in the evaluation of neonatal neurologic diseases, from the evaluation of pipecolic acid for pyridoxine-dependent epilepsy (PDE) to neurotransmitters in neonatal movement disorders. With the advent of rGS, this practice has fallen by the wayside and LP is not commonly used to evaluate genetic etiologies, especially in cases where such testing has longer TAT than rGS. Rather, LP may be used to confirm or refute certain conditions when there is diagnostic uncertainty such as by looking for elevated glycine levels in possible nonketotic hyperglycinemia or hypoglycorrhachia in suspected glucose transporter type I deficiency.

### *Newborn screening*

NBS is a public health program initiated in the 1960s in the United States. In the United States, a recommended panel of disorders for testing is available for state programs. However, state and national programs continue to vary widely around the world. Given the variability of programs, all physicians interfacing with NBS should have a good understanding of their state or country's NBS program. We have included additional resources in **Table 3** for reference. The American College of Medical Genetics and Genomics (ACMG) provides references on next steps for positive results on NBS called ACTion (ACT) Sheets (see **Table 3**).

Beyond knowing the disorders screened for by their local NBS program, physicians should have a basic understanding of NBS limitations. Firstly, NBS results are not

diagnostic—follow-up testing is required to confirm a finding. Many variables can impact a screening result leading to false positives or negatives. Result interpretation and follow-up should be decided with assistance from a local expert or NBS program. In critical care settings, clinicians must understand that symptoms can precede NBS results. If an IEM is suspected, diagnostic metabolic testing should be initiated regardless of screening status.

## CANNOT MISS/TREATABLE DIAGNOSES

PDE and molybdenum cofactor deficiency type A (MOCD-A) will typically present with seizures in the first month of life, frequently in the first days (**Table 4**). If these disorders are even considered, genetic testing should be selected to include these conditions. Early presentations may be suggestive of HIE without clear inciting event.[27] Specific biochemical patterns are recognizable in MOCD-A with reduced plasma uric acid and homocysteine levels, as well as a characteristic pattern on urine purine and pyrimidine analysis. Treatment of MOCD-A was approved by the US Food and Drug Administration in 2021 with *fosdenopterin*, a substrate replacement therapy.[28] For PDE, no specific markers are available although alpha-aminoadipic acid may be elevated. This can also be seen in MOCD-A and sulfite oxidase deficiency. If PDE is being considered, an empiric trial of pyridoxine may be used while awaiting molecular testing.[29] Treatment with lifelong pyridoxine is required for seizure control in PDE with or without use of lysine-restricted diet and arginine supplementation.[29]

The final group of disorders to not miss are the intoxication syndromes. This term encompasses a variety of different IEMs. Specific testing varies by disorder. Many have general lab abnormalities such as metabolic anion gap acidosis, hyperlactatemia, hyperammonemia, or ketoacidosis. Infants presenting with unexplained, acute neurologic symptoms should be assessed with general chemistries, blood gas, ammonia, glucose, lactate, and ketones followed by basic biochemical studies, including plasma amino acids and acylcarnitine profile with free and total carnitine and urine organic and orotic acids. Biochemical studies can be tailored to suggested disease states (eg, urine orotic acid in UCD). rGS should be performed in conjunction to help with interpretation and reduce time to treatment. In the United States, many of these conditions are included in state NBS programs, but symptoms often occur before results are available. Importantly, many of these intoxicating disorders are responsive to nutritional management[30] and/or ammonia scavenging therapies[31] such that life-saving interventions can be started empirically while diagnostic testing is in process.

## GENETIC BASIS OF COMMON NEONATAL PRESENTATIONS

Despite the evidence generally supporting early and aggressive use of GS for neonatal neurologic presentations, implementation studies and our own experience suggest that delayed recognition of the role of genetic testing in neonatal neurologic presentations is common.[17] These delays are greatest when the presentation is a common neonatal presentation where there may be a lack of awareness of the growing body of literature supporting a contribution of monogenic etiologies to the burden of disease. Here we describe the current research regarding the presence of underlying genetic etiologies for common neurologic presentations in the NICU.

### *Neonatal seizures*

While many seizures are considered acute symptomatic reflecting acquired brain injury, a significant minority will represent neonatal-onset epilepsy.[32] These neonatal epilepsies can be broadly categorized as epileptic encephalopathies, benign familial

**Table 4**
**Treatable/cannot miss diagnoses**

| Presentation | Disorders | Clinical Clues | Testing | Imaging | Treatment | Guideline-s (Reference Number) |
|---|---|---|---|---|---|---|
| Central hypotonia | Infantile-onset Pompe disease | Cardiomyopathy (rare <4 mo)<br>Weakness | Enzyme analysis creatine kinase (CK)<br>Urine Hex4<br>Molecular (acid alpha glucosidase, *GAA*) | Echo | Lumizyme | Kishnani et al,[48] 2006 |
| | Spinal muscular atrophy | Absent reflexes, fasciculations, bell-shaped chest | Molecular (survival motor neuron 1, *SMN1*) | | Nusinersen<br>Zolgensma<br>Risdiplam | Schroth et al,[50] 2024; Mercuri et al,[51] 2018 |
| Seizures | *KCNQ2/3* | Tonic seizures | Molecular | | Na channel blockers | Kuersten et al,[33] 2020 |
| | Pyridoxine dependent Epilepsy | Refractory seizures and progression to burst suppression pattern on electroencephalography; movement disorder | Molecular (aldehyde dehydrogenase 7 family, member A1; *ALDH7A1*)<br>Urine alpha-aminoadipic acid (nonspecific) | MRI Brain | Pyridoxine<br>Lysine restriction<br>Arginine | Coughlin et al,[29] 2021 |
| Neonatal encephalopathy | MOCD-A | Seizures<br>Lens ectopia<br>Atypical facial features | Uric acid and Homocysteine (blood), total<br>Purine and pyrimidine panel (urine)<br>Molecular (molybdenum cofactor synthesis gene 1, *MOCS1*) | MRI brain with signal changes in caudate, putamen, and globus pallidus | Fosdenopterin | Schwahn et al,[28] 2024 |

All testing is on blood unless otherwise specified.

neonatal encephalopathies, or secondary to congenital brain malformations. Clinically, infants with neonatal epilepsy are more likely to present with tonic or myoclonic seizures than the typical clonic or electrographic seizures seen in neonates with acute provoked seizures.[2] Genetic etiologies are frequently identified when testing is sent. Amongst neonatal epileptic encephalopathies, pathogenic variants are identified in more than 80% of tested infants, most commonly in *KCNQ2* followed by *SCN2A*.[32] Neonates with benign neonatal familial epilepsy were less likely to undergo testing, but of those tested, two-third had identified pathogenic variants. In infants with brain malformations, diagnostic yield is lower, but still significant, at ~25%.[32] In total, more than 75% of infants with neonatal epilepsies have identifiable genetic etiologies.[32]

Specific genetic etiologies may suggest ideal medication choices such as the use of the sodium channel blocking antiseizure medications in channelopathies.[33] Conversely, there is reasonable evidence to suggest that phenobarbital, the widely used first treatment of choice, is ineffective in genetic epilepsies.[34] Both observations are important, as rapid, effective treatment potentially mitigates the harmful effects of seizures on the still developing brain.[34,35] Additionally, knowing a particular etiology can guide discussions regarding prognosis and goals of care and link families to online support communities. As technology advances, more specific targeted treatments such as gene therapies are likely to become available.

### *Hypoxic ischemic encephalopathy/neonatal encephalopathy*

Mounting evidence supports the consideration of genetic testing in infants with neonatal encephalopathy (NE).[27] This is particularly true for neonates with a clinical picture resembling HIE without clear sentinel events.[36] Additionally, infants with underlying genetic conditions may be more predisposed to HIE itself. Clinical features that support the need to consider other etiologies, particularly genetic conditions, include congenital anomalies, microcephaly or macrocephaly, contractures, intrauterine growth restriction, and hepatosplenomegaly.[27]

Several large studies have attempted to determine the incidence of genetic conditions in infants suspected of HIE. Amongst participants in the High Dose Erythropoietin for Asphyxia and Encephalopathy trial,[37] 5% of infants were diagnosed with a genetic or congenital anomaly in addition to their HIE.[36] This percentage, however, likely underestimates the total number of underlying diagnoses as genetic testing was only performed "when clinically indicated" and not universally amongst all participants. Neurodevelopmental impairment and/or death were also more common in infants with a genetic or congenital anomaly.[36] Similarly, 5% of infants in a retrospective Canadian sample of patients with history of HIE were identified to have pathogenic genetic variants.[38] Amongst infants with NE not attributed to HIE, diagnostic yield of genetic testing varied by type of test from 10% for chromosomal studies to 69% for ES.[39]

We recommend strong consideration of rGS in infants without a clear sentinel event for HIE and/or with other clinical features that would support an underlying diagnosis. With the decrease in cost of testing and increase in availability, it is possible that all infants with NE may have rGS in the near future. Identifying an underlying genetic condition is important as such patients have a higher rate of adverse outcomes.[36]

### *Intraventricular hemorrhage*

Intraventricular hemorrhage (IVH) is a common neurologic complication of prematurity with significant morbidity and mortality. The IVH is typically related to the fragility of immature germinal matrix and changes in cerebral blood flow in infants less than 32 to 33 weeks gestation.[40] IVH, particularly severe grades, is less common in infants greater than 32 weeks gestation or while still in utero. In these cases, additional

investigation should be undertaken for additional risk factors predisposing to the hemorrhage. Amongst retrospective reviews of fetal intracranial hemorrhage, *COL4A1* and *COL4A2* variants were identified in approximately 20% to 30% of cases, respectively.[41,42] Atypical IVH, defined as antenatal onset or late in postnatal course in the absence of preceding sudden deterioration in clinical condition, has been associated with variants in a variety of genes.[43] In more typical IVH, while twin studies demonstrate that approximately 40% of the risk for developing IVH can be accounted for by shared genetic and environmental risk factors[44] important monogenic contributions have yet to be identified.[45]

### *Neonatal hypotonia*

Hypotonia is a symptom of many conditions in the NICU both with neurologic origins such as hypoxic ischemic encephalopathy or without neurologic origins such as sepsis or hypoglycemia. These causes are important to consider. However, when these secondary causes of hypotonia are ruled out, it is essential to consider primary causes. Amongst neonates with unexplained hypotonia, yield of ES/GS is very high, ranging from 30% to 80% depending on the study. A recent consensus paper combined these prior studies, noting that overall yield was 56%.[46] Seventy-four percent of the patients had a change in clinical treatment after diagnosis.[46] Gene therapy is available or is under development for several causes of neonatal hypotonia including spinal muscular atrophy (SMA),[47] *MTM-1* related congenital myopathy, giant axonal neuropathy, and aromatic L-amino acid decarboxylase deficiency. Additionally, disease-modifying therapy is available or underway for others such as Pompe disease[48] and some forms of Batten's disease.[46] Other targeted treatments include the use of mestinon in congenital myasthenic syndromes. The early identification and initiation of treatment is essential for optimizing outcomes. Even when treatment is not available, early use of ES/GS to identify a diagnosis can minimize other invasive testing such as skin or muscle biopsy, electromyography/nerve conduction study or LP, as well as facilitate important discussions about long-term prognosis.[49]

While ES/GS has greatly enhanced our ability to make many of these important diagnoses, there are a few important causes of neonatal hypotonia that may be missed by some sequencing-based approaches. Most notably, these include myotonic dystrophy (repeat expansion), Prader-Willi syndrome (uniparental disomy), and SMA[50,51] (homology). The neurologic examination and other more systemic findings can provide clues to these diagnoses such as the presence of bilateral club feet and/or bilateral facial diplegia in myotonic dystrophy, cryptorchidism in Prader-Willi syndrome, and a bell-shaped chest in SMA. Depending on TAT of ES/GS at a given center, it may be prudent to send targeted testing for these conditions in parallel versus sequentially if results are expected quickly (see **Fig. 1**).

### *Neonatal breathing disorders*

While neonatal breathing disorders and central hypoventilation are not commonly managed by the neurologist, neurology is commonly involved in the initial evaluation. The neonatal presentation classically includes unexplained shallow breathing with hypoventilation, abnormal ventilatory drive, and autonomic nervous system dysregulation including apnea.[52] After neonatal seizures and congenital brain malformations are ruled out via electroencephalography and imaging, respectively, the diagnostic work up pivots toward genetic testing. Central congenital hypoventilation syndrome (CCHS) is classically caused autosomal dominant pathogenic variants in *PHOX2B*.[52] Unlike with many other conditions discussed in this article, ES/GS is not

recommended as first line for suspected CCHS as the most common variants (polyalanine repeats) may not be detected. Rather, one should obtain testing dedicated to this condition.

## SUMMARY

The combination of falling cost and improving TAT, along with increasingly comprehensive results, has revolutionized the role of genetic testing in neonatal neurocritical care. It is no longer necessary to pursue comprehensive and longitudinal phenotyping along with a series of trial and error empiric therapies all while subjecting the patient and family to a year's long diagnostic odyssey. Rather, the combination of basic phenotyping by skilled clinicians and early and aggressive use of rGS can lead to precise molecular diagnoses for many neurologically abnormal neonates which in turn reduce unnecessary and potentially harmful medical care while also accelerating access to precision therapies. Even when GS is nondiagnostic, it significantly lowers the posterior probability of many diagnoses on the differential while also serving as the first step to enrolling in rare disease research studies which may ultimately provide families diagnoses and/or treatments.

***Best Practices***

Based on the cumulative evidence of benefit from GS in critically ill and hospitalized neonates[6] and congruent with a recent consensus approach to neonatal hypotonia,[46] our recommendation for early and aggressive use of rGS in neurologically abnormal neonates is depicted in **Fig. 1**.

## DISCLOSURES

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# Novel Approaches to the Treatment of Preterm White Matter Injury through Targeting Remyelination

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**KEYWORDS**

• White matter injury • Prematurity • Remyelination • Preterm brain injury

**KEY POINTS**

- White matter injury (WMI) is a common form of acquired brain injury in premature neonates that can lead to lifelong neurologic symptoms and disability.
- Current management of preterm WMI is focused on prevention and rehabilitation.
- Newly identified remyelinating, or "pro-myelinating," compounds promote processes that are inhibited in preterm WMI, including oligodendrocyte differentiation and myelination.
- Pro-myelinating compounds stimulate remyelination in animal models and in patients with demyelinating disorders and may have therapeutic potential for preterm WMI.

## INTRODUCTION

Preterm white matter injury (WMI) is the most common cause of acquired brain injury in premature neonates. Preterm WMI is associated with adverse neurodevelopmental outcomes including developmental delays, cognitive and motor disability, and behavioral challenges.[1] Current management strategies are centered around early initiation of rehabilitative therapies to maximize developmental potential.[2] No targeted treatments are available. However, the identification and development of novel remyelinating compounds for demyelinating diseases have the potential to significantly alter the treatment landscape for preterm WMI.[3–11] Here, the authors provide an overview of cellular and molecular mechanisms that promote and inhibit myelination in preterm WMI and in demyelinating diseases. They review remyelinating therapies in preclinical

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| Abbreviations | |
|---|---|
| CNS | central nervous system |
| Epo | erythropoietin |
| FDA | Food and Drug Administration |
| GA | gestational age |
| MS | multiple sclerosis |
| NDI | neurodevelopmental impairment |
| OL | oligodendrocyte |
| OPC | oligodendrocyte precursor cell |
| PK | pharmacokinetics |
| preOL | pre-oligodendrocyte |
| T3 | triiodothyronine |
| WMI | white matter injury |
| WM | white matter |

and clinical development and discuss potential applications in neonatal brain disorders.

## WHITE MATTER COMPOSITION AND DEVELOPMENT

When considering mechanisms of disease and potential therapeutic targets for preterm WMI, it is useful to review white matter (WM) composition in the most vulnerable brain region, the periventricular WM, and during the highest risk period of brain development, 23 to 32 weeks gestational age (GA).[1,12] The WM of the central nervous system (CNS) consists predominantly of dense collections of similarly oriented axons organized into tracts. In the mature brain, many axons are wrapped by myelin sheaths, which are lipid-rich structures formed by concentric wraps of the cell membrane of oligodendrocytes (OLs).[13] Myelin acts to increase axonal membrane resistance and enable voltage-gated sodium channel clustering at nodes of Ranvier, thereby allowing for saltatory conduction of action potentials along axons.[13] OLs also provide nutritional and metabolic support to axons and buffer extracellular potassium.[13] In the preterm brain, most axons are still unmyelinated.

OLs are derived from oligodendrocyte precursor cells (OPCs), which first appear in the CNS around 9 weeks GA.[14] OPCs migrate from germinal zones of origin to locations throughout the CNS and begin to differentiate into pre-oligodendrocytes (preOLs) throughout the second trimester.[12] OPCs and preOLs comprise the majority of OL lineage cells during the highest risk period for WMI.[15] Differentiation into mature OLs, axon wrapping, and compact myelin formation occurs gradually in a region-specific manner.[16] Myelin is first apparent in the brain stem, cerebellum, and motor tracts around 30 weeks GA.[16] Myelination progresses in a caudal-to-rostral fashion, and the bulk of brain myelination occurs postnatally, with most tracts achieving mature myelination patterns by the age of 2 years.[16]

Vascularization of the preterm WM is characterized by arterial border and end zones, which is thought to increase the susceptibility of this region to ischemia.[12] Microglia and astrocytes can be found throughout the healthy preterm WM.[17] Other immune cell types, such as lymphocytes, may invade the WM in cases of injury or ischemia.[18]

## PATHOPHYSIOLOGY OF PRETERM WHITE MATTER INJURY

The unique vulnerability of the preterm WM is attributed to several factors. Due to the anatomy of the periventricular WM in the preterm brain and the impaired

autoregulation and vasoconstriction of its immature vasculature, this region is particularly susceptible to fluctuations in blood flow and oxygen delivery.[19] Immature OL lineage cells are more susceptible than axons, astrocytes, or microglia, to injury from hypoxia-ischemia, which causes OL differentiation arrest and a failure of myelination.[1,20] PreOLs are also affected by a variety of chemical mediators that are commonly found in critically ill premature neonates, including reactive oxygen species, inflammatory cytokines, and glutamate released in the setting of excitotoxicity.[21] An immature respiratory system and frequent need for ventilatory assistance may contribute to brain hypoxia.[19,22] Additional mechanisms of injury include microglial activation and reactive astrocytes,[12] lymphocyte infiltration,[18] and the prolonged absence of myelin leading to neuroaxonal injury and death.[12]

## DEFINING WHITE MATTER INJURY SEVERITY IN PRETERM NEONATES

WMI in preterm neonates encompasses a spectrum of injury to the developing WM, and the incidence is inversely correlated with GA at birth.[19] Whereas the most severe pattern, cystic WMI (also known by the pathologic diagnosis of cystic periventricular leukomalacia) can be seen on cranial ultrasound, the predominant forms of WMI are best imaged by MRI (**Fig. 1**).[1,23,24] In contemporary cohorts, punctate and diffuse non-cystic microstructural WMI is most prevalent, and studies have shown an overall decrease in the burden of both cystic and punctate WMI in recent decades.[12,25] Several neuroimaging-based grading scales have been developed to define WMI severity on cranial ultrasound and brain MRI in premature neonates, which have been reviewed elsewhere.[26]

The pattern, severity, and location of WMI are associated with neurodevelopmental outcomes. A detailed discussion of motor, cognitive, language, and behavioral development following WMI is outside of the scope of this review.[1,23] Briefly, more severe WMI correlates with risk of cerebral palsy and degree of motoric impairment, with increased risk of more severe impairment among those with cystic WMI in particular.[1,23] Location of punctate WMI in the frontal lobes, and abnormal myelination of the posterior limb of the internal capsule at term-equivalent age, are predictive signs of motor impairment on term-equivalent MRI.[27,28] Meta-analysis data demonstrate that more severe WMI on brain MRI at term-equivalent age has a sensitivity of 77% (95% confidence interval 53%–91%) for cerebral palsy, and a specificity of 72% (95% confidence interval 51%–93%).[29] More severe WMI is also associated with cognitive and language outcomes[1]; however, meta-analysis data show that

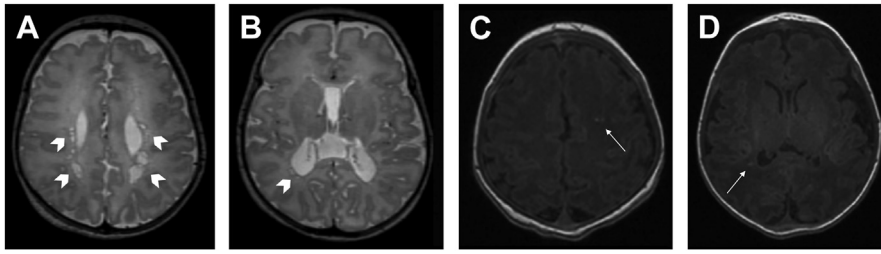


**Fig. 1.** Spectrum of WMI on term-equivalent MRI. Axial T2-weighted MRI (*A*, *B*) showing cystic periventricular WMI (*chevrons*) with ex vacuo dilatation of the ventricles in an infant born at 27 weeks, with delivery complicated by placental abruption. Axial T1-weighted MRI (*C*, *D*) showing punctate T1 hyperintense foci of WMI (*arrows*) in an infant born at 31 weeks' gestation imaged at term-equivalent age.

prognostic accuracy for neurocognitive and behavioral function is more limited than for motor function.[29]

## CURRENT MANAGEMENT STRATEGIES FOR PRETERM NEONATES WITH WHITE MATTER INJURY

Current management strategies for preterm neonates with WMI are largely limited to supportive care.[2] Mounting data indicate the influence of multiple comorbidities of prematurity on the development of WMI and WM dysmaturation.[1,12] Prevention and treatment of neonatal complications associated with risk of WMI are central to the prevention of WMI.[30] Such complications include recurrent postnatal infections, necrotizing enterocolitis, and bronchopulmonary dysplasia.[30] Suboptimal early nutrition and postnatal growth,[31] as well as recurrent painful procedures,[32] are also associated with WM dysmaturity. These findings have supported the development of neuroprotection bundles for bedside neonatal intensive care to prevent brain injury in the preterm population through close daily management of blood pressure, partial pressure of carbon dioxide, prevention of acidosis, minimizing painful procedures, and maintaining normal electrolytes.[1,30] Key complementary elements of these care practices also include environmental measures to decrease stimulation and encourage parent involvement, kangaroo care, optimizing nutrition, and pain management.[30]

The primary approach to the treatment of preterm WMI is early intervention therapy, with physical therapy, occupational therapy, feeding therapy, and/or speech therapy.[1,33] Detection of WMI in preterm infants by MRI enables a maximally proactive approach to development through earlier implementation of rehabilitative therapies in those at higher risk for neurodevelopmental impairment (NDI).[34]

## STUDIES OF NEUROPROTECTIVE THERAPIES

Historically, the focus of therapeutic development for preterm WMI has been preventative strategies for neuroprotection, a term that broadly refers to reducing brain tissue injury and improving neurodevelopmental outcomes.[30,35–39] Most treatments in development are thought to exert neuroprotective effects by targeting inflammation and reducing oxidative stress.[30,40] Many neuroprotective therapies in development, including erythropoietin (Epo), stem cells, melatonin, and caffeine, also have specific antiapoptotic, pro-differentiation, and/or pro-myelination effects on OLs[30,41,42] (**Table 1**). Accordingly, there has been increasing interest in using neuroprotective therapies to promote remyelination and axonal protection in patients with demyelinating disorders, such as multiple sclerosis (MS).[43–50]

While multiple neuroprotective therapies have been studied in clinical trials in preterm neonates, none have definitively demonstrated efficacy for preterm WMI.[40,41,51–54] The randomized Preterm Erythropoietin Neuroprotection Trial showed no benefit of Epo on the primary outcome of death or severe NDI at 2 years,[51] nor an effect on multiple markers of inflammation.[55] Multiple early phase (phase I/II) studies of stem cells have demonstrated safety; however, these are limited by heterogeneity in inclusion criteria, treatment protocols, and types of perinatal brain injuries studied.[30,41] A small randomized controlled trial showed melatonin was associated with decreased lung injury due to mechanical ventilation in preterm infants.[56] This study also showed melatonin was associated with lower levels of F2-isoprostanes,[56] prostaglandin-like molecules that correlate with WMI severity.[31] Administration of caffeine, which is used in preterm neonates to treat apnea of prematurity, is also associated with improved neurodevelopmental outcomes and measures of WM integrity on brain MRI.[57,58] The results of these studies suggest that neuroprotective therapies may

**Table 1**
**Neuroprotective therapies with pro-myelinating properties**

| | | Demyelinating Disorders | | Preterm Brain Injury | | |
|---|---|---|---|---|---|---|
| **Treatment** | **Mechanism** | **Preclinical Studies** | **Clinical Trials: Results Published** | **Preclinical Studies** | **Clinical Trials: Results Published** | **Clinical Trials: Ongoing** |
| Caffeine | Methylxanthine | Improved motor function and reduced inflammation in rat EAE model.[44] | | Enhanced myelination in mouse chronic hypoxia model of preterm WMI.[42] | Caffeine given for apnea of prematurity reduced incidence of CP and cognitive delay at 18–21 mo[52] | |
| Erythropoietin | Stimulates erythropoiesis, has antioxidant, anti-inflammatory, and antiapoptotic properties. | Improved functional recovery in mouse EAE model.[35] | Did not improve long-term vision outcomes or reduce conversion to MS in patients with optic neuritis.[48,49] | Improved blood brain barrier integrity in lamb model of preterm WMI.[36] | Prophylactic erythropoietin in preterm infants improved cognitive outcomes in one meta-analysis,[53] but 2 large clinical trials showed no benefit.[51,54] | |
| Melatonin | Neuromodulator with antioxidant and immune-modulatory properties. | Enhanced remyelination in mouse EAE model.[46] | | Improved OL maturation, myelination, and reduced inflammation in preterm sheep model.[37,38] | No evidence of improved white matter integrity in Phase 2 study investigating melatonin in preterm neonates born <31 wk GA.[40] | NCT05651347 (Phase 3 investigating neuroprotective effects of antenatal melatonin for fetal growth restriction) |

(*continued on next page*)

**Table 1**
**(*continued*)**

| | | Demyelinating Disorders | | Preterm Brain Injury | | |
|---|---|---|---|---|---|---|
| **Treatment** | **Mechanism** | **Preclinical Studies** | **Clinical Trials: Results Published** | **Preclinical Studies** | **Clinical Trials: Results Published** | **Clinical Trials: Ongoing** |
| Stem Cells | Trophic support and immune regulation | Promote functional remyelination in mouse cuprizone model.[47] | Reduced disability and decreased brain MRI lesion accumulation in patients with MS, did not affect relapse rate.[50] | Reduced inflammation and gliosis and improved OL maturation and myelin protein expression, in preterm sheep model.[39] | Early phase studies demonstrated safety, with possible clinical applicability limited by heterogeneity in inclusion criteria, treatment protocols, and types of perinatal brain injuries studied.[41] | ACTRN-12619001637134 (Phase 1 safety and feasibility study)<br>NCT03696745 (Phase 1, umbilical cord stem cells for encephalopathy in preterm infants) |

We included neuroprotective treatments that also have specific effects on the OL lineage and have been explored as preventative strategies for preterm brain injury. These treatments may also have applications in demyelinating disorders.

*Abbreviations:* CP, cerebral palsy; EAE, experimental autoimmune encephalitis; GA, gestational age; MS, multiple sclerosis; OL, oligodendrocyte; WMI, white matter injury.

reduce the incidence or severity of preterm WMI, but the evidence is not strong enough to support routine administration for this indication. These data highlight the need for further study of neuroprotective compounds in larger randomized trials, as well as novel approaches for promoting neurorecovery and myelination in preterm WMI. Future trials of neuroprotection should also consider stratification by WMI severity to improve understanding of the potential spectrum of neuroprotective benefits in specific subgroups.

## DEMYELINATING DISEASES AND THE PROMISE OF REMYELINATION

Neuroprotective therapies may be helpful for multiple WM disorders across the age spectrum. Similarly, advances in drug development for demyelinating disorders may be applicable to preterm WMI. Demyelinating diseases are characterized by the destruction of myelin in previously intact WM.[10] MS, the most common demyelinating disease, is a major cause of nontraumatic neurologic impairment in young adults.[59] MS is a chronic inflammatory disorder thought to be driven by aberrant autoimmune targeting of OLs, which is often accompanied or followed by axonal death and progressive neurologic decline.[60] After attacks of demyelination, some degree of remyelination occurs spontaneously. New myelin can be generated by existing OLs or by newly differentiated OLs produced by OPCs or adult stem cells that persist in the adult CNS.[10] However, newly formed myelin is thinner than developmental myelin, and many OPCs in MS lesions fail to differentiate and form new myelin sheaths.[11]

Established therapies for MS predominantly target inflammation and are largely ineffective at preventing disability accumulation over time.[43] Recent efforts have focused on developing strategies for protecting axons and stimulating myelin regeneration, or remyelination, which is postulated to limit disability accumulation over the lifespan.[10] Mechanisms of remyelination reflect processes that are also critical for developmental myelination and include OPC proliferation, migration to undamaged axons, differentiation into mature OLs, and wrapping of axons[10] (**Fig. 2**). Research into the molecular pathways controlling remyelination has led to the establishment of new therapeutic targets currently being explored in animal models of demyelinating disease and, more recently, in clinical trials[3,61–71] (**Table 2**).

## A ROLE FOR REMYELINATION IN NEONATAL WHITE MATTER DISORDERS

Compounds that promote remyelination may have applications for neonatal brain disorders characterized by a failure of normal developmental myelination. Factors that inhibit remyelination in demyelinating diseases, such as a low density of local OPCs, a lack of intact axons, or excessive inflammation or astrogliosis, are likely to limit the success of remyelinating therapies in neonatal WM disorders.[11] Genetic conditions that affect axon structure, OL function, or myelin integrity may be poor candidates for treatment in the neonatal period with remyelinating therapies, as evidenced by negative preclinical studies investigating the effect of a remyelinating compound in a mouse model of a genetic leukodystrophy.[72] Conversely, preterm WMI appears well suited for novel applications of remyelinating therapies, given the prolonged presence of immature OL lineage cells and intact axons that may be amenable to myelination.[12,15]

## PRO-MYELINATING COMPOUNDS

A major strategy for promoting remyelination involves stimulating signaling pathways that control OL differentiation or myelin production.[10,11] Several groups have developed in vitro screening platforms to identify compounds that promote these

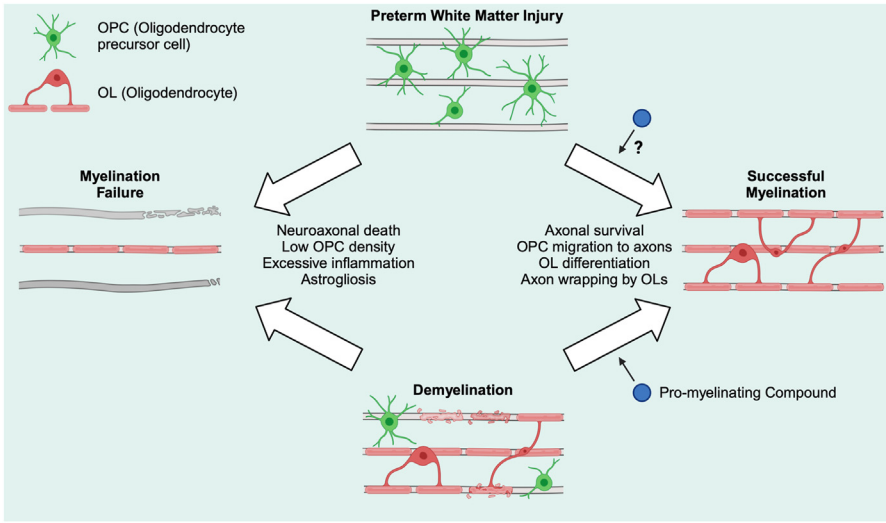


**Fig. 2.** Shared mechanisms of developmental myelination and remyelination. Oligodendrocyte precursor cells (OPCs) are depicted in green and oligodendrocytes (OLs) in red, while pro-myelinating compounds are depicted as blue circles. Similar factors lead to myelination failure or success in preterm white matter injury (WMI) and demyelinating disease. Pro-myelinating compounds developed for demyelinating disorders may have therapeutic potential for preterm WMI. (*Created in* BioRender. Ostrem, B. (2025) https://BioRender.com/i84w790.)

processes.[3–9] It may be more accurate to refer to compounds that promote OL differentiation and/or myelination as "pro-myelinating," instead of the more narrow term "remyelinating." Demyelination was not a feature of any of the screening platforms. Therefore, identified compounds likely have the potential to stimulate both remyelination and primary (developmental) myelination.

Many of the best performing compounds in screens for pro-myelinating activity were subsequently tested in adult animal models of demyelinating disease (see **Table 2**). Compounds with in vivo evidence of pro-myelinating activity in adult animals include benztropine,[73,74] clemastine,[3,75] bazedoxifene,[65] hydroxyzine,[76] amiloride,[77] tamoxifen,[78] triiodothyronine (T3),[68,69] olesoxime,[66] metformin,[79] and quetiapine.[45,80] Several pro-myelinating compounds with promising preclinical results have progressed to clinical trials in human patients with demyelinating diseases.[64,81–86] A prime example is clemastine: daily treatment for 3 months with oral clemastine in patients with MS and chronic optic neuritis led to improved visual evoked potentials[64] and neuroimaging measures of myelination in the corpus callosum[81] in a recent phase II trial. Additional clinical trials for clemastine are ongoing (NCT02521311, NCT05338450, NCT05131828).

Clemastine has been shown to exert its pro-myelinating effects via antagonism of the muscarinic M1R acetylcholine receptor on OPCs.[63] A phase II trial testing a more selective M1R antagonist, PIPE-307, is currently enrolling patients with MS (NCT06083753). In addition to investigation into muscarinic antagonists, phase I trials have demonstrated the safety of T3 and olesoxime in adult patients with MS,[67,87] and clinical trials of several other agents are underway, including bazedoxifene (NCT04002934) and ifenprodil (NCT06330077).

**Table 2**
**Remyelinating therapies with potential clinical application for white matter injury in preterm neonates**

| | | Demyelinating Disorders | | Preterm Brain Injury |
|---|---|---|---|---|
| **Treatment** | **Mechanism** | **Preclinical Studies** | **Clinical Trials: Results Published** | **Preclinical Studies** |
| Triiodothyronine (T3) | Thyroid hormone | Promoted remyelination in cuprizone mouse model.[68,69] | Phase I study demonstrated short-term safety and tolerability in patients with MS.[87] | Reduced apoptosis in the white matter in mouse model of periventricular leukomalacia.[89] |
| Benztropine | Anticholinergic | Enhanced remyelination in metronidazole-induced Xenopus model.[61] | | |
| Clemastine | First generation antihistamines with anticholinergic activity | Promoted remyelination in metronidazole-induced demyelination Xenopus model[61] and in mouse EAE[70] and lysolecithin[3] models. | Reduced visual evoked potential latency[64] and enhanced myelination on brain MRI[81] in patients with MS and chronic optic neuropathy (ReBUILD Phase II trial). | Improved myelination and motor outcomes in mouse models of preterm white matter injury.[62,63,91] |
| Hydroxyzine | | Reduced progression and severity of rat EAE model.[76] | Open label pilot study demonstrated stability in patients with MS who received hydroxyzine.[82] | |
| Tamoxifen | Selective estrogen receptor modulator | Accelerates remyelination in rat ethidium bromide model.[78] | | Reduced brain weight loss in postnatal day 7 rat hypoxia-ischemia injury model.[92] |
| Amiloride | Sodium Channel Blocker | Improved clinical score and protected axons in mouse EAE model.[77] | No improvement in radiographic disease progression in phase 2b trial in patients with progressive MS[83] despite small pilot study suggesting positive effects.[84] | Amiloride analog reduced brain tissue loss in postnatal day 7 mouse hypoxia-ischemia injury model.[93] |

(*continued on next page*)

**Table 2**
**(*continued*)**

| | | Demyelinating Disorders | | Preterm Brain Injury |
|---|---|---|---|---|
| **Treatment** | **Mechanism** | **Preclinical Studies** | **Clinical Trials: Results Published** | **Preclinical Studies** |
| Metformin | Anti-hyperglycemic | Accelerates remyelination in mouse cuprizone model.[79] | Decreased MRI activity in pilot study of patients with MS and obesity.[85] No difference in disease progression in phase 2 study adding metformin as adjuvant to interferon beta 1a.[86] | Increased OLs and reduced inflammation in postnatal day 7 mouse hypoxia-ischemia injury model.[94] |
| Quetiapine | Atypical antipsychotic | Promoted remyelination in cuprizone mouse model.[71] | | |
| Olesoxime | Cholesterol-like compound with neuroprotective properties | Accelerates remyelination in lysolecithin and cuprizone mouse models.[66] | Phase Ib study demonstrated safety in adult patients with MS.[67] | Increased myelin in newborn mice when mothers supplemented with olesoxime.[66] |

Included are pro-myelinating compounds with demonstrated efficacy as remyelinating agents in animal models of demyelinating conditions and/or clinical trials in human patients. All medications have reported use in pediatric populations. No neonatal clinical trials for prevention or treatment of WMI have yet been reported for these medications.

*Abbreviations:* EAE, experimental autoimmune encephalitis; MS, multiple sclerosis; OL, oligodendrocyte; WMI, white matter injury.

There have been no published clinical trials of pro-myelinating compounds for preterm WMI, although one ongoing trial is testing metformin as a neurorecovery agent in children ages 5 to 18 years with a diagnosis of cerebral palsy (NCT03710343). Encouragingly, many pro-myelinating compounds identified in drug repurposing screens are currently approved by the Food and Drug Administration (FDA) in children for other indications or have been routinely used off-label in pediatric populations (see **Table 2**). Pro-myelinating compounds with previously reported use in infants and/or young children include the anticholinergic drugs benztropine[3] and oxybutynin,[3] antihistamines clemastine[3] and hydroxyzine,[4] anti-seizure medication oxcarbazepine,[6] sodium channel blocker amiloride,[6] antihyperglycemic metformin,[88] selective estrogen receptor modulator tamoxifen,[9] and the atypical antipsychotic quetiapine.[3] Several pro-myelinating compounds have shown efficacy in animal models of preterm WMI, including thyroid hormones[89,90] and clemastine.[62,63,91] Tamoxifen[92] and amiloride[93] reduced brain injury in a model of hypoxic-ischemic brain injury in rodents at postnatal day 7, a time point where brain myelination is similar to late preterm neonates. Metformin increased OL differentiation in the same model.[94] Treatment with the small, cholesterol-like compound olesoxime increased myelin production in healthy newborn mice, suggesting potential utility for neonatal brain conditions involving hypomyelination.[66] Additional testing in neonatal animal models, followed by phase I studies of neonatal safety and pharmacokinetics (PK), is needed prior to proceeding with randomized controlled trials in preterm neonates with WMI.

## SPECIAL CONSIDERATIONS FOR DRUG DEVELOPMENT IN NEONATES

The expanding arsenal of pro-myelinating compounds suggests that new treatments for preterm WMI are on the horizon. However, drug development for neonatal neurologic indications presents unique challenges, even when considering the use of repurposed, FDA-approved medications.[95,96] Awareness of these challenges from the earliest stages of preclinical drug development will increase the likelihood of successful translation from animal models to human neonates.

The neonatal period is characterized by rapid growth and maturation of tissues, organs, and body systems. Medications that are safe in adults, children, and even in infants older than age 1 month may adversely impact critical early developmental processes.[97,98] Thus, preclinical toxicity testing in neonatal animals is often required prior to clinical trials of new or repurposed medications in neonates.[99] Drugs that act in the CNS are often subject to requirements beyond general toxicity studies, including expanded neurohistopathological analyses and animal behavioral testing.[99,100] Preclinical studies are typically costly and may require funding strategies beyond typical grant mechanisms, including collaboration with industry partners.

Once preclinical testing is complete and investigational new drug application approval is achieved if required, phase I studies in neonates may commence. Drug formulations should be designed to optimize volume of delivery and to minimize potentially toxic excipients, such as ethanol and polyethylene glycol, in oral formulations.[98] Clinical trials in neonates should take into account the unique PK and pharmacodynamic profiles in these patients.[96] The dose levels and administration intervals required to achieve target drug exposures in neonates are often different than those in older patients, an observation driven by factors such as reduced oral bioavailability, immature liver enzyme expression levels, and low body fat content in neonates.[96] Adaptive trial design approaches such as PK-guided dose adjustments during phase I studies can help optimize dosing strategies prior to larger efficacy studies. Neonates

exposed to CNS-acting agents must receive developmental follow-up through at least the age of 2 years.[97] Laboratory and imaging-based prognostic biomarkers may accelerate future clinical development in this population, given the extended follow-up periods required to assess efficacy and safety in neonates.[98]

## SUMMARY

Preterm WMI leads to significant morbidity in children worldwide and is associated with a substantial cumulative economic burden.[101] Despite the challenges inherent to drug development for neonatal brain disorders, the need for new treatment options is great. The similarity in cellular and molecular mechanisms of developmental myelination and remyelination, and the dual efficacy of several drugs in animal models of preterm WMI and adult demyelinating disease, suggest that pro-myelinating compounds represent an untapped source of potential therapeutics for preterm WMI and other newborn brain disorders.

***Best Practices***

***What is the current practice for preterm WMI?***

- Current standard of care for preterm WMI is focused on implementation of preventative strategies, early detection of WMI, and timely referral to rehabilitative therapies.

***What changes in current practice are likely to improve outcomes?***

- Optimizing care for preterm neonates in the neonatal intensive care unit to focus on brain health.
- Future strategies may include implementation of specific, disease mechanism-directed treatments after completion of further nonclinical testing and clinical trials of neuroprotective and pro-myelinating therapies.

***Is there a clinical algorithm?***

No.

***Pearls/pitfalls at the point-of-care:***

- Limited prenatal care and uncertainty regarding GA at birth.
- Suboptimal environment in the neonatal intensive care unit, which may include preventable infections, prolonged mechanical ventilation, and recurrent painful procedures.
- Lack of screening protocols to detect WMI and other types of brain injury in at-risk premature neonates.
- Late initiation of rehabilitative therapies (physical, occupational, feeding, and/or speech therapy).

***Major recommendations:***

- Antenatal corticosteroids and magnesium for fetal neuroprotection prior to delivery.
- Prevent and treat neonatal complications associated with risk of WMI, such as postnatal infections, necrotizing enterocolitis, and bronchopulmonary dysplasia.
- Optimize early nutrition, limit painful procedures, and increase parental involvement and kangaroo care.
- Consider brain MRI at term-equivalent age for early detection of WMI in all neonates born before 32 weeks GA, particularly when additional risk factors for WMI are present, or screening cranial ultrasound shows parenchymal abnormalities.
- Early initiation of rehabilitative therapies.

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## DISCLOSURES

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# Preterm Hemorrhagic Brain Injury

## Recent Advances on Evaluation and Management

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**KEYWORDS**

• Hydrocephalus • Intraventricular hemorrhage • Newborn • Preterm • Treatment • Neurodevelopmental outcome

**KEY POINTS**

- The incidence of germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) increases with decreasing gestational age and is more likely to affect preterm infants born less than 32 weeks' gestation.
- Cranial ultrasonography (cUS) is the preferred neuroimaging modality to assess GMH-IVH and to detect related complications with high sensitivity in preterm infants.
- Timely interventions with close cUS monitoring for post-hemorrhagic ventricular dilatation is crucial to prevent adverse neurodevelopmental outcomes.

## INTRODUCTION

Preterm germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH) are common complications of prematurity affecting up to 45% of infants born extremely preterm.[1] The risk of GMH-IVH increases with decreasing gestational age and is more likely to affect preterm infants born less than 32 weeks' gestation.[2] GMH-IVH generally occurs soon after birth, with 50% of the hemorrhages occurring within 1 day, and 90% within 3 days after birth, although antenatal and later postnatal presentations are possible.[3] GMH-IVH can present unilaterally or bilaterally and is classified

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| Abbreviations | |
|---|---|
| AAP | American Academy of Pediatrics |
| AHW | anterior horn width |
| BDNF | brain-derived neurotropic factor |
| CPS | Canadian Pediatric Society |
| CSF | cerebrospinal fluid |
| DRIFT | drainage, irrigation, and fibrinolytic therapy |
| GMH-IVH | germinal matrix hemorrhage and intraventricular hemorrhage |
| MSC | mesenchymal stem cell |
| NEL | neuroendoscopic lavage |
| PHVD | posthemorrhagic ventricular dilatation |
| PVHI | periventricular hemorrhagic infarction |
| TOD | thalamo-occipital distance |
| VI | ventricular index |
| VP | ventriculoperitoneal |

based on the extent of hemorrhage and coexisting acute ventricular dilatation. The most commonly used classification systems for grading GMH-IVH have been proposed by Papile and Volpe.[4,5] In a recent Canadian consensus article,[6] GMH-IVH was classified based on the Volpe classification: grade I is hemorrhage within the germinal matrix, grade II is hemorrhage within the lateral ventricles without dilatation of the ventricle, grade III is hemorrhage in the lateral ventricles occupying more than greater than 50% of the ventricles causing acute ventricular dilatation, and periventricular hemorrhagic infarction (PVHI) is an ipsilateral hemorrhagic infarction in the periventricular white matter secondary to GMH-IVH. In this review, we discuss the pathophysiology, risk factors, evaluation, management, and neurodevelopmental outcome trajectories of GMH-IVH and its complications. We focus on evaluation and management of GMH-IVH and posthemorrhagic ventricular dilatation (PHVD) and highlight best practices based on recent studies. Emerging therapies for PHVD are also reviewed.

## HEMORRHAGIC BRAIN INJURY AND ASSOCIATED CONDITIONS

GMH-IVH can lead to further complications including PVHI, PHVD, and brain dysmaturation.[3] PVHI was previously thought to be an extension of GMH-IVH; however, it is now widely accepted that the white matter injury in PVHI results from impaired venous drainage following GMH-IVH, which leads to ischemia and hemorrhagic infarction.[7] Gestational age is an important risk factor for PVHI, as it occurs more commonly in preterm infants born at earlier gestations.[8] PVHI is usually unilateral and tends to occur more frequently with ipsilateral high-grade GMH-IVH.[9] The white matter injury can range from a focal to extensive lesion in the frontal, parietal, temporal, or occipital regions.[9,10] PHVD is progressive dilatation of the ventricles secondary to GMH-IVH. The presence of blood in the ventricles can impair cerebrospinal fluid (CSF) flow and absorption, leading to obstruction and ventricular dilatation. Hypersecretion of CSF from the choroid plexus also contributes to PHVD.[11] PHVD is seen in up to 25% of infants with GMH-IVH and is more common with high-grade GMH-IVH.[12] Similar to PVHI, PHVD is also more likely to occur in infants born at earlier gestational ages.[13] Brain dysmaturation refers to abnormalities in brain growth and development with or without brain injury.[14] These brain changes include reduced cortical, gray and white matter volumes, ex vacuo ventriculomegaly, and abnormal white matter maturation, which are commonly seen in preterm infants on term-equivalent age scans.[14]

Perinatal risk factors for GMH-IVH include maternal hypertension, chorioamnionitis, and vaginal delivery with prolonged labor.[15–18] Infants who were outborn, or transferred

to a tertiary center have higher rates of GMH-IVH compared with inborn infants.[19,20] Antenatal corticosteroids have been shown to be protective against GMH-IVH.[21,22] Similarly, delayed cord clamping is associated with a lower risk of GMH-IVH.[23] Among neonatal risk factors, lower gestational age has consistently been found to be associated with a greater risk for GMH-IVH.[2,24] Several studies have found that rapid fluctuations in blood pressure and low oxygen saturation can increase the risk of GMH-IVH.[25–27] While resuscitation efforts and admission to the neonatal intensive care unit (NICU) are lifesaving for preterm infants, increased number of intubation attempts and both high-frequency oscillatory and conventional ventilation are associated with increased rates of GMH-IVH.[28–30] Routine everyday features of the NICU such as procedural pain, loud noise, frequent handling, non-midline head positioning, lumbar punctures, frequent suctioning, and rapid fluid boluses can also increase the risk of GMH-IVH.[15,31,32]

## ASSESSMENT

### *The Indispensable Role of Cranial Ultrasonography*

GMH-IVH is typically clinically silent but may also present with sudden or progressive clinical deterioration.[3] Given that GMH-IVH can present without clinical signs, routine neuroimaging of preterm infants is required. Cranial ultrasonography (cUS) is the preferred neuroimaging modality to assess the presence, severity, and timing of GMH-IVH and to detect related complications with high sensitivity in preterm infants. There are several advantages of using cUS, including accessibility, portability, and the lack of ionizing radiation. Assessment of GMH-IVH with cUS should include views from the anterior fontanelle and supplemental acoustic windows. Based on the extent of hemorrhage, and the presence or absence of acute ventricular dilatation, GMH-IVH can be graded on a scale of I to III.[6] PVHI, which is noted separately, may present as a globular or fan-shaped echogenic lesion, ipsilateral to the side of GMH-IVH.[3] The natural evolution of PVHI involves the formation of a single large porencephalic or multiple small cysts, which are easily seen with cUS.[3,10] PHVD once detected, requires serial cUS at least weekly to monitor progression.[33]

Considering that the majority of GMH-IVH occurs within the first 3 days after birth, the first cUS should be performed in the first week. There are several published guidelines for the timing of cUS in preterm infants.[33,34] Guidelines published by the Canadian Pediatric Society (CPS) recommend that very preterm infants born less than 32 weeks' gestation should have initial imaging 4 to 7 days after birth, and repeat imaging 4 to 6 weeks after birth.[33] The same protocol should be considered for preterm infants born between 32 weeks and 36 weeks with risk factors. The CPS guidelines also state that a routine cUS at term-equivalent age should be performed for neonates born before 26 weeks' gestation. The CPS guidelines are similar to the American Academy of Pediatrics (AAP) guidelines, which also recommend the first cUS within 7 days after birth, and repeat imaging at 4 to 6 weeks in infants born less than 30 weeks.[34] A recent expert opinion paper by Inder and colleagues recommended more frequent cUS scans for very preterm infants, with scans on day 1 (optional), 3, 7, 14, 28, every other week until 34 weeks postmenstrual age, and a final scan at term-equivalent age or discharge.[35] Outside of these guidelines, additional cUS should be performed for any preterm infant with altered level of consciousness, neurologic signs, or clinical deterioration.

### *The Supportive Role of Brain Magnetic Resonance Imaging*

Brain MRI can be helpful in assessing GMH-IVH, parenchymal brain injury, and PHVD. The advantages of MRI include the high spatial resolution allowing for detailed

assessment of the brain parenchyma and lack of ionizing radiation. T1-weighted and T2-weighted images are ideal for assessing intracranial hemorrhage and parenchymal lesions (Fig. 1). Susceptibility-weighted imaging sequences can detect subtle areas of hemorrhage, particularly for grade I GMH-IVH or hemorrhage in less typical locations. Currently, there are no guidelines recommending routine brain MRI for preterm infants. However, a term-equivalent age brain MRI should be considered for preterm infants with abnormalities detected on cUS, greater burden of risk factors and for more detailed neuroprognostication. A review by Inder and colleagues described the importance of a term-equivalent age brain MRI in detecting less overt signs of preterm brain injury, or brain dysmaturation which may be seen following GMH-IVH.[35] The authors also suggest a brain MRI at term-equivalent age for preterm infants born less than 28 weeks or less than 1000 g, and for those born 28 to 32 weeks with risk factors or abnormal cUS findings.[35] Considering the diagnostic and prognostic capabilities of brain MRI, we strongly recommend considering brain MRI at term-equivalent age for the extremely preterm population.

## MANAGEMENT

### *Updates on Monitoring and Management of Posthemorrhagic Ventricular Dilatation*

Despite preventative strategies,[15,36] GMH-IVH will continue to occur in a substantial proportion of preterm infants and can progress to PHVD. Ventricular size monitoring is important in infants with PHVD and can be done with serial cUS (see Fig. 1). Ventricular index (VI) and anterior horn width (AHW) have been studied, and normal ranges for preterm infants across postmenstrual age have been published.[37–39] Measuring the occipital horn, or the thalamo-occipital distance (TOD), in the sagittal plane is also suggested as there can be a discrepancy between the enlargement of the anterior

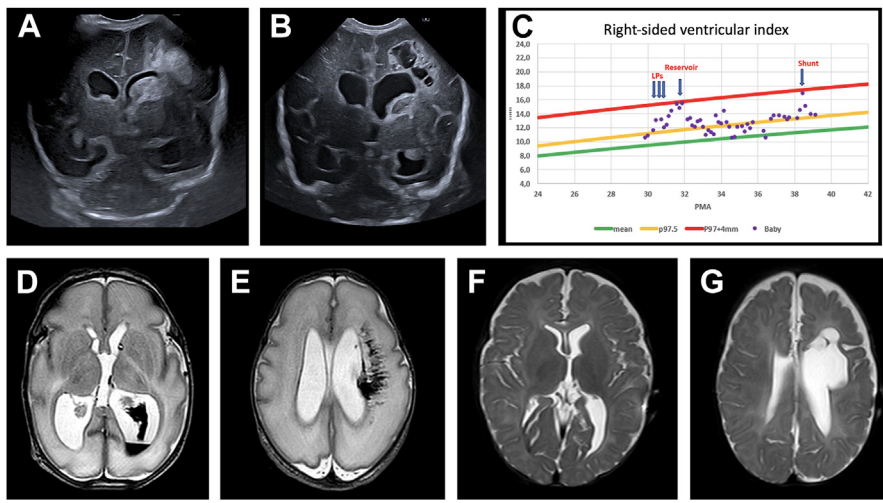


**Fig. 1.** (*A*) Coronal cUS scan of a preterm infant who was born at $29^{1/7}$ weeks' gestation and scanned on postnatal day 3 presenting with left-sided grade III GMH-IVH and PVHI. (*B*) The same infant at postnatal 5 weeks shows cystic changes in the left periventricular white matter area. (*C*) The chart shows measurements of the right ventricle and the timing of interventions for PHVD. (*D*, *E*) Early brain MRI (T2 sequence) on day 6 demonstrating left-sided grade III GMH-IVH and PVHI. (*F*, *G*) MRI (fast T2 sequence) at 6 months corrected age with expected evolution of PHVD into a porencephalic cyst.

and posterior horn. Alternative ventricular measurements are described (eg, frontal occipital horn ratio and frontal temporal horn ratio),[40] however, AHW and VI are the preferred measurements for monitoring PHVD.[41] PHVD is defined as the persistence of acute ventricular dilatation with VI greater than 2 standard deviations or greater than 97th percentile, and/or AHW greater than 6 mm.[37,38] When ventricular size exceeds these cut-offs, patients should be closely monitored with serial cUS for progression. A framework for monitoring PHVD describes 3 risk categories, green, yellow, and red, with each category having radiological and clinical criteria and management recommendations.[42]

There is an ongoing debate about the best time to intervene for progressive PHVD, with many centers waiting for clinical symptoms (rapid increase in head circumference, bulging fontanelle, split sutures, apnea, bradycardia) to occur, while others prefer early intervention, based on an increase in the ventricular measurements, as documented with serial cUS. Medical management for PHVD using acetazolamide and furosemide is not recommended as it is associated with increased mortality.[43,44] Although the drainage, irrigation, and fibrinolytic therapy (DRIFT) method demonstrated sustained cognitive benefits to 10 years of age in preterm infants with PHVD, it also increased the rate of secondary hemorrhages and is an invasive technique.[44,45] Today, PHVD-related interventions typically begin with lumbar punctures to decompress the ventricles followed by temporizing interventions such as insertion and taps from a ventricular reservoir or insertion of a ventriculo-subgaleal shunt.[42,46] In patients with ventricular reservoirs, CSF can be aspirated once or twice a day beginning with 10 mL/kg with an aim to reduce the VI over the next 7 to 10 days to within the normal range.[47] When infants with a ventricular reservoir reach 2000 to 2500 g, CSF removal can be held for a few days as a challenge. If ventricular indices increase during the challenge, then insertion of a ventriculoperitoneal (VP)-shunt should be considered.[47] The (Early versus Late Ventricular Intervention [ELVIS]) study demonstrated that early interventions based on cUS measurements reduced the VP-shunt rate to a range of 20% to 25%, compared with 40% to 60% reported in previous literature.[48] Complications of VP-shunts include obstruction, shunt malfunction, and infection,[49] therefore, earlier interventions should be implemented to avoid VP-shunt insertion.

Recently, the Children's Hospitals Network Consortium reported significant intercenter variation in the rate of intervention reflecting variability in care and referral patterns.[46] Considerable variability was also reported in the management of PHVD among Canadian centers and between Canadian and European practices.[50] There is accumulating evidence supporting the benefits of earlier interventions for PHVD.[51–53] A multicenter retrospective observational study by Leijser and colleagues compared early intervention for PHVD based on ventricular measurements to late intervention based on clinical signs of increased intracranial pressure. In this study, preterm infants who received early intervention for PHVD had better neurodevelopmental outcomes at 18 to 24 months than those who received late intervention.[53] Among the preterm infants in the early intervention group, those who required a VP-shunt had similar cognitive and motor outcomes as those who did not require a VP-shunt. In contrast, among infants who received late intervention, those who required a VP-shunt had worse cognitive and motor outcomes than infants without a shunt.

The recent randomized controlled ELVIS trial also studied the timing of PHVD interventions.[48,52] In this study, 126 preterm infants with progressive PHVD were prospectively recruited into a low-threshold for intervention (VI >97th percentile and AHW >6 mm and/or TOD >25 mm) or high-threshold intervention (VI >97th percentile + 4 mm and AHW >10 mm). In both groups, interventions were based on cUS

measurements and initiated in asymptomatic infants, to reduce ventricular size to less than 97th percentile. Although no difference in the VP-shunt rate was observed between groups, the need for VP-shunt placement in both groups was the lowest reported in the literature (19% and 23% in the low-threshold and high-threshold groups, respectively). In a nested substudy of the ELVIS trial, the high-threshold group had greater ventricular volumes and more brain injury compared with the low-threshold group, further demonstrating the benefits of early intervention.[52] A follow-up study of the same cohort at 2 years of age found that low-threshold intervention was associated with lower odds of death and neurodevelopmental impairment in the post hoc analysis.[51] In their meta-analysis, Lai and colleagues examined a cohort of 2533 infants with PHVD to assess if variability in the type and timing of temporizing neurosurgical interventions influenced patient outcomes.[49] They found that delaying temporary neurosurgical interventions was associated with an increased likelihood of progressing to VP-shunt placement and moderate-to-severe neurodevelopmental impairment.

The advantages of early intervention in PHVD may be due to the reduction of pressure on the surrounding brain tissue or decreased inflammation and neurotoxicity.[54–57] Isaacs and colleagues showed that PHVD was associated with diffuse white matter injury, including axonal and myelin injury, cellular infiltration, and inflammation.[54] Diffusion tensor imaging studies have found that PHVD was associated with abnormal white matter microstructure in the periventricular, parietal, and occipital white matter.[55,56] Similarly, lower fractional anisotropy values have been reported in the corpus callosum of infants with PHVD, which was in turn associated with cognitive and motor scores at 2 years.[57]

### *Emerging Therapies for Posthemorrhagic Ventricular Dilatation*

The search for additional PHVD management strategies is ongoing, with groups investigating the role of alternative neurosurgical techniques and the use of stem cells. Neuroendoscopic lavage (NEL) for PHVD has been studied, which involves using an endoscope to evacuate blood clots and irrigate the ventricles.[58–60] NEL can be performed once or serially to remove blood products from the ventricles, reduce inflammation, and prevent ventricular dilatation. One retrospective cohort study of 46 preterm infants with PHVD found that NEL was associated with smaller ventricular size and improved neurodevelopmental outcomes.[58] In terms of adverse effects, CSF infection was seen in 20%, leaks in 13%, and secondary hemorrhage in 7% of infants. The mortality rate was 7%, however, death was not related to NEL or postoperative complications. In a retrospective cohort study, 26 preterm infants who underwent NEL and endoscopic third ventriculostomy had a decreased need for VP-shunt.[59] Similarly, a second retrospective cohort study of 60 preterm infants found that NEL was associated with lower rates of VP-shunts relative to traditional neurosurgical approaches.[60] A recent consensus guideline has been proposed by a group of neurosurgeons to standardize the indications and procedures of NEL for PHVD.[61] In these guidelines, preterm infants can be considered for NEL if they are born preterm (<37 weeks) and have PHVD greater than 97th percentile + 4 mm. These guidelines state that there are no clear indications of repeat NEL, but it may be considered in cases with high clot burden or if repeat operation is required for temporizing device dysfunction.[61] An international multicenter prospective cohort study (Treatment of Posthemorrhagic Hydrocephalus [TROPHY]) evaluating surgical treatments, including NEL for the management of PHVD, is ongoing.[62] The first results of TROPHY reported that of 110 patients treated surgically for PHVD, 43% received NEL, and centers implementing NEL had lower rates of external ventricular drains.[63] A randomized

controlled trial in the United Kingdom examining outcomes of reservoir insertion compared with NEL (Endoscopic Lavage After Intraventricular Hemorrhage in Neonates [ENLIVEN] study) is actively enrolling participants and will provide further insight into the role of NEL in PHVD.

Stem cell therapy for PHVD has been investigated in preclinical studies and a phase-1 human study.[64,65] In a study by Ahn and colleagues intraventricular transplantation of human umbilical cord mesenchymal stem cells (MSCs) was found to attenuate PHVD and brain injury in newborn rats.[64] The underlying mechanism may relate to the reduction of inflammation and/or neuroprotective effects of MSC-secreted brain-derived neurotropic factor (BDNF).[66] A separate study by Ahn and colleagues[65] showed that MSC with intact BDNF function was associated with decreased neuronal death in vitro (newborn rat cortical cells), and reduced brain injury and progression of PHVD in vivo (newborn rats) compared with BDNF knockouts. The same group performed the first phase-1 clinical trial examining the safety and feasibility of intraventricular MSC transplantation in preterm infants with PHVD.[67] In this study, 9 preterm infants received incremental doses of MSC, which was well tolerated with no serious adverse effects or death. The same group also finished enrollment for a phase-2 study, but the results are pending. Further randomized controlled trials are needed to better understand the risks, benefits, and efficacy of stem cell therapy.

## NEURODEVELOPMENTAL OUTCOME TRAJECTORIES

Despite advances in the detection and management of GMH-IVH, it is associated with an increased risk for mortality, neurodevelopmental delays, and disability.[68–70] Mortality rate ranges between 10% and 50%, which is more commonly seen with high-grade GMH-IVH in the presence of PVHI and PHVD.[2,13] Mortality rates are also higher in preterm infants with GMH-IVH born at earlier gestational age or lower birth weight (<750 g).[3] It should be noted that the high mortality rate reported in some studies may be attributed to redirection of care practices often in the context of multisystem involvement or comorbidities.[9]

GMH-IVH is associated with adverse neurodevelopmental outcomes including motor delays and impairment, cerebral palsy, cognitive and behavioral concerns, neurosensory impairments, and epilepsy.[69,71] Outcomes will vary based on the grade of GMH-IVH, site and extent of parenchymal involvement, concurrent PHVD, and additional clinical factors.[69–73] PHVD is associated with neurodevelopmental impairments with infants requiring VP-shunts being at greatest risk for poor neurodevelopmental outcomes.[74] Timing of intervention for PHVD matters and better outcomes are consistently reported with early intervention.[51,53,75] Of note, approximately 1 in 3 newborns with PHVD may experience spontaneous resolution, and this subset of newborns will have lower rates of neurodevelopmental impairments.[76] It has also been shown that extremely preterm infants who survive to 10 years of age after PHVD have on average lower health-related quality of life than their peers in self-care, mobility, cognition, and dexterity domains.[77] In PVHI, there is parenchymal brain injury which may disrupt the descending motor tracts resulting in more severe motor impairment. Cerebral palsy, mostly unilateral spastic cerebral palsy, is seen in a higher proportion of children with PVHI.[9,51] Increasing size and severity of PVHI and involvement of the PLIC and trigone are associated with worse motor outcomes.[9,78] The presence of PLIC diffusion restriction on MRI, within a week of PVHI onset can help with early prediction of motor impairment. Other regions that can be affected in PVHI include frontal, temporal, and occipital lobes, which can lead to cognitive and language delays, visual impairments and social-emotional and behavioral difficulties.[75,79,80]

## SUMMARY

GMH-IVH is a leading cause of brain injury and neurodevelopmental disability in children born preterm. cUS is the preferred modality for the diagnosis and evaluation of GMH-IVH, and an initial scan should be performed in the first days of life. Subsequent timing of cUS can be determined based on gestational age, risk factors, and the presence of previous cUS abnormalities. The management of GMH-IVH begins with preventative strategies aimed at modifiable risk factors. Once hemorrhage is detected, serial cUS is required to monitor for progression, and earlier intervention for PHVD based on ventricular measurements is recommended. PHVD interventions should begin with lumbar punctures and temporizing interventions before proceeding to VP-shunt insertion, which will be required in a subset of the affected infants. There are ongoing studies examining new therapies for PHVD including alternative neurosurgical techniques and stem cell therapy. Neurodevelopmental outcomes of GMH-IVH will vary based on grade, location, extent, the presence of PHVD, PVHI, and additional clinical risk factors.

***Best Practices***

- cUS is the preferred neuroimaging modality to screen for GMH-IVH and monitor related complications.
- Prevention of GMH-IVH includes targeting modifiable perinatal and neonatal risk factors that can alter cerebral blood flow and intracranial pressure.
- Management of GMH-IVH involves serial cUS to monitor progression and enable early intervention for PHVD (based on ventricular measurements and prior to the emergence of clinical signs) with lumbar punctures, ventricular access device insertions, and eventually ventriculoperitoneal shunts.

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## DISCLOSURE

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# Updates in Treatment of Hypoxic-Ischemic Encephalopathy

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**KEYWORDS**

• Brain • Encephalopathy • Neonate • Neuroprotection • Neurorestoration

**KEY POINTS**

- Hypoxic-ischemic encephalopathy (HIE) remains one of the leading causes of nervous system disabilities around the world.
- Therapeutic hypothermia (TH) is the current standard of care treatment for HIE.
- Up to 29% of neonates with HIE treated with TH still experience adverse neurodevelopmental outcomes.
- Treatments for HIE targeting neuroprotection and/or neurorestoration are under investigation.
- Attentive daily management of the multiorgan failure during the first days of life is essential.

## INTRODUCTION

Birth asphyxia and the resulting hypoxic-ischemic encephalopathy (HIE) in neonates cause significant mortality and long-term morbidities. HIE is a subtype of neonatal encephalopathy (NE), characterized by a hypoxic-ischemic (HI) sentinel event around the time of birth and/or the development of the typical pattern of HI brain injury.[1] Currently, the standard treatment for neonates with HIE is therapeutic hypothermia (TH), which has improved outcomes in neonates with moderate and severe HIE. However, this treatment has several limitations: a sentinel event is not always clearly identified, and thus, clinical criteria for treatment are not met (eg, delays in diagnosis exceeding the optimal time limit for initiating TH); many hospitals around the world lack the resources to provide TH safely and reliably; and up to 29% of treated neonates still

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| Abbreviations | |
|---|---|
| aEEG | Amplitude-integrated electroencephalogram |
| cEEG | Continuous video electroencephalogram |
| EEG | Electroencephalogram |
| EPO | Erythropoietin |
| HI | Hypoxic-ischemic |
| HIE | Hypoxic-ischemic encephalopathy |
| HRV | Heart-rate variability |
| IV | Intravenous |
| MSC | Mesenchymal stem cell |
| NAA | *N*-acetylaspartate |
| NMDA | *N*-methyl-D-aspartate |
| NE | Neonatal encephalopathy |
| NSC | Neural stem cell |
| RCT | Randomized controlled trial |
| TH | Therapeutic hypothermia |
| UCBC | Umbilical cord blood cell |

develop disabilities despite TH.[2,3] Therefore, there is an important need for alternative treatment options for HIE.

In this review, the authors review the initial assessment of neonates when faced with a clinical suspicion of HIE, the current management practices for HIE, as well as the outcomes of the affected children.

## EVALUATION AND ASSESSMENT

NE is an altered level of consciousness, seizures, hypotonia, and altered reflexes in a neonate.[2] Although determining the cause of NE is not always straightforward, HIE is one of the most frequent causes.[4] The presentation of neonates with NE may thus vary,[5] because the origin of the NE may differ and/or the HI event may have occurred at a different time during the peripartum or intrapartum period. A low or variable level of consciousness, reduced spontaneous movements, seizures, low Apgar scores, or resuscitation at birth should prompt timely and thorough evaluation by neonatal health care providers.[6] Following resuscitation and stabilization, determination of eligibility for TH should be initiated as soon as possible within the first 6 hours of life. The initial evaluation should also investigate the cause of the NE, even though a clear cause is not always identified. Maternal history, obstetric history, and intrapartum events are relevant to collect to determine if an HI event is at cause for the NE.[1]

### *Clinical and Biochemical Assessments*

All neonates born at or after 36 weeks with a history of a sentinel HI event, a need for significant resuscitation at birth, acidemia from the cord or on a postnatal gas within the first hour of life, and/or a 10-minute Apgar score of 5 or less should be assessed for TH eligibility assessment (**Fig. 1**).[7] Sentinel events may include a variety of events, such as maternal (eg, uterine rupture), fetal (eg, fetal heart rate abnormalities), and/or placenta issues (eg, placenta abruptio).[2] Inclusion criteria for TH may vary slightly by location, but typically include evidence of fetal and/or neonatal distress associated with moderate to severe encephalopathy.[8] If a neonate meets the TH clinical criteria, but is born in a facility that does not provide this treatment, the health care providers should immediately communicate with and facilitate transfer to a center equipped to offer TH for the optimal management of these neonates.[9,10] If deemed appropriate, cooling can be started on transport for outborn neonates with servo-control devices

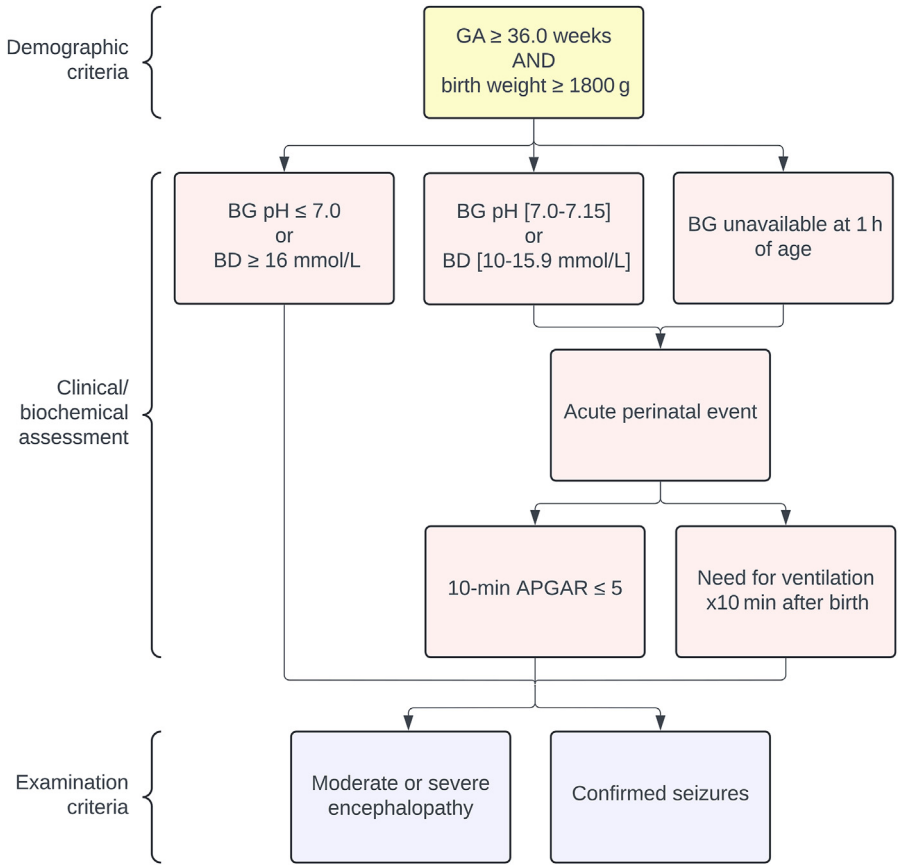


**Fig. 1.** Algorithm for quick assessment of eligibility for TH.[5,56] BD, base deficit; BG, blood gas; GA, gestational age.

or with closely monitored passive cooling, because it decreases the time-to-target temperature and improves outcomes.[11]

In addition to the brain, multiple organs may be affected by the NE/HIE and need to be monitored and supported until recovery. Affected neonates should be continuously monitored in terms of heart rate, respiratory rate, oxygen saturation, blood pressure, and temperature during the first days of life. Lactates levels may reflect the severity of the initial event, the hemodynamics, and/or ongoing organ injuries (brain, impaired glucose metabolism, and so forth).[12] Cardiac troponin I and creatine-kinase levels may more specifically reflect the hemodynamics.[13] Creatinine values are important indicators of acute kidney injury.[14,15] Glucose imbalance may worsen injury.[16] Other issues important to monitor are electrolytes abnormalities, coagulation, and liver function tests.[5,7]

Furthermore, histopathologic examination of the placenta is recommended to highlight features that could have predisposed the neonates to NE/HIE and contributed to associated brain injury.[17,18]

### *Neurologic Assessment*

After resuscitation and stabilization, the neonates meeting TH clinical/biochemical criteria should be evaluated through a standardized neurologic examination within

the first hours of life.[5] The most used scoring systems to determine the level of NE include the modified Sarnat score[5] and the Thompson score.[19–22] The modified Sarnat is based on the Sarnat scoring system, which has been modified over the years to enhance its application in clinical trials.[23] It is the score that has been the mostly widely used in TH trials.[24–28] This scoring system requires categorization of encephalopathy according to level of consciousness, spontaneous activity, posture, muscle tone, primitive reflexes, and autonomic reflexes[29]; neonates with 3 or more findings in the stage of moderate to severe encephalopathy fulfill the neurologic criteria for TH.[30] Alternatively, the Thompson score proposes a numeric score to describe the severity of encephalopathy. The severity of encephalopathy may vary during the first hours of life, so repeated examination should be performed within the first 6 hours of life if a neonate meets the TH clinical/biochemical criteria on the initial evaluation, but not the neurologic assessment criteria.[7]

### *Electrophysiologic Assessment*

Neonatal seizures are a common feature of NE/HIE. To optimize seizure detection and management, early monitoring using continuous video electroencephalogram (cEEG) or amplitude-integrated electroencephalogram (aEEG) is warranted.[7,31] Confirmed seizures are an additional inclusion criteria for TH.[32]

### *Neuroimaging*

Neuroimaging studies are used to diagnose pattern and extent of brain injury and to discuss prognosis with parents.[4] MRI remains the modality of choice in this context, even if a point-of-care head ultrasound may be considered on the first day of life to rule out major intracranial hemorrhage. A brain MRI is typically obtained after rewarming for diagnosis and prognosis; it may be repeated around day 10 of life to assess the full extent of injury, especially if the initial neuroimaging findings are inconsistent with the clinical status.[2,4,33] An MRI may also safely be performed during TH without treatment interruption[34,35] and already demonstrates extent of injury by day 2 of life[36,37]; this may be useful especially when withdrawal of care is contemplated or for research purposes.[36,37]

Anatomic T1- and T2-sequences are used to detect ischemia and hemorrhage; changes may be subtle within the first days of life and become more evident by the second week of life. Diffusion-weighted imaging allows early detection of edema and thus contributes to diagnosis of injury within the first days of life. Magnetic resonance spectroscopy is also commonly used in the context of NE/HIE to assess metabolic changes occurring after HI injury[4]; lactates and *N*-acetylaspartate (NAA) are the most reported metabolites.[4,38]

## MANAGEMENT

Management of neonates with NE/HIE is complex and should be personalized according to the illness severity during the first days of life.[7,39] It includes supportive treatments and TH if indicated.

### *Daily Management*

Daily management of neonates with NE/HIE should be first supportive with the target goal to re-establish homeostasis of the different body organs/systems.[7] Ongoing cardiac dysfunction, acute kidney injury, electrolyte imbalances, impaired gas exchange, and such, may all contribute to worsening of brain injury and thus subsequent adverse neurodevelopmental outcomes.[39–42] **Table 1** highlights the clinical features of HIE, the

**Table 1**
**System-based monitoring and management**[6,15,17,70–73]

| System | Clinical Features | Monitoring/Investigations | Management Considerations |
|---|---|---|---|
| Neurologic | Abnormal neurologic examination<br>Seizures | aEEG/cEEG<br>NIRS<br>MRI | IV phenobarbital is first-line ASM, should be used for EEG-confirmed seizures<br>Avoid systematic prescription of ASM at discharge |
| Respiratory | Hypoxemia<br>Hypocapnia<br>Respiratory acidosis | Cord blood gas<br>Arterial blood gas<br>CXR | Extubate when stable to limit hypocapnia<br>Use pH-stat for temperature-corrected blood-gas values interpretation[7]<br>Use lowest $F_iO_2$ effective to achieve $P_aO_2$ (50–70) mm Hg and $SpO_2 \geq 92\%$ |
| Cardiovascular | Hypotension<br>Shock<br>Arrythmias<br>Heart failure<br>Ischemia | Blood gas<br>Echocardiography<br>Cardiac troponin<br>Lactates | Correct hypotension; adjust treatment according to clinical pictures and lactates[7]<br>Sinus bradycardia is acceptable if adequate cardiac output<br>Consider ECMO if severe pulmonary hypertension |
| Metabolic | Hypoglycemia/hyperglycemia<br>Hypocalcemia<br>Hypomagnesemia<br>Metabolic acidosis<br>Hyponatremia | Blood glucose<br>Calcium<br>Lactates<br>Electrolytes | Start with 10% IV dextrose, customize as needed aiming for $\geq$2.6 mmol/L, avoid hyperglycemia<br>Customize IV fluids to meet electrolyte requirements |
| Renal | Acute tubular necrosis<br>Oliguria<br>Polyuria<br>Hematuria | Urea<br>Creatinine<br>Fluid balance (body weight, urine output, fluid intake) | Start with 60–70 mL/kg/d of IV fluid with customized electrolytes and glucose<br>Avoid systematic fluid restriction[7]<br>If oliguria, management based on cause of oliguria |
| Hematologic | Elevated nucleated RBCs<br>Thrombocytopenia<br>Bleeding, DIC<br>Thrombosis<br>Anemia | CBC<br>Coagulation profile | Transfuse platelets if needed<br>Transfuse FFP if needed<br>Transfuse cryoprecipitate if needed<br>Give supplemental vitamin K if needed<br>Transfuse PRBC if needed |
| Gastrointestinal | Feeding intolerance<br>GI bleeding<br>Necrotizing enterocolitis | LFTs | NPO during TH, but possible benefit of introduction of enteral breast milk if stable[7] |

(*continued on next page*)

**Table 1**
**(*continued*)**

| System | Clinical Features | Monitoring/Investigations | Management Considerations |
|---|---|---|---|
| Infectious | Sepsis | CBC<br>Blood culture | Initiate empiric antibiotics until sepsis is excluded |
| Temperature | Hypothermia/hyperthermia | Esophageal or rectal temperature | Start TH as soon as possible within the first 6 h of life<br>Avoid hyperthermia |
| Skin | Subcutaneous fat necrosis | Regular skin examination | Frequent repositioning of neonates on cooling during TH<br>Hyperhydration and diuretic treatment for SFN<br>Monitor for hypercalcemia |
| Comfort & sedation | Discomfort<br>Shivering | | Promote nonpharmacologic approaches (holding, parental presence)<br>Consider low-dose morphine |

*Abbreviations:* ASM, antiseizure medication; CBC, complete blood count; CXR, chest X ray; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; $F_{I}O_2$, fraction of inspired oxygen; GI, gastrointestinal; LFTs, liver function tests; NIRS, near-infrared spectroscopy; NPO, nil per os; $P_{a}O_2$, partial pressure of oxygen in arterial blood; PRBC, packed red blood cells; RBCs, red blood cells; SFN, subcutaneous fat necrosis; $Spo_2$, peripheral capillary oxygen saturation.

monitoring methods, and the management considerations, classified by body organ/system. Variations in the management of neonates with HIE have been demonstrated across neonatal intensive care units (NICUs) and may explain variations in outcomes, such as death and/or brain injury.[21,43,44] Further research in a large international cohort of neonates with HIE is needed to test optimal care practice bundle.[7]

Health care providers should promote shared decision making with parents. Frequent transparent and consistent communication, including discussion of upcoming events, as well as interpretation of prognostic markers, is helpful to families. Parents may be referred to social workers, psychologists, and peer-support groups to help them navigate this event. Parents should be encouraged to get involved in the daily care of their neonate and hold their baby, even during TH.[7] This may contribute to promoting bonding, improving comfort, and decreasing stress for the neonate and the family.[45]

### *Therapeutic Hypothermia*

Whole-body TH consists of decreasing core temperature to 33.5°C for 72 hours, followed by slow rewarming to normothermia.[27,46–49] It reduces the risk of death and severe disability when initiated within 6 hours of birth in neonates meeting TH inclusion criteria, with these benefits lasting into childhood.[50–53]

Upon HI injury, the lack of metabolic substrates to the brain leads to primary energy failure, which includes increased lactate production, excitotoxicity, cerebral edema, microvascular damage, and cell death.[54] After successful resuscitation, the brain enters a latent phase. About 6 to 8 hours later, secondary energy failure occurs with a burst of oxidative damage, inflammation, and cell death. This is thought to be due to failure to adapt to the aerobic condition following reperfusion.[55] Starting after the secondary energy failure and lasting weeks to months after, the tertiary phase takes place, with increased seizure susceptibility, persistent inflammation, and impaired connectivity and maturation.[54]

As a neuroprotective therapy, TH targets the latent phase.[56] TH prevents the injury caused by the secondary energy failure by decreasing metabolic demand, excitotoxicity, and cerebral edema, along with preventing apoptosis and stabilizing the blood-brain barrier.[55] TH should thus be initiated as soon as possible within the first 6 hours of life to maximize its chances to prevent secondary energy failure and injury.[55,56]

Whole-body cooling is usually preferred over selective head cooling, because none of the 2 methods has proven to be significantly better,[27,57] but whole-body cooling is less labor-intensive and less costly.[56] Deeper or longer cooling is not recommended.[58] Although no randomized controlled trial (RCT) has formally evaluated the rate of rewarming, neonates are typically rewarmed at a rate of 0.5°C per hour.[59] TH has been associated with systemic complications, such as sinus bradycardia, thrombocytopenia, and coagulopathy, but these issues can be monitored and managed.[60]

In the original TH trials, only the neonates with moderate to severe NE/HIE were selected.[27,46–49] However, over time, practices have deviated to include neonates with mild NE and/or to start cooling beyond 6 hours of life.[61,62] Mild HIE has also been associated with a risk of cognitive and motor impairments,[63,64] and some retrospective studies have suggested possible benefit of TH for mild HIE in reducing the incidence of MRI brain injury, and improving cognitive composite scores.[61,62,65,66] However, a recent RCT suggested that TH did not reduce brain MRI biomarkers in neonates with mild HIE.[67] Additional RCTs are ongoing in neonates with mild HIE to formally test safety and efficacy of TH. The only published RCT about late (ie, beyond 6 hours of life) cooling did not demonstrate significant benefits.[58]

Another area of uncertainty is whether TH is safe and efficient in late preterm neonates. Two TH RCTs used 35.0 weeks of gestational age as the lowest boundary of the demographic inclusion criteria and demonstrated the benefit of TH; however, the number of neonates born between 35.0 weeks and 35.6 weeks in both studies was small.[47,68] Although some retrospective studies suggest that the use of TH for the treatment of HIE in preterm (34.0–35.6 weeks of gestational age) neonates is safe and feasible,[69] a formal RCT is ongoing to test its safety and efficacy. Until then, the decision to cool late preterm neonates should be based on clinical judgment and shared decision making with families.[3]

### *Therapies Under Investigation*

Although TH may *prevent* the development of brain injuries in some neonates with HIE by avoiding the secondary energy failure after birth asphyxia, it is often not successful,[28,46,48,70–73] because up to 30% of the neonates with HIE treated with TH still develop brain injury and thus significant neurodevelopmental impairments.[27,74] Also, it remains debated if TH is efficient in low- and middle-income countries.[75] The search for further therapies is thus actively ongoing. **Table 2** presents a summary of the therapeutic interventions currently being investigated, classified by mechanisms of action. The authors differentiated neuroprotective therapies *preventing* the development of brain injuries and neurorestorative therapies *repairing* brain injuries. Here some of these potential therapies are discussed. For many of these therapies, optimal dosing and timing of treatment to give the therapy still need to be determined.

#### *Neuroprotective therapies*

**Melatonin.** In animal models of HIE, melatonin was neuroprotective as a monotherapy and as an adjunct therapy to TH with a potentiating effect.[76] In preclinical models, effect was optimal when administered in the hours after the initial event.[77] Dosage varied between 10 and 20 mg/kg with a first dose right after injury, and repeat doses usually at 24 and 48 hours after injury, mostly through intraperitoneal route.[78] So far, in human clinical trials, both the intravenous (IV) and the oral routes are being explored.[79] A few RCTs in human neonates have demonstrated encouraging results,[79,80] although sample sizes remained small.[81] Larger RCTs are needed to establish safety and efficacy of melatonin.

**Allopurinol.** Allopurinol is a xanthine oxidase inhibitor with antioxidative action.[82] In preclinical models, allopurinol was given as a single intraperitoneal injection 15 minutes after the HI event.[83] A phase III RCT is underway to evaluate outcome in neonates with HIE receiving allopurinol in addition to TH. In this trial, neonates are receiving a first dose of allopurinol intravenously less than 30 minutes after birth, and a second dose 12 hours later.[84]

**Caffeine.** Caffeine, which is already widely used in the NICU for apnea of prematurity, has been suggested as an adjuvant to TH.[85] Preclinical studies have suggested improved functional outcomes when combined with TH.[86] In studies in rodents, caffeine was given intraperitoneally or enterally.[86] It appeared to reduce moderate to severe brain damage only when given directly after the HI injury, but not 6, 12, or 24 hours later.[87] In a phase I trial in human neonates, a loading dose of 20 mg/kg of caffeine citrate was given intravenously, with up to 2 subsequent doses of 5 mg/kg at 24-hour intervals,[88] without significant adverse event.[88]

**Magnesium sulfate.** Magnesium sulfate therapy may modulate the *N*-methyl-D-aspartate (NMDA) receptors and, through this mechanism, reduce excitotoxicity.[89] In preclinical models, it has been used both prenatally and postnatally for

**Table 2**
**Novel therapeutic agents by mechanism of action (by alphabetical order)**[55,78,81,82,84,86,88,90,97,102,107,111,126,143–145]

| | Neuroprotective | | | | | |
|---|---|---|---|---|---|---|
| **Therapies** | **Antiexcitatory** | **Antiapoptotic** | **Anti-inflammatory** | **Antioxidative** | **Neurorestorative** | **Route, Dosing, and Schedule** |
| Allopurinol | | | ✓ | ✓ | | Pre: IP, 135 mg/kg immediately post-HI<br>RCT: IV, 20 mg/kg post-HI (30 min after birth)<br>+ 10 mg/kg H12 if TH |
| Azithromycin | | | ✓ | | | Pre: IV or IV, 1.5–150 mg/kg 15 min–4 h post-HI or 2 h post-HI + H24 + H48 |
| Caffeine | | | ✓ | | | Pre: IP or PO, 5–20 mg/kg immediately post-HI<br>RCT: IV, 20 mg/kg post-HI (before 24 h of life)<br>+ 5 mg/kg q24h ×2 doses |
| Erythropoietin | ✓ | ✓ | ✓ | ✓ | ✓ | Pre: IV, 5000 U/kg 3 h post-HI<br>+ 833.3 U/kg/h × 69 h or 1000 U/kg immediately post-HI + H24 + D7<br>RCT: IV, 1000 U/kg post-HI (before 26 h of life) + D2 + D3 + D4 + D7 |
| $MgSO_4$ | ✓ | ✓ | ✓ | ✓ | | Pre: IP, SC, or IV, 100–1000 mg/kg immediately post-HI<br>RCT: IV 250 mg/kg within 6 h post-HI<br>+ H24 + H48 |
| Melatonin | ✓ | ✓ | ✓ | ✓ | | Pre: IP, 10–20 mg/kg immediately post-HI + H24 + H48 or 0.5 mg/kg/h infusion × 2 h or 10–15 mg/kg immediately post-HI<br>RCT: PO or IV, single dose on admission or q2h<br>×8 doses or daily ×3–5 d |

(*continued on next page*)

**Table 2**
**(*continued*)**

| Therapies | Neuroprotective: Antiexcitatory | Neuroprotective: Antiapoptotic | Neuroprotective: Anti-inflammatory | Neuroprotective: Antioxidative | Neurorestorative | Route, Dosing, and Schedule |
|---|---|---|---|---|---|---|
| Sildenafil | | ✓ | ✓ | | ✓ | Pre: IP immediately post-HI or PO 12 h post-HI<br>RCT: PO 2–3 mg/kg q12h × 7 d starting D2/3 |
| Stem cells | | ✓ | ✓ | | ✓ | Variable, usually single dose |
| TH | ✓ | ✓ | ✓ | | | 33.5°C × 72 h started within 6 h |
| Topiramate | ✓ | | | | | Pre: IP 20–100 mg/kg immediately post-HI + H2 or PO 50 mg/kg immediately post-HI<br>+ H2 + q12h × 5 d<br>RCT: PO 5 mg/kg post-HI (at TH initiation) + 3 mg/kg/d × 5 d |
| Xenon | ✓ | ✓ | | | | Pre: Inhaled 50% Xe × 3 h immediately or up to 2 h post-HI<br>RCT: Inhaled 30% Xe × 24 h immediately post-HI |

*Abbreviations:* D, day postinsult; H, hours postinsult; IP, intraperitoneal; $MgSO_4$, magnesium sulfate; PO, oral administration; Pre, preclinical studies; SC, subcutaneous; Xe, xenon.

neuroprotection. For postnatal administration, rodents received a single dose between 100 and 1000 mg/kg by subcutaneous or intraperitoneal route, whereas large animals received 160 to 400 mg/kg IV.[90] In a clinical trial in 134 neonates testing magnesium sulfate as an adjunct to TH, the neonates received either 250 mg/kg of magnesium sulfate IV within 6 hours of birth, with 2 subsequent doses at 24-hour intervals, in addition to TH, or TH only; magnesium sulfate therapy in addition to TH did not significantly reduce neonatal mortality and neurodevelopmental outcome at 1 year of age.[91] Another clinical trial with a sample size of 200 neonates followed the same regimen of administration of magnesium sulfate as monotherapy and suggested that it improved mortality and short-term outcome defined as early discharge and oral feeding.[92] However, a systematic review and meta-analysis, including 20 RCTs and a total of 1485 infants, found that, when used alone, magnesium sulfate did not significantly reduce death or abnormal neurologic examination at NICU discharge.[93]

**Topiramate.** Topiramate is an antiseizure medication used for treating neonatal seizures, with potential neuroprotective properties, primarily through antiexcitatory mechanisms. In preclinical models, monotherapy reduced brain injury,[55,94] when administered in rodents as 2 intraperitoneal injections (20–100 mg/kg), immediately after and 2 hours after the HI event, or by oral route (50 mg/kg) immediately after the HI event, 2 hours after, and at 12-hour intervals for 5 days.[95] All formulations were neuroprotective, but starting treatment 2 hours after HI was not protective.[95] An RCT with 110 neonates with HIE, who received either topiramate at an initial dose of 5 mg/kg and maintenance dose of 3 mg/kg/d for 5 days orally in addition to TH or a placebo, showed a trend toward less mortality and seizures, but the difference was not significant; no improvement was seen on MRI brain injuries.[96]

**Xenon.** Xenon is a noble gas, which acts as a noncompetitive antagonist of the NMDA subtype of the glutamate receptor and decreases excitotoxicity and apoptosis.[97] Preclinical studies have shown that xenon attenuated brain damage and improved neurobehavioral function.[97] Although xenon acted synergistically with TH, it was most effective as monotherapy.[97] An RCT in 92 neonates with HIE demonstrated that administration of xenon was safe and feasible, but did not demonstrate improvements in MRI markers of brain injury,[98] and did not report long-term neurodevelopmental outcome.[99]

**Azithromycin.** Azithromycin is an antibiotic with anti-inflammatory properties.[100] In rodent models of HIE, azithromycin administered intraperitoneally with a 3-dose regimen beginning 2 hours post-HI (45.0 mg/kg), and repeated at 24 hours and 48 hours (22.5 mg/kg), was most effective at improving sensorimotor function and reducing the extent of brain damage, although single-dose protocols still displayed neuroprotection, with efficacy depending on dose and time to treatment.[100] In lambs, IV azithromycin treatment allowed earlier extubation, improved ability to feed and activity assessed in the first week of life.[101] Research in preclinical models of HIE is ongoing to look into the efficacy and safety of azithromycin combined with TH.[102] No RCTs have yet investigated the safety or efficacy of azithromycin in the context of neonatal HIE; its previous use in neonates has been associated with QT prolongation.[102]

### *Neurorestorative agents*

Most of these neurorestorative therapies aimed at repairing brain injuries may also have neuroprotective properties.

**Erythropoietin.** Erythropoietin (EPO) was proposed as another potential therapy for neonatal HIE after it displayed neuroprotective and neurorestorative effects in

preclinical models.[103] It acts in the brain by decreasing neuronal death and promoting neurogenesis and angiogenesis.[103] In preclinical studies in a lamb model of HIE, who received a loading dose of 5000 units/kg of recombinant EPO IV, followed by continuous infusion of 833.3 unit/kg/h for 72 hours, with or without TH, neuroprotection was observed from both TH and EPO individually.[104,105] However, EPO had limited additional benefits when given in combination with TH.[104,105] After phase I and phase II trials demonstrated the safety of EPO for neonates with HIE,[106–108] a larger phase III RCT in 500 neonates with HIE did not demonstrate significant benefit regarding the combined death and neurodevelopmental outcome at 22 to 36 months of age.[109] Additional trials testing this therapy are ongoing.[110] Darbepoetin, a longer-acting form of EPO, is also being tested in neonates with HIE.[111,112] The timing and the dose of EPO may be crucial factors to obtain its full effects.

**Stem cells.** Stem cells therapies have been widely investigated in the last years. In the context of HIE, most promising sources include umbilical cord blood cells (UCBCs), mesenchymal stem cells (MSCs), and neural stem cells (NSCs).[113] UCBCs could be used for autologous transplantation and may thus have low immunogenic potential. Various sources of stem cells have been tested in rodents, such as UCBCs, umbilical cord tissue-derived MSCs, placenta-derived MSCs, endothelial progenitor cells, or bone-marrow MSCs; they were given intraperitoneally, intravenously, intrathecally, or via the intraventricular route, and the time of treatment varied between 3 hours post-HI and 3 weeks post-HI, with some studies using a single dose, whereas others using repeated doses.[114,115] In preclinical models, UCBCs promoted neurogenesis, differentiation, and maturation of NSC and angiogenesis, in addition to having antiapoptotic and anti-inflammatory effects.[113] Clonally expanded immortalized MSCs from adult bone marrow grafts have been delivered intranasally in a rodent model of neonatal HIE, producing a stronger anti-inflammatory effect and inducing neural regeneration,[114] reducing HI-induced cognitive deficits in adolescence.[114] Phase I trials in neonates with HIE have deemed the administration of autologous UCBCs to be safe and feasible.[113,116,117] Additional studies are needed to determine the optimal type of stem cells, and the best timing and method of delivery in the context of neonatal HIE.

Interestingly, a recent RCT evaluating cord milking in 1730 neonates demonstrated that it reduced the rate of moderate to severe HIE and the need for TH.[118] This result widely contrasted with the practice of avoiding delayed cord clamping in nonvigorous term and near-term neonates. It led to a change in the Neonatal Resuscitation Program recommendation on cord handling, and now the option of cord milking in nonvigorous term and near-term neonates is included.[119]

**Sildenafil.** Sildenafil is a phosphodiesterase type 5 inhibitor, already used in neonates for the treatment of pulmonary hypertension. It has been found to prevent neuronal death, enhance neurogenesis and synaptic plasticity, and improve motor outcomes in preclinical models of HIE.[120–122] In these models, sildenafil was administered either intraperitoneally immediately after HI[123,124] or enterally with a delay after HI.[121,122] Moreover, it appeared to have a synergistic effect in reducing neuroinflammation when administered along with TH.[125] A phase I RCT demonstrated the feasibility and safety of administering sildenafil along with TH in a limited number of neonates with HIE.[126] Further trials are needed to assess efficacy.

**Outcomes.** In neonates with HIE, TH has improved survival without major neurologic disabilities at 18 months,[27,53,60,127] and this beneficial effect persisted at least until 6 to 7 years of age.[53] However, worldwide, HIE remains the second leading cause of

nervous system disability-adjusted life-years, a time-based measure combining years of life lost owing to premature mortality and years of healthy life lost owing to disability.[128] More than one million infants still die annually from birth asphyxia and the resulting neonatal HIE, especially those with severe HIE[5,129]; one in 4 HIE survivors still develop significant neurodevelopmental sequelae.[53,130,131] Children who survive neonatal HIE are at risk for major disabilities, including cerebral palsy (especially spastic quadriplegia and dyskinetic subtypes), cognitive delay, epilepsy, hearing loss, and blindness, depending on the associated brain injury.[2,5] Among children without major disabilities, many will demonstrate cognitive, educational, and behavioral issues affecting their school-readiness.[53,132] Sequential neurodevelopmental follow-ups through childhood are essential for early detection of neurodevelopmental disabilities and interventions in these children.[66]

### *Predictors of Outcome*

#### *MRI*

Neuroimaging is a sensitive prognostic tool for HIE.[4] Basal-ganglia-thalamus injury pattern, watershed injury pattern, and near-total injury pattern are the most frequently observed patterns in neonates with HIE.[4] Different scoring systems have been developed to standardize the description of brain injury and have been shown to successfully predict adverse outcomes at 18 to 24 months[4,133] and potentially up to 6 to 7 years of age.[4,133] Neonates without brain injury on MRI are unlikely to develop substantive motor of cognitive deficits.[53,133] In addition, decreased NAA and increased lactate-to-NAA ratio measured in the thalamus by magnetic resonance spectroscopy (MRS) have been shown to be a highly sensitive and specific marker for predicting adverse outcomes at 2 years.[4] Further MRI biomarkers may need to be developed to test efficacy of neurorestorative therapies.

#### *Amplitude-integrated electroencephalogram/electroencephalogram*

Electrophysiology is useful to guide clinical management and for prognostication. Although single recordings may have low specificity and sensitivity, serial electroencephalograms (EEGs) or continuous EEG have better prognostic value. The severity of EEG abnormalities is correlated with the severity of neurologic insult and can help identify neonates who are at risk of adverse outcomes.[134] A cohort study found that selected features of aEEG (eg, continuity, background) at 6 and 24 hours of life were significantly correlated with early clinical outcome.[135]

#### *Other biomarkers*

Recent studies have suggested serum lactates in the first 6 hours of life or on the fourth day of life as an independent predictor of adverse outcomes in neonates with HIE treated with TH.[136] Measurement of heart-rate variability (HRV) via continuous recordings of electrocardiogram has also been shown to consistently predict the neuroimaging and neurodevelopmental outcomes of these neonates, with a higher HRV being associated with more favorable outcomes.[137,138] Blood biomarkers, such as serum tau protein,[139] S100B,[140] neuron-specific enolase,[141] and neutrophil-to-lymphocyte ratio,[142] have been studied to predict the severity of HIE and neurodevelopmental outcomes; however, validation studies in a larger sample is necessary before these markers can be used in clinical practice.[139,141,142]

## SUMMARY

In conclusion, although TH has significantly improved short- and long-term outcomes of neonates with HIE, birth asphyxia remains a significant cause of mortality and long-

term neurodevelopmental disabilities in children around the world. The limitations of TH underscore the need for alternative treatment approaches. Ongoing research into novel therapeutic agents, particularly those with neurorestorative properties, holds promise for improving outcomes of neonates with HIE, especially those ineligible or nonresponsive to TH.

***Best Practices***

***What is the current practice for hypoxic-ischemic encephalopathy (HIE)?***

Therapeutic hypothermia (TH) is the current standard of care treatment for HIE.

***Best Practice/Guideline/Care Path Objective(s)***

To provide controlled TH to prevent further brain injury, and to re-establish homeostasis of the different body organs/systems to prevent further brain injury.

***What changes in current practice are likely to improve outcomes?***

Variations in the management of neonates with HIE have been demonstrated across NICUs and may explain variations in outcomes, such as death and/or brain injury. Further research in large international cohort of neonates with HIE is needed to test optimal care practice bundle.

***Is there a Clinical Algorithm?***

See **Fig. 1**

***Pearls/Pitfalls at the point-of-care***

See **Table 1**

***Major Recommendations***

Daily management of neonates with NE/HIE should be first supportive with the target goal to re-establish homeostasis of the different body organs/systems. Ongoing cardiac dysfunction, acute kidney injury, electrolytes imbalance, impaired gas exchange, and similar may all contribute to worsening brain injury and thus subsequent adverse neurodevelopmental outcomes. Health care providers should promote shared decision making with parents. Parents should be encouraged to get involved in the daily care of their neonate and hold their baby, even during TH.

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## DISCLOSURE

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# Mimickers of Hypoxic Ischemic Encephalopathy

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**KEYWORDS**

• Neonatal encephalopathy • Selective serotonin reuptake inhibitor withdrawal
• Inborn error of metabolism • Viral meningoencephalitis • Vector-borne infections
• Neonatal spinal cord injury

**KEY POINTS**

- Neonatal encephalopathy has a broad range of etiologies.
- Selective serotonin reuptake inhibitor withdrawal may present with hypotonia, hypertonia, tremors, tachycardia, respiratory distress, and hypoglycemia. Treatment is supportive.
- Inborn errors of metabolism (IEM) may present with seizures, encephalopathy and abnormal tone. The evaluation for IEMs may require extensive investigations.
- Viral infections including vector-borne infections should be considered in the differential of neonates presenting with encephalopathy.
- Conditions mimicking encephalopathy, such as spinal cord injury, should have a high level of suspicion.

## INTRODUCTION

Neonatal encephalopathy (NE) is defined as a clinical syndrome of disturbed neurologic function in the earliest days of life in the term infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness, and often seizures.[1] The estimated prevalence of NE is 238 per 100,000 live births globally. NE is a significant contributor to the global disease burden.[2] Hypoxic ischemic encephalopathy (HIE) is one of the most common causes of encephalopathy in this age group and is discussed elsewhere in this issue. Importantly though, encephalopathy itself is a nonspecific symptom; thus, a careful history and examination may help the clinician establish an accurate etiology, prompt

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| Abbreviations | |
|---|---|
| CHIKV | Chikungunya |
| CSF | Cerebrospinal fluid |
| EEG | electrogencephalogram |
| FAOD | fatty acid oxidation disorder |
| GSD | glycogen storage disorder |
| HIE | Hypoxic ischemic encephalopathy |
| HPeV | Human Parechovirus |
| IEM | Inborn errors of metabolism |
| MOCD | Molybdenum cofactor deficiency |
| NE | Neonatal encephalopathy |
| NKH | non-ketotic hyperglycinemia |
| OAD | Organic aciduria disorder |
| PCR | polymerase chain reaction |
| PDE | Pyridoxine-dependent epilepsy |
| PLP | pyridoxal 5-phosphate |
| SCI | spinal cord injury |
| SNRI | serotonin-norepinephrine reuptake inhibitor |
| SSRI | selective serotonin reuptake inhibitor |
| UCD | urea cycle disorder |
| ZSD | Zellweger spectrum disorder |

treatment, and provide adequate prognostic guidance to families. Mimickers of HIE include withdrawal to in utero exposure of pharmacologic substances such as selective serotonin reuptake inhibitors (SSRIs), inborn errors of metabolism presenting in the neonatal period, central nervous system (CNS) infections, and traumatic myelopathies, among others. This article reviews key features that may aid in the clinical recognition (**Table 1**) and diagnosis of these conditions (**Table 2**).

## SELECTIVE SEROTONIN REUPTAKE INHIBITOR WITHDRAWAL

Medication toxicity or withdrawal in neonates can result in encephalopathy, frequently mimicking HIE. Neonatal exposure to exogenous medications is typically through maternal uptake of medications that cross the placenta and enter the fetal bloodstream. As rates of peripartum depression are increasing over recent decades,[3,4] more neonates are exposed to SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) prenatally. Prenatal exposure to SSRIs can lead to SSRI withdrawal syndrome; some studies suggest up to 30% of infants exposed to SSRIs are affected.[5] Paroxetine seems to confer higher risk than other SSRIs.

Symptoms of SSRI withdrawal include hypotonia, hypertonia, tremors, tachycardia, respiratory distress, and hypoglycemia (see **Table 1**).[6–8] A recent systematic review and meta-analysis of neonatal SSRI withdrawal syndrome laid out diagnostic criteria as described in **Box 1**. The features most useful in distinguishing from HIE are symptom onset, if delayed from birth, and exposure to SSRIs, which underscores the importance of an accurate maternal medication history. Though "seizures" have been reported with SSRI withdrawal, this typically refers to clinical convulsions in the absence of electrographic data, and therefore may more accurately represent tremors.[9] Confirmed electrographic seizures should therefore give pause in diagnosis of suspected SSRI withdrawal syndrome.

SSRI withdrawal syndrome tends to increase length-of-stay of newborn admission and leads to increased risk of intensive care unit admission.[8,10] Treatment is primarily supportive, although some cases have been documented with successful response to

**Table 1**
**Clinical features of selected mimickers of hypoxic-ischemic encephalopathy**

| Disorder | Similarities | Differences |
|---|---|---|
| SSRI withdrawal syndrome | Hypotonia<br>Encephalopathy<br>Tremors<br>Tachycardia<br>Respiratory distress | Hypoglycemia<br>SSRI exposure<br>Onset day of life 1–4 |
| Inborn errors of metabolism | Encephalopathy<br>Poor feeding<br>Hypotonia<br>Seizures<br>Brain injury patterns on MR diffusion-weighted imaging | Dysmorphisms/congenital malformations<br>Metabolic laboratory abnormalities<br>Disease specific changes on MR spectroscopy |
| Enterovirus encephalitis | Acute symptomatic seizures<br>Encephalopathy<br>Periventricular white matter restricted diffusion | Elevated inflammatory markers<br>Exanthem<br>Prodrome<br>Affected sibling/exposure |
| Vector-borne encephalitis | Acute symptomatic seizures<br>Encephalopathy<br>Periventricular white matter restricted diffusion on MR imaging | Fever<br>Thrombocytopenia<br>Hepatomegaly<br>Exanthem<br>Intracranial Hemorrhage |
| Spinal cord injury | Hypotonia<br>Decreased extremity movements<br>Respiratory distress | Areflexia<br>Paradoxic breathing<br>Spinal cord level on examination |

phenobarbital,[11] chlorpromazine,[9] or clonidine.[12] Symptoms generally resolve within 2 weeks.[7]

Similar to SSRIs, prenatal exposure to SNRIs can lead to withdrawal in neonates after birth.[13] Symptoms of SNRI withdrawal most often include poor feeding, jitteriness, myoclonus, and respiratory distress.[14] Symptoms present within 24 hours after birth but can be as late as the fourth day of life.[15] Some authors suggest that symptoms may be due to SNRI toxicity rather than withdrawal, based on serum drug concentrations[16] and rapid symptom improvement.[17] In other cases, symptoms have improved with administration of SSRIs, suggesting a true withdrawal phenomenon.[18] Given this discrepancy, symptoms following prenatal exposure to SNRIs are typically termed a "discontinuation syndrome".[14] As with SSRI withdrawal, treatment is primarily supportive, and symptoms generally resolve within 2 to 3 weeks.

It is important to note that SSRI/SNRI exposure does not increase the risk of stillbirth or neonatal death[19]; therefore, given the morbidity associated with maternal peripartum depression, it is prudent for obstetricians to carefully weigh the risks and benefits of SSRI or SNRI administration.

## METABOLIC DISORDERS PRESENTING WITH ENCEPHALOPATHY

Inborn errors of metabolism (IEM) are a rare but serious cause of neurologic dysfunction in neonates. IEMs represent an array of genetic disorders affecting metabolism of the main energy sources: carbohydrates, proteins, and fats.[20] This leads to either an accumulation of toxic metabolites or a deficiency in vital energy compounds. In a neonate, the most common presenting symptoms of IEM include encephalopathy, poor feeding, breathing abnormalities, hypotonia, and seizures.[21] It can be challenging

**Table 2**
**Suggested investigations for neonatal encephalopathy**

| | |
|---|---|
| Pregnancy/ birth history | Maternal medication/Drug exposure<br>Fetal movements<br>IUGR<br>Delivery complications<br>Apgar scores |
| Family history | Consanguinity<br>Early fetal or neonatal death<br>Metabolic/genetic conditions |
| Physical examination | Dysmorphisms and congenital malformations<br>Level of consciousness<br>Cranial nerve examination<br>Brainstem and primitive reflexes<br>Tone, peripheral reflexes, contractures<br>Sensory examination<br>Skin examination<br>Formal ophthalmologic examination for infectious or metabolic etiologies |
| Baseline testing | Umbilical or arterial blood gas, anion gap<br>Serum electrolytes and calcium<br>Complete blood count<br>Liver enzymes<br>Plasma lactate<br>Plasma ammonium<br>Urine ketones<br>Head Ultrasound<br>MRI brain<br>MR spectroscopy |
| Second tier laboratories | CSF cell count, glucose, protein<br>CSF culture, meningitis/encephalitis PCR panel, parvovirus PCR, parechovirus PCR<br>Plasma amino acids<br>Urine organic acids<br>Plasma carnitine and acylcarnitine profiles<br>Urine amino acids<br>Urine reducing substances<br>CSF amino acids |

to distinguish these conditions from HIE, especially if they manifest on the first day of life. Prompt recognition and early treatment may improve outcomes in some IEM, making it imperative to consider and test on the newborn screen. Results from the newborn screen take time; therefore, additional clinical and biochemical clues may

**Box 1**
**Diagnostic criteria for selective serotonin reuptake inhibitor withdrawal syndrome**

A. Maternal SSRI exposure in at least the third trimester of pregnancy

B. *At least one of the following signs: hypoglycemia, tremors, hypotonia, and/or tachycardia. Rapid breathing, respiratory distress, and/or hypertonia can cooccur*

C. Signs in criterion B are characterized by a peak of onset within the perinatal period after delivery and last for up to 2 weeks (depending on drug elimination half-life)

D. Signs in criterion B are clinically relevant and in need of monitoring or treatment

E. Signs are not better accounted for by a general medical condition

*Adapted from* Wang et al. 2021.[8]

be needed provide an early diagnosis. Early genetic testing with rapid genome sequencing should also be considered. In this section, we will review the diagnosis of IEM disorders with onset in the neonatal period that can mimic HIE.

### *Disorders with Abnormal Metabolites*

#### *Hyperammonemia*

Hyperammonemia results from the inability to convert ammonia, a nitrogen-based byproduct, into urea.[22] Neurologic symptoms are a direct result of the elevated ammonia, leading to cerebral edema, neuronal and glial cell death, and abnormal synaptic connectivity.[23] As ammonia levels start to rise, the neonate will become irritable or somnolent, will be unable to feed and may have emesis, and will develop a respiratory alkalosis from hyperventilation. Increasing levels of ammonia lead to cerebral edema with compression of the brainstem, leading to worsening encephalopathy, grunting, abnormal posturing, and hypoventilation and eventually death. Electrographic only seizures are common in neonates with hyperammonemia but do not necessarily correlate with increasing ammonia levels.[24]

In neonates, a major cause of hyperammonemia is urea cycle disorders (UCD) **Box 2**.[23,25] Hyperammonemia with a normal anion gap, normal glucose, or respiratory alkalosis is highly suggestive of a UCD. Other metabolic disorders, such as organic acidemias and fatty acid oxidation disorders, may also cause hyperammonemia but are distinguished by metabolic acidosis or hypoglycemia. If a UCD is suspected, plasma and urine amino acids should be drawn. Elevations or depressions in arginine, citrulline, ornithine, argininosuccinate, and/or orotic acid will help narrow down the specific defect in UCD.

Neuromonitoring tools including MRI, MR spectroscopy, and electroencephalogram (EEG) should be utilized to assess and mitigate the risk of brain injury in UCD. Brain MRI restricted diffusion is seen in the peri-insular region followed by extension into the frontal, parietal, temporal, and finally occipital regions.[26] Prolonged hyperammonemia can also lead to signal changes in the thalamus. MR spectroscopy shows elevated glutamate/glutamine peak and decreased myoinositol and choline levels.[26] Treatment is centered around ammonia detoxification using nitrogen scavenger drugs, or in more severe cases, hemodialysis or hemofiltration.[25] There is no clear threshold for irreversible brain injury in UCD but if recognized and treated early, the prognosis is more favorable.

#### *Metabolic acidosis*

A neonate with progressive encephalopathy, poor feeding, and persistent metabolic acidosis should raise suspicion for an IEM causing a primary lactic acidosis or organic

**Box 2**
**Primary defects in urea cycle disorder**

Carbamylphosphate synthetase 1 deficiency

N-Acetylglutamate synthetase deficiency

Ornithine transcarbamylase deficiency

Argininosuccinate synthetase deficiency (citrullinemia 1)

Citrin deficiency (citrullinemia 2)

Argininosuccinate Lyase Deficiency (Argininosuccinic Aciduria)

Arginase Deficiency (Hyperargininemia),

Ornithine Translocase Deficiency

aciduria.[27] Primary lactic acidosis occurs due to defects in pyruvate metabolism or in the mitochondrial electron transport chain. These 2 broad etiologies of primary lactic acidosis can be differentiated by certain clinical and biochemical attributes (**Table 3**). MR spectroscopy will show a prominent lactate peak. Prognosis is poor in most causes of primary lactic acidosis. Vitamins such as thiamine, biotin, riboflavin, and/or Coenzyme Q10 can be initiated but treatment is typically supportive.[27] Secondary lactic acidosis can also occur, particularly if lacticemia is mild or transient, and can be caused by HIE, sepsis, necrotizing enterocolitis, bronchopulmonary dysplasia, or cyanotic congenital heart disease.

Organic aciduria disorders (OAD) cause a metabolic acidosis from the accumulation of organic acids, such as propionic acid, methylmalonic acid, glutaric acid, isovaleric acid, or branched chain amino acids (leucine, isoleucine, and valine). Neurologic symptoms predominate in neonates with OAD manifested mainly by encephalopathy, abnormal tone, and seizures. Laboratory findings may reveal a mild lactic acidosis, ketoacidosis, hypoglycemia, and/or hyperammonemia, but the elevation of the respective organic acid makes the diagnosis. MRI may show T2 hyperintensities in the brainstem and periventricular white matter.[28] Swift identification is paramount as early treatment, particularly protein restriction, renders favorable outcomes.

**Table 3**
**Overview of inborn errors of metabolisms associated with metabolic acidosis in neonates[27,28,88]**

| IEM | Clinical and Biochemical Findings |
|---|---|
| *Primary lactic acidosis* | |
| Disorders of pyruvate metabolism (*Pyruvate dehydrogenase complex deficiency=PDHD*[a]*, Pyruvate carboxylase deficiency=PCD*) | • Lactic acidosis (>10mmol/L)<br>• Hyperammonemia<br>• Normal lactate:pyruvate ratio<br>• Plasma amino acids: elevated alanine and proline; elevated citrulline in PCD<br>Congenital malformation and dysmorphisms: dysgenesis of corpus callosum, microcephaly, frontal bossing, long philtrum |
| Mitochondrial respiratory chain/electron transport chain disorders (*deficiency in complex I-V, CoQ10 deficiency*) | • Lactic acidosis (>10mmol/L)<br>• Hyperammonemia<br>• Elevated lactate:pyruvate ratio<br>• Plasma amino acids: elevated alanine, proline ± glutamine<br>• Congenital malformation and dysmorphisms: hypertrophic cardiomyopathy, dysgenesis of corpus callosum, congenital cataracts, lens clouding, arthrogryposis, genitourinary malformations<br>• High rates of IUGR and prematurity |
| *Organic acidurias* | |
| • Propionic aciduria[a]<br>• Methylmalonic aciduria<br>• Glutaric aciduria<br>• Maple syrup urine disease<br>• Isovaleric aciduria | • Ketoacidosis<br>• Mild lactic acidosis (5–10mmol/L)<br>• Hyperammonemia<br>• Hypoglycemia<br>• Disease specific elevation of organic acids |

[a] Most common etiology in age group.

### *Hypoglycemia*

Hypoglycemia is the most common metabolic abnormality in neonates. Prolonged or recurrent hypoglycemia is particularly harmful to the metabolically active brain and can result in neuronal injury via excess glutamate production and increased calcium influx into cells, leading to excitotoxicity.[29] Clinically, the neonate may exhibit encephalopathy, irritability, jitteriness, poor feeding, hypotonia, and seizures. Etiologies include transient hypoglycemia of the newborn, hyperinsulinism, growth hormone deficiency, cortisol deficiency, and inborn errors of metabolism.[30] It is also an early finding in conditions that impair glucose regulation, such as sepsis, HIE, or intrauterine growth restriction. Brain injury patterns in severe hypoglycemia may mimic HIE with involvement of cortical, subcortical, and white matter areas with a predilection for posterior regions. Workup for hypoglycemia should be initiated for persistent levels below 50 mg/dL. During the hypoglycemic episode, critical blood and urine samples should be drawn to help guide the diagnosis: lactate, bicarbonate, beta-hydroxybutyrate, and free fatty acids.[31]

Hypoglycemia is the primary feature of some IEMs, such as glycogen storage disorders (GSD) and fatty acid oxidation disorders (FAOD). GSD is a group of disorders with impaired glucose storage or release.[31] There are several different types affecting the liver, skeletal muscle, and/or cardiac muscle.[32] GSD type 1 can have neonatal onset with hypoglycemia, ketoacidosis, elevated beta-hydroxybutyrate, and elevated lactate. Prognosis is generally good in most types of GSD if caught and treated early. Treatment is directed at avoiding fasting states and administering complex carbohydrates during hypoglycemic episodes.

FAOD cause disruption in fatty acid metabolism through failure of oxidation or transportation in the mitochondria via carnitine.[33] Symptoms manifest during fasting or high energy demand states, such as illness. Neonatal onset cases can be severe or even fatal due to hypoketotic hypoglycemia, liver dysfunction, and cardiomyopathy. Measurement of serum free fatty acids, carnitine, and acylcarnitine profiles are helpful in establishing the type of FAOD. Treatment is directed at avoidance of fasting and strenuous exercise, special diets, and supplementation with carnitine. Prognosis is generally good if caught early and there is no cardiac involvement.

### *Metabolic Epileptic Encephalopathies*

IEM are often associated with seizures in neonates; some may cause a severe presentation termed early infantile developmental and epileptic encephalopathy. This clinical syndrome is hallmarked by refractory seizures, encephalopathy, and a slow and disorganized EEG background pattern.[34] Although rare, early diagnosis of a metabolic epileptic encephalopathy is important, as some disorders have specific treatments. A few will be discussed here including non-ketotic hyperglycinemia (NKH), molybdenum cofactor deficiency (MOCD), and vitamin-dependent epilepsies.

NKH is caused by mutations in the *GLDC/AMT* genes affecting glycine degradation and leading to glycine accumulation.[35] Clinical signs are heralded by intractable myoclonic seizures, sometimes reported in-utero as persistent prenatal hiccups, and symptoms of lethargy, hypotonia, poor feeding, and respiratory depression.[34] The EEG shows a severe, burst suppression pattern. Glycine elevation in the cerebrospinal fluid (CSF) with a notable glycine peak on MR spectroscopy is observed. Treatment options are limited and may include a trial of sodium benzoate, but outcomes are generally poor.

MOCD causes a buildup of sulfites due to dysfunction of the enzyme sulfide oxidase. There are 3 major types—MOCD type A, B and C—with type A being most common and arising from mutations in the *MOSC1* gene.[36] Neonates present in the first

days of life with encephalopathy, irritability, and poor feeding, progressing to apnea, opisthotonic posturing, and myoclonic seizures.[37] The EEG can be normal or with mild changes initially, and then evolve into a severe, burst suppression pattern. Typical abnormalities on MRI include diffuse cerebral edema and cystic lesions, particularly in the basal ganglia.[35] Laboratory testing in MOCD reveals an elevation of urine sulfites, S-sulfocysteine, thiosulfate and xanthine, and a decrease in plasma homocysteine.[36] Fosdenopterin is the first Food and Drug Administration-approved replacement therapy for MOCD type A and reduces the 3-year mortality in infants.[38] However, prognosis remains poor and most develop severe developmental delays and refractory seizures with death in the first few years of life.

Vitamin-dependent epilepsies constitute a group of metabolic epilepsies with targeted therapies. In neonates with refractory seizures and encephalopathy of unclear cause, it is recommended to trial pyridoxine, pyridoxal 5-phosphate (PLP), and folinic acid while waiting for biochemical and genetic testing to result. Pyridoxine-dependent epilepsy (PDE) is caused by a mutation in the antiquitin gene (*ALDH7A1*), and a subset may also develop a secondary folinic acid deficiency requiring supplementation.[34] Pyridoxamine phosphate oxidase deficiency is a related disorder that typically responds better to PLP. The improvement of the encephalopathy in PDE (both clinically and on EEG) may lag the seizure abatement, and thus it is prudent to continue treatment until there is biochemical or genetic confirmation.[39]

### *Peroxisomal Disorders*

Peroxisomal disorders are a heterogenous group of disorders caused by mutations in *PEX* genes resulting in dysfunction of peroxisomes and accumulation of toxic metabolites.[40] Previously known as Zellweger syndrome, neonatal adreno-leukodystrophy, and infantile Refsum disease-they are all now known as Zellweger spectrum disorders (ZSD), as well as D-bifunctional protein deficiency. Neonatal onset disease presents the most severe phenotype. Symptoms include severe hypotonia that is often mistaken for severe encephalopathy along with seizures and sensorineural hearing loss.[41] Distinguishing features of neonatal onset ZSD also include hepatic dysfunction, ocular abnormalities such as cataracts, and craniofacial dysmorphisms (broad nasal bridge, high forehead, and epicanthal folds), as well as CNS abnormalities such as polymicrogyria, ventriculomegaly among others.[40] Biochemical testing reveals elevated very long chain fatty acids, phytanic, pristanic and pipecolic acids, as well as bile acids. The prognosis of neonatal onset of ZSD is poor and many infants die in the first year of life.

## INFECTIONS

Neonatal infections affecting the CNS may present as a mimicker of HIE, particularly with shared neuroimaging features. Obtaining a pregnancy and travel history are crucial, as human migration patterns and changes to global climate may increase the likelihood of presentations of tropical disorders, such as Dengue and Chikungunya (CHIKV) virus in areas with previously low incidence of these infections.[42] Perinatal infections affecting the CNS may present with seizures and encephalopathy, features shared by HIE. However, there is typically a prodrome after birth and before presentation, which may help distinguish these conditions. We discuss several viral infections that may cause NE as follows.[43,44]

### *Viral Encephalitides*

Enterovirus and parechoviruses from the *Picornaviridae* family are known to cause neonatal meningoencephalitis and are among the most common causes of viral

meningitis in neonates.[45] Human Parechovirus 3 (HPeV3) is the most common serotype associated with meningoencephalitis in neonates. The seasonal distribution is typically in the summer-fall, with outbreaks every other year.[46] Infants present with respiratory symptoms in the days prior to the onset of neurologic symptoms. This is followed by fever or hypothermia, and fussiness or lethargy.[47] Seizures are common in HPeV infections and less common in enteroviral infections. CSF in neonates with HPeV infection may include pleocytosis in up to 30% of infants, but no alterations in protein or glucose are noted.[46] Commonly, CSF analysis of neonates with enterovirus demonstrates mild pleocyteosis.[48] Reverse transcriptase real-time polymerase chain reaction (PCR) may confirm the infection in both cases. EEG patterns for neonates with enterovirus and HPeV infections are noted to have generalized slow background activity and focal abnormalities.[45] Radiologically, HPeV infections present with diffusion restriction in a radiated distribution in the periventricular white matter and the splenium of the corpus callosum.[47,49] Treatment for both enterovirus and HPeV meningoencephalitis is supportive. Outcomes have been heterogenous noting normal neurodevelopment in some cases[50,51]; however, some studies have reported neurodevelopmental abnormalities including motor impairment and expressive language impairment.[52]

Rotavirus associated leukoencephalopathy typically presents with acute symptomatic seizures around 5 days of life, generally in infants without history of perinatal complications. Acute neuroimaging is characterized by symmetric white matter and corpus callosum diffusion restriction[53]; these findings resolve over time.[54] For most patients with rotavirus associated leukoencephalopathy, CSF does not show pleocytosis and the virus is not isolated.[55] A small series reporting on outcomes showed adverse neurodevelopmental outcomes in neonates with this infection, typically correlated with the extent of white matter abnormality noted on the MRI.[56]

### *Vector-Borne Diseases*

Perinatal transmission of vector-borne diseases has been previously published in the literature. Neonatal presentations have been more commonly reported with CHIKV and Dengue virus than with other vector-borne viruses such as West Nile Virus, Yellow fever, or Zika virus.[57,58] Diagnosis is typically made with immunologic and molecular assays or antibody testing, although there needs to be careful consideration of the sensitivity and specificity of these tests for adequate diagnosis.[44]

Intrapartum exposure to CHIKV may result in perinatal infection in 28% to 48% of cases in direct relationship with the maternal viremia and time of birth. Affected neonates are typically asymptomatic during the incubation period of 2 to 5 days, after which they present with decreased feeding and encephalopathy, as well as fever, hepatic, and hematologic abnormalities.[59,60] Some neonates with CHIKV illness may also present with a blistering hyperpigmented rash in the face.[61] Neuroimaging with MRI may demonstrate diffusion restriction in the periventricular white matter, the corpus callosum, and centrum semiovale and in some cases subcortical cavitations.[62,63] Molecular diagnosis with PCR confirms the diagnosis. Treatment is supportive. Neonatal CHIKV illness has a high fatality rate of up to 37.5%.[57] The neurodevelopmental outcome is heterogeneous but affected neonates have been reported to have increased incidence of motor impairment and expressive language impairment,[64] thus longitudinal follow-up is recommended.

Dengue virus infection is a vector-borne infection transmitted by the *Aedes* mosquito species. Fetal infections have been noted near term.[65] The presentation of neonatal dengue encephalitis is characterized by fever and encephalopathy. Systemic symptoms may present in the first day of life to 11 days after birth (depending on the

maternal exposure), and include viral exanthem, petechiae, hepatomegaly, and thrombocytopenia. The time from systemic symptoms to the presentation of neurologic symptoms has been reported from 3 to 6 days. Typically, CSF analysis shows leukocytic pleocytosis with normal protein and glucose, and the diagnosis is made with the presence of a positive Dengue Virus RT PCR on blood and CSF.[66] Treatment is supportive. Outcomes after dengue encephalitis are favorable.[67]

### *SARS-Co-V-2 Virus*

During the COVID-19 pandemic there were several cases of neonatal infections that presented with neurologic manifestations consistent with encephalopathy.[68] Neonates with SARS-Co-V-2 infection were described to have clonic seizures, encephalopathy, and neuroimaging notable for diffusion restriction in the bilateral white matter and the corpus callosum.[69–71] The most reliable test for SARS-CoV-2 infection in neonates is RT-PCR.[68] The outcomes of neonates with SARS-CoV-2 infection have not been consistently examined, but there have been reports of long-term neurologic dysfunction.[72]

## NEONATAL MYELOPATHY

In some cases, hypotonia or weakness may be so severe that the presentation is mistaken for neonatal encephalopathy, when in fact there is a normal level of consciousness and normal cerebral function.[73] One such instance is neonatal myelopathy due to spinal cord injury (SCI).

Neonatal SCI is a rare occurrence but has been well-documented in neuropathologic studies.[74-76] The most common clinical scenario for neonatal SCI is an uncomplicated pregnancy followed by a difficult delivery at term, though SCI has also been described after uncomplicated vaginal delivery.[77] Classically, breech presentation has been considered a risk factor, but neonatal SCI can also occur with cephalic presentation. Multiple multicenter retrospective reviews have found a possible association with forceps-assisted delivery.[78–80] Spinal cord lesions are most often cervical or upper thoracic; some studies have suggested that upper cervical injury is more likely with cephalic presentation, while cervicothoracic injury is more likely with breech presentation.[80]

Lower cervical or upper thoracic lesions may involve only the lower extremities, typically resulting in flaccid paraparesis or paraplegia.[81] High cervical lesions more frequently result in quadriplegia or quadriparesis, and often are accompanied by apnea or hypopnea requiring mechanical ventilation.[78,80] Such lesions are often therefore life-limiting or result in withdrawal of life supporting measures.[76,82] However, there are also case reports of high cervical spine lesions with relatively subtle presentations of upper extremity weakness, hoarse voice, and swallow dysfunction, or autonomic dysregulation.[83,84] Given the overlap in symptoms, neonatal SCI is often mistaken for HIE, resulting in delayed diagnosis.[80] The distinguishing features of neonatal SCI include identification of a spinal cord level on examination and absence of encephalopathy on examination, such as a brisk grimace in response to a central noxious stimulus. Abnormal cutaneous reflexes (for example abdominal, Galant, or cremasteric) may provide a clue for a sensory level on examination. Areflexia can also be more suggestive of SCI than HIE, though can also be seen in peripheral nervous system disorders.[74] The definitive diagnosis is made with MRI, but SCI can also occasionally be visualized on ultrasound.[75,76] Ancillary studies demonstrating normal cerebral function, such as normal EEG, can also aid in the correct diagnosis of neonatal SCI.[85,86]

Management of neonatal SCI typically involves supportive care and neuroprotective measures. There are some cases in which steroids have been used[83,84]; however, it is not standard-of-care given limited data and side effects. Therapeutic hypothermia has been considered because HIE can be accompanied by ischemic changes to the spinal cord, compounding the motor and sensory deficits.[74,87] In other cases, therapeutic hypothermia is employed for treatment of presumed HIE before discovery of the correct diagnosis of SCI.[82,85,86] There is no clear benefit of therapeutic hypothermia for management of neonatal SCI.

The prognosis of neonatal SCI is generally poor. Particularly after high cervical spine injuries that result in ventilator dependence, there is minimal motor recovery and an increased risk of death during childhood.[76,80] Additionally, spontaneous breathing on the first day of life is associated with mild disability, while apnea on the first day of life and minimal motor recovery within the first 3 months of life is associated with ventilator dependence and long-term disability.[78] However, there have been cases of cervical spine injuries with only upper extremity symptoms that improve over time.[76,77,84,85] Regardless, neonatal SCI is a serious condition that requires prompt recognition, so that infants can receive proper developmental surveillance and therapies to maximize developmental outcome.

## SUMMARY

Neonates may present with symptoms that may resemble HIE. Careful evaluation for alternate etiologies should be considered when the clinical history and neonatal examination do not meet criteria for HIE. Conditions such as SCI or a variety of genetic and metabolic conditions may present as encephalopathy and thus a careful examination with the subsequent appropriate testing may provide an accurate diagnosis, which can ultimately alter treatment plans or even prognosis. Longitudinal follow-up may help optimize neurodevelopmental outcome for neonates with any form of neonatal encephalopathy.

***Best Practices***

***Best Practice Objective(s)***

Consider multiple etiologies during the evaluation of the encephalopathic neonate.

***What changes in current practice are likely to improve outcomes?***

Epidemiologic considerations, earlier genetic testing, and high index of suspicion is likely to help identify the etiology of neonatal encephalopathy.

***Is there a Clinical Algorithm?***

Please refer to **Table 2** for suggested evaluations of the encephalopathic neonate.

***Pearls/Pitfalls at the point-of-care:***

- Consider monitoring and providing supportive care for symptoms like hypotonia, hypertonia, tremors, tachycardia, respiratory distress, and hypoglycemia in neonates who may be experiencing selective serotonin reuptake inhibitor (SSRI) withdrawal.
- Ensure a thorough evaluation for inborn errors of metabolism (IEMs) in neonates presenting with seizures, encephalopathy, or abnormal muscle tone, including the possibility of conducting extensive investigations beyond the standard newborn screening.
- Include viral infections, particularly vector-borne infections, in the differential diagnosis for neonates presenting with encephalopathy.
- Maintain a high level of suspicion for conditions that mimic encephalopathy, such as spinal cord injuries, when assessing affected neonates.

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## DISCLOSURES

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# Neonatal Neurocritical Care in Low-Resource Settings

## Challenges and Innovations in Hypoxic-Ischemic Encephalopathy

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**KEYWORDS**

• Therapeutic hypothermia • Neonatal neurocritical care • Low-resource settings
• Birth asphyxia

**KEY POINTS**

- The incidence of HIE is 1-2 per 1000 births in developed countries but is estimated to be 5-20 times higher in low-income and middle-income countries.
- Mortality related to hypoxic-ischemic encephalopathy is 20% in high-income countries but estimated to be over 50% in low-income and middle-income countries.
- In 2020, ILCOR stated that therapeutic hypothermia should only be considered in specialized neonatal neurocritical care facilities that are often not available in low-resource settings.
- There is insufficient evidence to support use of erythropoietin, melatonin, or prophylactic anti-seizure medications in low-resource settings either as monotherapy or as an adjunctive therapy during therapeutic hypothermia.
- Telemedicine and remote monitoring are modern solutions available that may guide decision-making and reduce disparities between the high-resource and low-resource settings.

## INTRODUCTION

In recent decades, advances in neonatal care have significantly improved the survival of newborns. Central to these advancements is the concept of neonatal neurocritical care (NNCC), a multidisciplinary approach whose purpose is to improve the

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| Abbreviations | |
|---|---|
| aEEG | amplitude-integrated encephalography |
| BA | birth asphyxia |
| EEG | electroencephalography |
| EPO | erythropoietin |
| GNI | gross national income |
| HIC | high-income country |
| HIE | hypoxic-ischemic encephalopathy |
| ILCOR | International Liaison Committee on Resuscitation |
| LMIC | low-income and middle-income country |
| NICU | neonatal intensive care unit |
| NIRS | near-infrared spectroscopy |
| NNCC | neonatal neurocritical care |
| PCM | phase-changing material |
| sHIC | small high-income country |
| TH | therapeutic hypothermia |

neurodevelopmental outcomes of neonates.[1] NNCC represents a collaborative health care model integrating various medical disciplines to optimize neonatal outcomes. NNCC facilitates timely access to specialized diagnostics, therapeutic interventions, and multidisciplinary care crucial for early detection and management of brain injury in neonates. This early intervention is pivotal, as prompt diagnosis and treatment significantly improve neurologic outcomes and reduce long-term disabilities.

An example is hypoxic-ischemic encephalopathy (HIE), for which the timely intervention of therapeutic hypothermia (TH) in the first 6 hours of life is optimal.[2] In high-income countries (HICs), the approach for neonates with HIE includes joint evaluation and management by neonatology and neonatal neurology teams and use of sophisticated equipment such as continuous electroencephalography (EEG) or amplitude-integrated encephalography (aEEG), near-infrared spectroscopy (NIRS) and advanced neuroimaging modalities such as MRI and MR spectroscopy. In low-income and middle-income countries (LMICs) and to a lesser extent in rural and underserved areas of affluent nations, the burden of HIE remains a significant challenge, particularly impacting regions with limited health care resources where the implementation of NNCC has not kept pace with HIC.[3] This review aims to explore the global burden of HIE, diagnostic challenges, and barriers to implementation of NNCC in low-resource settings, therapies under investigation, and the innovations that may impact management strategies for HIE in lower resource settings.

## GLOBAL BURDEN OF BIRTH ASPHYXIA

Each year, worldwide, it is estimated that 4 million deaths occur in newborns, 25% of which are attributed to birth asphyxia (BA), with countries in Sub-Saharan Africa and Asia disproportionately affected.[4] BA is term variably defined as failure to initiate or establish spontaneous respirations at birth according to the World Health Organization,[5] or as a 5 min Apgar score of less than 7.[3] BA accounts for one of the single highest rates of disability-adjusted life years with, according to some estimates, 90% of the disease burden affecting LMICs.[6] The diagnosis of HIE in LMIC is fraught with challenges including lack of documentation of the complications surrounding delivery and the inability to obtain confirmatory testing (eg, EEG and MRI). Additionally, reporting does not always account for stillbirths,[5] especially those that occur outside of a medical setting and are unlikely to account for neonatal deaths that occur either in the intrapartum period or shortly after birth.[3] The high rates of HIE in LMIC are,

therefore, likely an underestimate but are known to affect as many as 14.9 per 1000 live births in Sub-Saharan Africa and 10.4 per 1000 in South Asia compared to the 1 to 2 per 1000 live births in HIC.[7] The global prevalence of neonatal encephalopathy affects 18,600 individuals per 100,000 people with a high impact on disability-adjusted life-years of 58,600 per 100,000 people due to the effect throughout the life course.[8] Neonatal encephalopathy is considered, by the Global Burden of Disease Study of 2021, the second most common cause of disease burden and the most frequent cause for children younger than 5 years.[8]

## THE LOW-RESOURCE SETTING

Low-resource medical settings are environments where health care systems face significant limitations in providing basic medical services due to a lack of resources, infrastructure, or trained personnel. Globally, these settings are often found in LMICs, defined by the World Bank by a metric of gross national income (GNI) divided by the population (**Fig. 1**).

Insufficient income can lead to systemic challenges in health care delivery, such as shortages of medications, medical equipment, and health care professionals. Small high-income countries (sHICs) or rural/underserved regions of HIC may also experience resource constraints despite their overall wealth, often due to geographic isolation, small population sizes, or dependence on external aid for specialized care. Within HICs, health care deserts refer to regions, often in rural or underserved urban areas, where access to primary and specialized medical services is severely limited, despite the country's overall advanced health care system. Medical deserts have been recently defined by an international consensus effort as "areas where population health care needs are unmet partially or totally due to lack of adequate access or

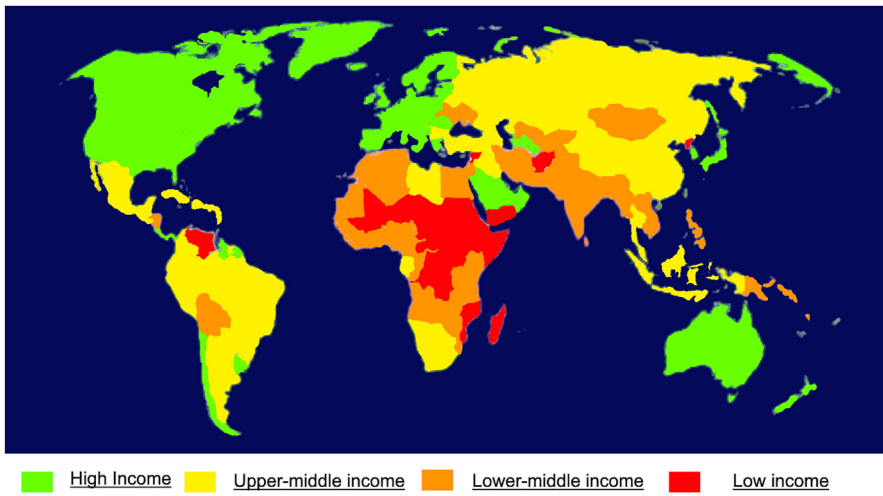


**Fig. 1.** Low-income countries fall below the threshold of $1,145 per person per year, lower middle-income countries have a GNI between $1,146 and $4,515, upper middle-income countries between $4,516 and $14,005 and high-income countries greater than $14,005 per person per year according to 2023 data.[9] Note: Map lines delineate study areas and do not necessarily depict accepted national boundaries. World Bank (2024) – with major processing by Our World in Data. "World Bank income groups" [dataset]. World Bank, "Income Classifications" [original data]. Retrieved March 12, 2025 from https://ourworldindata.org/grapher/world-bank-income-groups.

improper quality of health care services caused by (1) insufficient human resources in health, (2) facilities, (3) long waiting times, (4) disproportionate high costs of services, or (5) other sociocultural barriers."[10] These health care deserts, like low-resource settings globally, exacerbate health disparities and necessitate targeted interventions to improve access and equity in health care delivery. Throughout the remainder of this article, the term "low-resource settings" will be used to refer to LMICs, sHICs, as well as rural underserved regions and health care deserts within HICs.

## BARRIERS TO NEONATAL NEUROCRITICAL CARE IN LOW-RESOURCE SETTINGS

Barriers to providing NNCC in low-resource settings are multifaceted and related to systemic and infrastructural challenges. These barriers collectively contribute to the disparity in the quality of NNCC care between low-resource settings and more well-resourced environments, ultimately impacting neonatal outcomes and survival rates.

### *Equipment Scarcity*

A major barrier to providing NNCC in low-resource settings is the limited availability of specialized equipment. Essential tools such as devices to measure blood gases[11] or perform resuscitations[12] can be limited, let alone more sophisticated monitoring technologies like aEEG or conventional EEG machines or advanced neuroimaging modalities such as MRI.[13] The absence of these tools creates a significant gap in care, potentially leading to missed or delayed diagnoses, suboptimal treatment outcomes, and ultimately, higher mortality and morbidity rates among affected neonates.[14]

### *Logistical Issues*

Logistical challenges pose a significant obstacle to delivering effective NNCC in low-resource settings. Many low-resource settings are characterized by remote, and rural areas where access to health care facilities is limited.[15] The absence of reliable transportation infrastructure, such as roads and ambulances, makes it difficult for patients to reach care in a timely manner. Additionally, the lack of robust referral systems means that even when neonates do arrive at a health care facility, there may be delays in transferring them to specialized centers equipped to handle neurocritical care.[16]

### *Inadequate Infrastructure*

The lack of adequate health care infrastructure is a critical barrier to the provision of NNCC in low-resource settings. Infrastructure challenges are not limited to physical space but extend to the availability of essential services, such as reliable electricity, clean water, and waste management systems, all of which are crucial for maintaining a sterile and safe environment in neonatal intensive care units (NICUs). Unreliable electricity, for instance, makes it impossible to use incubators to maintain and regulate temperature for prematurely born neonates or to utilize cooling devices for term neonates with HIE.[17]

### *Work Force Shortages*

Another profound challenge in low-resource settings is the scarcity of trained health care professionals who specialize in NNCC.[18] This shortage is especially acute among neonatologists and pediatric neurologists, who play a crucial role in managing complex neonatal neurologic conditions. In many low-resource settings, there is also a significant lack of basic obstetric experts, such as obstetricians, midwives, and nurses, who are essential for safe childbirth and the early detection of neonatal complications.[19] Lay midwives who deliver the majority of infants in low-resource settings often lack the necessary training in basic obstetric practices making it more challenging to

identify and/or manage high-risk pregnancies and newborns at risk of developing neurologic issues.

### *Financial Constraints*

Financial constraints represent a significant barrier to the establishment and sustainability of NNCC in low-resource settings.[20] The costs associated with setting up and maintaining NICUs that can support NNCC are prohibitively high. These expenses include not only the procurement of specialized equipment but also the ongoing costs of training staff, maintaining facilities, and ensuring a steady supply of essential medications and durable medical equipment. In many low-resource settings, health care budgets are limited and often directed toward more immediate or widespread health concerns.

### *Cultural Issues*

Cultural practices and beliefs can also serve as significant barriers to the provision of NNCC in low-resource settings.[21] In some cultures, practices such as female circumcision, early marriages, and adolescent pregnancies are prevalent, which can lead to adverse neonatal outcomes. These practices not only increase the risk of complications during childbirth but can also affect the health of the newborn, necessitating specialized care that may not be readily available. Furthermore, cultural beliefs about health care can influence the decision to seek care, with some communities placing more trust in traditional healers or home remedies rather than formal medical care. Addressing these cultural barriers requires not only medical interventions but also community education and engagement to shift perceptions and encourage the timely use of available health care services.

## NEUROPROTECTION STRATEGIES IN LOW-RESOURCE SETTINGS

TH is considered the primary evidence-based treatment of HIE. TH involves lowering the newborn's temperature and slowing metabolic processes with the goal of reducing brain injury. TH is achieved using servo-controlled devices either by selectively reducing the brain or the whole-body core temperature. The standard protocol involves cooling the infant to a target temperature of 33.5°C for 72 hours, followed by gradual rewarming for infants who are over 36 weeks gestational age, within 6 hours of birth, with evidence of acidemia on blood gases, depressed Apgar scores and clinical signs of moderate-to-severe encephalopathy. Numerous research studies conducted in higher income settings demonstrate that TH significantly reduces the risk of mortality and severe disability in infants with HIE.[22,23] However, it is not universally effective. The number needed to treat is 7 to reduce the combined outcome of mortality or major neurodevelopmental disability at the age of 18 months.[24] Research is ongoing to identify whether TH can be employed in low-resource settings, to identify optimal modalities for cooling, and to develop new neuroprotective adjunct therapies such as, for example, erythropoietin (EPO), melatonin, and administration of prophylactic anti-seizure medications, which will each be described (**Table 1**).

### *Active Cooling in Low-Income and Middle-Income Countries*

Recent evidence has raised questions about whether TH is beneficial in low-resource settings. The "HELIX" trial evaluated the efficacy of active whole-body hypothermia in reducing mortality and disability when conducted in tertiary-care centers in 3 LMICs including India, Bangladesh, and Sri Lanka.[11] Key findings from the trial demonstrated no benefit in the combined outcome of death or disability at 18 months but instead found significantly increased rate of mortality. Additionally, in a secondary analysis,

**Table 1**
**Evidence-based neuroprotection strategies used in neonatal neurocritical care facilities and experimental strategies with or without current open clinical trials**

| | Category | Therapy |
|---|---|---|
| Evidence-based | Therapeutic hypothermia | Whole-body cooling |
| | | Selective head cooling |
| | Neuromonitoring | conventional EEG/aEEG |
| | | Seizure control |
| | | NIRS |
| | Supportive care | Mechanical ventilation |
| | | Blood glucose levels |
| | | Fluid and electrolyte management |
| | | Inotropic support |
| | | Sedation and analgesia |
| | Neuroimaging | Cranial ultrasound and Doppler |
| | | MRI |
| | | MR spectroscopy |
| Experimental | Pharmacologic agents | Erythropoietin |
| | | Melatonin |
| | | Topiramate/Phenobarbital |
| | | Allopurinol |
| | | N-Acetylcysteine |
| | | Xenon |
| | | Dexmedetomidine |
| | | Caffeine |
| | | Non-steroidal anti-inflammatory drugs |
| | | Exendin-4 |
| | Invasive procedures | Stem cell therapy |
| | Nutritional supplements | Polyunsaturated fatty acids (Omega 3) |
| | | Probiotics |

TH was not associated with reductions in brain injury by MRI injury scores, tract-based spatial statistics of whole-brain white matter fractional anisotropy, or by standard MR spectroscopy parameters.[25]

Furthermore, a recent meta-analysis that included trials in LMICs with passive and active cooling modalities revealed little to no difference in clinical outcomes and an uncertain effect on neonatal mortality.[26,27] The authors of the HELIX trial suggest that the lack of neuroprotection from TH in LMICs may relate to several of the barriers to NNCC previously described including limited access to prenatal care, maternal malnutrition and elevated incidence of intrauterine growth retardation, birth in low-level clinics, suboptimal quality of resuscitation and supportive care during transport, and genetic differences.[11] Given the limited data on safety and improved outcomes associated with use of TH in low-resource settings, the International Liaison Committee on Resuscitation (ILCOR) issued a statement in 2020 that "TH should only be considered, initiated, and conducted under clearly defined protocols with treatment in neonatal care facilities with the capabilities for multidisciplinary care and availability of adequate resources to offer intravenous therapy, respiratory support, pulse oximetry, antibiotics, anticonvulsants, transfusion services, radiology including ultrasound, and pathology testing"; otherwise, it may lead to harm.[28]

### *Passive Cooling*

Passive cooling is a method of reducing a neonate's body temperature without the use of specialized cooling equipment. Passive cooling often employs strategies that

minimize external heat sources (eg, lower room temperature) and decrease heat retention in the neonate (eg, do not dress or swaddle the neonate). Recommendations for the use of passive cooling in HIC most often occur in the setting where a neonate is awaiting the arrival of the tertiary care center transport team to initiate active cooling with a servo-controlled device.[29,30]

However, passive cooling is also being employed in low-resource settings as a therapeutic strategy employed in place of active cooling. In a small study in Malaysia for instance, passive cooling was employed for neonates with stage 2 and 3 encephalopathy.[31] In South Africa, passive cooling was achieved through the combined use of a custom-made, servo-control fan that was directed cephalocaudally over the neonate combined with use of a servo-control radiant warmer.[32] Difficulties can, however, arise for both achieving and sustaining the target temperature with one study in Ghana finding that temperatures were in the target range only about 20% of the time when the environmental temperature was the primary variable being manipulated.[33]

In Uganda, water bottles filled with tap water were placed in the cot with the neonate and were able to maintain the temperature in the desired range.[34] Currently, the most common low-cost devices being used are those with phase-changing material (PCM). PCMs are made of salt hydride, fatty acid, and esters or paraffin and are engineered to melt and solidify at specific temperatures suitable for therapeutic cooling. In India, cloth-covered gel packs have been employed for hypothermia treatment in low-resource settings with reduction in the risk of death or developmental delay at the age of 6 months[35] and with a reduction in markers of oxidative stress in a separate study.[36] PCMs are associated with a stable cooling effect for an extended period.

### *Erythropoietin*

EPO has been considered a promising treatment due to its antiapoptotic, anti-inflammatory, neurotrophic, and antioxidant properties as well as having been shown to have neuro-regenerative potential through a mechanism of stimulation of growth factors and neurogenesis, oligodendrogenesis, and angiogenesis possibilities.[37–39] EPO was first tested as an adjunctive therapy during TH. The "HEAL" trial, in which high doses of EPO were administered in conjunction with TH for moderate or severe HIE, showed an increased rate of adverse events compared to placebo, and no significant difference in the severity of brain injury by MRI, death, or neurodevelopmental outcome at the age of 2 to 3 years.[40]

EPO is also being trialed as monotherapy in limited resource settings without access to TH.[41] In a meta-analysis of 5 studies with nearly 350 subjects, EPO without TH was administered to participants from 4 LMIC (Romania, Egypt, China, and India). In 3 of these studies, EPO significantly reduced the risk of the composite outcome of death or cerebral palsy by the age of 18 months.[42] Although individual outcomes were reported only by 2 studies, EPO significantly reduced the risk of cerebral palsy.[42] However, EPO did not reduce the individual risk of neonatal mortality or death reported at the age of 19 months. In a recent feasibility pilot study in 8 tertiary NICUs (7 in India and 1 in Bangladesh), 50 neonates with HIE were randomized to placebo or EPO 500 U/kg/day starting within 6 hours of birth and continuing daily for 9 days.[43] This study demonstrated that a double-blinded randomized control trial could be performed in LMIC but was not powered for an efficacy outcome.

### *Melatonin*

Melatonin is another medication that has been investigated as a therapy for HIE. Preclinical data demonstrated their antiapoptotic properties by neutralizing reactive oxygen and nitrogen species and decreasing pro-inflammatory cytokines and

polymorphonuclear leukocyte recruitment.[44] Early evidence from small pilot studies in newborns has shown that melatonin as a monotherapy has a neuroprotective effect against HIE.[45] At a dose of 10 mg/kg per day for 5 days, it was associated with a decreased mortality rate and improved neurodevelopmental outcomes at the age of 6 months. However, there were no significant differences in EEG or MRI injury. A more recent study used 5 mg/kg of intravenous melatonin during the first 3 days of life and found improvements in cognitive development at the age of 18 months.[46] While there is strong preclinical evidence for melatonin, the clinical evidence is still quite limited and more trials are needed.[47]

### *Prophylactic Anti-seizure Medications*

Several studies have explored the possibility of using anti-seizure medications such as phenobarbital and topiramate for the purpose of neuroprotection. Phenobarbital, which facilitates gamma-aminobutyric acid-mediated opening of chloride channels, results in an inhibitory effect in neurons, therefore decreasing cerebral metabolism and oxygen consumption. Prophylactic treatment with phenobarbital for neonates with HIE is not recommended as it has no evidence for decreased neonatal mortality, brain injury on MRI, or neurodevelopment long-term outcomes.[48–50] Topiramate is a medication that is excitatory via the glutamate pathway via its AMPA (α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate receptors. Experimental studies have shown an association with decreased excitotoxic damage and increased survival of pre-oligodendrocytes and neurons. Although topiramate is known to reduce seizure activity, use of topiramate has not impacted survival, rates of MRI brain injury, or short-term neurodevelopmental outcomes.[51,52]

## INNOVATIONS FOR LOW-RESOURCE SETTINGS

Telemedicine, remote monitoring, and telehealth are terms often used to describe how technology facilitates connections between medical providers and patients. These innovations hold significant promise for enhancing the delivery of NNCC in low-resource settings. These technologies enable real-time specialist consultation, continuous patient monitoring, and provide opportunities to train health care providers, bridging gaps in expertise and resources. These innovations have been found in HIC to be cost-effective; [53,54] however, global adoption of these innovations is hindered by infrastructure challenges such as broadband access and financial constraints previously described.[55] Expenses may include the initial purchase and subsequent maintenance of equipment, purchase and maintenance of software, upgrading and maintaining Internet connectivity, deployment to and support of equipment in remote locations, and the hiring and training of skilled local health care workers to use of the equipment. While relatively inexpensive devices such as tablets or iPads can be used, more expensive options with telemedicine carts on wheels that have cameras with zoom and pan capabilities are also available. Despite these expenses, telemedicine programs can offer significant financial savings by reducing patient travel costs, decreasing hospital readmissions, and optimizing resource utilization.[56,57] Furthermore, by improving access to care and enabling early intervention, telemedicine can lead to better health outcomes.[58]

### *Telemedicine*

Telemedicine specifically refers to the use of telecommunications technology such as videoconferencing to provide clinical health care services from a distance. Examples of telemedicine include virtual doctor visits and real-time video consultations for

diagnosis, treatment, and follow-up care. Telemedicine has played a crucial role in improving access to specialized care for conditions like HIE through applications supporting neonatal resuscitation,[59,60] assessment of encephalopathy,[61,62] and neurodevelopmental follow-up after hospital discharge.[63,64] These types of telemedicine programs provide patients in low-resource settings with increased access to experts, reduction in ambulance transfers, better continuity of care, and improved communication between clinical teams at both hospitals and with parents.[65]

### *Remote Monitoring*

Remote monitoring involves the continuous or periodic collection of health data from patients, such as vital signs or glucose levels, using digital technologies like wearable devices and home monitoring systems, which are then transmitted to health care providers for disease management. One NNCC example of remote monitoring is continuous electroencephalogram that allows for surveillance of seizures and prompt intervention when needed. In Brazil for example, a multicenter study across 32 hospitals demonstrated that a single site could be employed to centrally review amplitude-integrated EEG on nearly 900 newborns undergoing TH.[66] Challenges such as equipment costs and the need for trained personnel are hurdles in the low-resource setting, but the ability to remotely monitor EEGs presents a promising avenue for improving outcomes in neonatal encephalopathy, bridging gaps in health care delivery, and enhancing timely interventions.

### *Telehealth*

Telehealth is a broader term that encompasses elements of both telemedicine and remote monitoring, as well as other nonclinical services such as health education, administrative meetings, and remote training. Telehealth leverages various technologies to support a wide range of health-related activities, providing a comprehensive approach to health care delivery that extends beyond direct clinical services. An example of telehealth is implementation of remotely delivered educational interventions to support the delivery of TH care and reduce care variation.[67] Another example of telehealth involves teaching and periodically reinforcing the technical skills involved in neonatal resuscitation. Simulation training is a way in which these skills are taught; however, in-person simulation events tend to be infrequent in low-resource settings due to expenses associated with travel. Alternatively, telesimulation can be employed. During a telesimulation event, a neonatal resuscitation is locally simulated by the medical team but remotely monitored by the resuscitation experts who can than provide feedback on performance.[68]

## SUMMARY

In conclusion, HIE remains a significant cause of neonatal morbidity and mortality, with incidence rates of 1 to 2 per 1000 live births in developed countries, but alarmingly higher in LMICs. Mortality rates reflect this disparity, being approximately 20% in high-income countries compared to over 50% in low-resource settings. While TH stands as the most effective neuroprotective strategy, its implementation is recommended by the ILCOR only in specialized NNCC facilities, which are often unavailable in resource-limited regions. Furthermore, there is currently insufficient evidence to endorse the use of EPO, melatonin, or prophylactic anti-seizure medications in these settings, either as standalone treatments or adjuncts to TH. Telemedicine and remote monitoring present promising solutions to mitigate these disparities by facilitating better decision-making and access to specialized care. However, additional research is

essential to validate the effectiveness of these adjunctive therapies and telehealth interventions in improving outcomes for neonates with HIE in low-resource environments. Addressing these challenges is crucial to reducing the global burden of HIE and achieving equitable neonatal care worldwide.

***Best Practices***

***What is the current practice for HIE?***

- TH currently is considered the standard of care for newborns diagnosed with moderate or severe HIE. It effectively reduces mortality and improves long-term neurologic outcomes in high-income countries.

***What changes in current practice are likely to improve outcomes?***

- Low-resource settings face difficulties implementing NNCC approaches due to the lack of trained professionals, financial constraints, equipment scarcity, and inadequate infrastructure. Other neuroprotective strategies, such as EPO, melatonin, and prophylactic anti-seizure medications, are currently being investigated. Telemedicine and remote monitoring are other options that could assist delivery of NNCC in low-resource settings.

***Pitfalls at the point-of-care:***

- Low-resource settings often face limitations in key resources required to effectively reduce the incidence and mortality of HIE, such as prenatal care programs, multidisciplinary teams, continuous EEG or aEEG, NIRS, and advanced neuroimaging modalities.

***Major recommendations:***

- The ILCOR states that "TH should only be considered, initiated, and conducted under clearly defined protocols with treatment in neonatal care facilities with the capabilities for multidisciplinary care and availability of adequate resources to offer intravenous therapy, respiratory support, pulse oximetry, antibiotics, anticonvulsants, transfusion services, radiology including ultrasound, and pathology testing"; otherwise, it may lead to harm as demonstrated in the HELIX trial.

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## DISCLOSURES

The authors have nothing to disclose.

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# Updates in Neonatal Seizures

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**KEYWORDS**

• Neonates • Seizures • Epilepsy • Antiseizure medications • EEG

**KEY POINTS**

- Neonatal seizures occur with an incidence of 1 to 5 per 1000 live births.
- Neonatal seizures are categorized as electroclinical or electrographic-only, with the former having both clinical manifestations as well as EEG correlates.
- The most common etiologies in high-income countries include hypoxic-ischemic encephalopathy, arterial ischemic stroke, and intracranial hemorrhage; in low- and middle-income countries, infections are more common.
- Most neonatal seizures are provoked by acute neurologic disorders and do not constitute epilepsy.
- Prognosis varies with seizure etiology and severity; higher neonatal seizure burden correlates with worse neurodevelopmental outcome and risk of later epilepsy.

## INTRODUCTION

The neonatal period represents the highest risk period of life for seizures to occur, with an estimated incidence of 1 to 5 per 1000 live births, higher in low-income and middle-income than high-income countries and in preterm versus term-born neonates.[1] Seizures refer to the electrographic ± clinical manifestations of abnormal excessive or synchronous neuronal activity. Neonatal seizures are a medical emergency, requiring prompt treatment and identification of treatable or reversible causes.

The etiology of neonatal seizures is dependent on gestational age at birth. In high-income countries, the three most common etiologies in term neonates are hypoxic-ischemic encephalopathy (HIE), arterial ischemic stroke, and intracranial hemorrhage (ICH).[2] HIE is the most common cause in term, post-term, or late preterm neonates, whereas intraventricular hemorrhage (IVH) is more common in neonates born before 32 weeks gestational age.[3] Infection is a more common cause in low-income and

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| Abbreviations | |
|---|---|
| aEEG | amplitude-integrated EEG |
| ASM | antiseizure medication |
| CNS | central nervous system |
| CSF | cerebrospinal fluid |
| cUS | cranial ultrasound |
| HIE | hypoxic-ischemic encephalopathy |
| ICH | intracranial hemorrhage |
| IESS | infantile epileptic spasms syndrome |
| PD-DEE | pyridoxine-dependent developmental and epileptic encephalopathy |
| PNPO | pyridoxamine 5′-phosphate oxidase |
| P5PD-DEE | pyridoxamine 5′-phosphate oxidase deficiency developmental and epileptic encephalopathy |

middle-income countries. The majority (67%–80%) of neonatal seizures are provoked by an acute insult[2,4]; thus, they do not meet the definition for epilepsy, which requires two or more unprovoked seizures separated by at least 24 hours or one seizure and a recurrence risk of greater than 60%, or an epilepsy syndrome. The remainder of neonatal seizures are attributable to neonatal-onset epilepsy, in which there is an enduring predisposition to ongoing seizures, the etiology of which may be structural and/or genetic, including inborn errors of metabolism.

This review synthesizes the current knowledge and terminology for the diagnosis of neonatal seizures, followed by an in-depth analysis of available pharmacologic treatments. Emphasis is placed on the critical importance of rapid and appropriate identification of seizures, diagnosis of etiology(ies), and effective treatment to improve neurologic outcomes.

## DEFINITIONS

Neonatal seizures can be categorized as electroclinical or electrographic-only. Electroclinical seizures are clinically apparent seizures with a definite electrographic correlate. For neonatal seizures with a clinical correlate, the clinical semiology can be described as motor (eg, automatisms, clonic, epileptic spasms, myoclonic, or tonic) or nonmotor (eg, autonomic, behavior arrest), or sequential. The predominant clinical feature defines the seizure type. If a seizure has a sequence of predominant clinical features, the term sequential seizure can be applied. Neonatal seizures are often short, lasting less than two minutes, and have a focal onset. Neonatal seizures do not have a generalized onset.

Electrographic-only seizures are visualized on electroencephalogram (EEG) as a repetitive pattern with a minimum voltage of 2 μV (measured peak to peak) and a minimum duration of 10 seconds, that evolves in frequency, location, morphology, or voltage,[5] without overt clinical manifestations. Electrographic-only seizures are also referred to as “subclinical” or “clinically silent” seizures. Subclinical seizures may be sensory seizures that neonates cannot express, or seizures where the neonate is obscured by a blanket/isolette, limiting visual assessment of clinical correlates. Finally, treatment with antiseizure medications (ASMs), such as phenobarbital, in neonates can result in electroclinical uncoupling, where there is lack of propagation of cortical discharges through motor tracts and thus electroclinical seizures become electrographic-only seizures.

Historically, clinical-only seizures were considered a third classification to describe clinically suspicious events without an ictal EEG correlate. It is theoretically plausible that seizures could arise from deep structures of the brain without detection by

conventional scalp EEG, as occurs with seizures arising from the orbitofrontal or mesial temporal lobes in older children and adults. However, there is no current evidence for an epileptic mechanism for clinical-only seizures in neonates, thus this category no longer exists in the current International League Against Epilepsy (ILAE) classification.

## ETIOLOGY

Most neonatal seizures are acute provoked seizures, resulting from an acute acquired insult to the brain. The most common etiologies are related to ischemic and/or hemorrhagic insults (HIE, ischemic or hemorrhagic stroke, or ICH), transient metabolic disturbances (eg, hypocalcemia, hypomagnesemia, hypoglycemia), acute infections of the central nervous system (CNS) ( $\pm$ systemic infections), in utero/congenital infections, drug withdrawal, or toxin. Seizures from HIE often present within the first 12 to 24 hours after birth, and/or during rewarming from therapeutic hypothermia and can have multiple different semiologies and locations of onset. Seizures from stroke, hemorrhage, or infection typically present later. Seizures from arterial ischemic stroke are often unilateral clonic seizures with onset from the location of infarction and present 24 to 48 hours after birth. Tonic and myoclonic seizures are more common in newborns with neonatal epilepsy syndromes than with acute provoked seizures.

Seizures that do not have an acute provoking etiology and are likely to recur are classified as neonatal epilepsy. Etiologies of neonatal epilepsy include cerebral dysgenesis (eg, holoprosencephaly, lissencephaly, polymicrogyria, schizencephaly, focal cortical dysplasia), inborn errors of metabolism (eg, biotinidase deficiency, molybdenum cofactor deficiency, peroxisomal disorders, pyridoxine-dependent developmental and epileptic encephalopathy (PD-DEE), pyridoxamine 5′-phosphate oxidase (PNPO) deficiency developmental and epileptic encephalopathy (P5PD-DEE), urea cycle disorders), and genetic neonatal epilepsy syndromes. The neonatal epilepsy syndromes comprise well-defined electroclinical phenotypes and include self-limited (familial) neonatal epilepsy, self-limited (familial) neonatal-infantile epilepsy, early infantile developmental and epileptic encephalopathy, KCNQ2-developmental and epileptic encephalopathy, PD-DEE, and P5PD-DEE. Acute provoked seizures in neonates often resolve within 72 to 96 hours.[6] If there is no clinical, imaging, or laboratory evidence to support an acute provoked or congenital structural etiology and seizures persist beyond the first days after birth, further investigations should be pursued to elucidate another etiology such as a neonatal epilepsy syndrome or inborn error of metabolism.

Among premature neonates, the most common cause of seizures is HIE in neonates born at greater than 32 weeks gestational age, versus large IVH with or without periventricular venous hemorrhagic infarction in neonates born less than 32 weeks gestational age.[3] CNS infections are another important cause of seizures, while seizures due to arterial ischemic stroke are uncommon in premature neonates. Conventional video-EEG (cvEEG) monitoring is important in premature neonates as they have high rates of subclinical-only seizures.[3]

## CLINICAL PRESENTATION AND DIAGNOSIS

The differential diagnosis for seizures or spells of abnormal movements in neonates includes clonus, hyperekplexia, jitteriness, motor automatisms (eg, chewing, bicycling leg movements, blinking, eye deviation, tongue movements, sucking), physiologic sleep myoclonus, tonic posturing, tremors, normal newborn behaviors, benign neonatal myoclonus, and vital sign changes. A diagnostic work-up should be quickly

undertaken to identify the etiology of neonatal seizures as they may be a symptom of a potentially treatable disease. Other paroxysmal abnormal movements in the neonate, even if confirmed to be nonepileptic, may require further diagnostic investigation as they may be signs of CNS dysfunction. Treatment of seizures, as detailed below in *Treatment*, should occur in parallel with the diagnostic work-up.

A thorough history and physical examination should aim to elucidate risk factors for seizure etiology, including prenatal, perinatal, neonatal, and family/social history. Basic laboratory tests should be performed to rule out treatable infectious and metabolic etiologies. An infectious work-up should be undertaken in any neonate with new seizures and empiric antibiotics and antivirals should be administered without delay. Blood, urine, and cerebrospinal fluid (CSF) cultures and herpes simplex virus PCR should be obtained. Brain MRI is the neuroimaging modality of choice and should ultimately be performed in all neonates with seizures, including conventional T1-weighted and T2-weighted sequences and diffusion-weighted imaging to detect congenital and acquired structural abnormalities. Magnetic resonance angiogram and magnetic resonance venogram should be included with conventional MRI sequences if there is suspicion for arterial ischemic stroke or venous thrombosis, respectively. Magnetic resonance spectroscopy may support a diagnosis of metabolic abnormalities associated with disorders such as HIE, nonketotic hyperglycinemia, creatine metabolism disorders, and mitochondrial disorders. Subtle brain malformations may be difficult to detect by brain MRI in the neonatal period. If there is high suspicion for a brain malformation, a high-resolution MRI should be repeated after 24 months of age, when myelination is mostly complete and gray matter malformations are easier to detect. Cranial ultrasound (cUS) can be employed in timely manner at the bedside to evaluate for structural lesions such as large hemorrhage or hydrocephalus that may require urgent surgery or other change in management. Although CT is quick and widely available, it should be avoided due to the consequences of exposure to ionizing radiation, except when cUS or fast MRI is unavailable and a neurosurgical emergency is suspected.

Clinical features that distinguish seizures from other abnormal movements in neonates are the slow, rhythmic, nonsuppressible movements of clonic seizures. In contrast, nonepileptic movements may be suppressible, provoked by stimulation, or spontaneous. cvEEG is required to differentiate seizures from nonepileptic movements, as clinical events are often misdiagnosed as seizures, leading to inappropriate treatment with ASMs. Conversely, without cvEEG, electrographic-only seizures will be unrecognized and untreated. In a study of neonatologists, pediatricians, residents/fellows, nurses, and nurse midwives in an Irish neonatal intensive care unit (NICU), only 50% of clinical events were correctly identified by providers as seizures.[7] In another study from the same center, only 27% of electroclinical seizures were recognized clinically by medical and nursing staff, while 73% of clinically suspected seizures had no EEG correlate.[8] For these reasons, cvEEG is the gold standard to diagnose neonatal seizures.[9] That said, if clinical suspicion for seizure is high, treatment should not be delayed to obtain cvEEG confirmation of seizures.

Vital sign changes as a possible indicator of seizure often prompts neurology consultation and request for cvEEG monitoring in the NICU. When vital sign changes occur as part of an electroclinical seizure, they are usually accompanied by other clinical phenomena such as motor or ocular manifestations. In a study of greater than 300 cvEEGs performed to evaluate paroxysmal vital sign changes in pediatric patients, the presence of other clinical manifestations increased the likelihood that a vital sign change was a manifestation of seizure, particularly for apnea.[10] No events of isolated hypertension, hypotension, or bradycardia were epileptic, however, there were rare events of isolated apnea or desaturation that were epileptic.

Even without clinically suspected seizures, neonates at high risk of seizures should undergo cvEEG monitoring so that electrographic-only seizures are not missed. Risk factors that should prompt cvEEG include neonatal encephalopathy or suspected HIE, cardiac/pulmonary risks for brain injury (including extracorporeal membrane oxygenation), suspected or confirmed CNS infection, ischemic or hemorrhagic CNS injury, CNS trauma, inborn errors of metabolism, genetic disease involving the CNS, premature neonates with acute high-grade IVH, and in high-risk neonates in whom a reliable clinical examination is precluded by pharmacologic neuromuscular blockade or sedation.[9]

Given the intensive resources required for cvEEG monitoring, studies have investigated the optimal duration of recordings. The median time from onset of EEG recording to electrographic seizure detection was 7 hours in a study of greater than 400 neonates with heterogeneous causes for their seizures (most commonly HIE, ischemic stroke, and ICH).[2] The American Clinical Neurophysiology Society recommends a minimum of 24 hours of cvEEG recording and consideration of discontinuation at this point if the EEG background is stable, or 24 hours after the last recorded seizure.[9] One exception to this recommendation is neonates with HIE being treated with therapeutic hypothermia, who should be monitored until rewarming has been completed due to the heightened risk of seizures during rewarming.[9] Some groups have investigated predictors of seizures to determine if a shorter duration of cvEEG is sufficient for some neonates,[11,12] but this is not yet widely applied.

cvEEG consists of a full montage of 9 to 17 electrodes, applied by an EEG technologist and interpreted by a highly trained neurophysiologist. The widespread use of cvEEG is limited by equipment cost, access to technologists, and availability of specially trained neurophysiologists for 24/7 interpretation. Amplitude-integrated EEG (aEEG) is a one-channel or two-channel recording derived from 2 to 4 electrodes (plus ground electrode), resulting in 1 to 2 channels that are filtered, compressed, and visually displayed. Several hours of aEEG are displayed in a compressed timeframe over a single screen, allowing for rapid identification of seizures or background changes. In addition to detecting seizures, assessment of the aEEG background can be used to evaluate severity of encephalopathy and as a biomarker for prognosis in neonates with HIE.[13,14] However, there are pitfalls to aEEG interpretation. Seizures that are short in duration can be missed due to the time compression. Seizures that are spatially distant from the 2 to 4 centrally-placed electrodes can also be missed. Artifactual tracings (such as pulse artifact, electrocardiogram (EKG) artifact, ventilator artifact, and artifact due to nonepileptic ballistic movements or handling) can result in false positive detection of seizures, as aEEG lacks simultaneous video or other channels (respiratory, EKG) to verify these artifacts. For these reasons, cvEEG remains the gold standard for the diagnosis of neonatal seizures. There are a handful of automatic seizure detection algorithms with rates of sensitivity of 80% to 95% and specificity of 84% to 98% when compared with review by human clinical neurophysiologists,[15–20] but they are also prone to high rates of false positives. Models incorporating clinical information and both qualitative and quantitative EEG assessment have been developed to predict which patients with HIE are at high risk of seizures.[21,22] A novel method using artificial intelligence-driven sonification to allow for acoustic detection of neonatal seizures has been proposed but is not yet commercially available. Similar "brain stethoscopes" are commercially available and approved by the Food and Drug Administration (FDA) for use in adults.[23]

In the absence of the identification of an acute provoked etiology, genetic testing is strongly recommended. In one study, genetic testing had a yield of 83% in neonatal epileptic encephalopathy, 26% in brain malformations, and 67% in self-limited familial

neonatal epilepsy.[4] If the clinical phenotype is consistent with a known monogenic syndrome, targeted genetic testing may be sent as an initial step. If this is negative, an epilepsy gene panel and chromosomal microarray could be considered, although rapid whole exome or genome sequencing has the highest yield. Whole genome sequencing is increasingly available either as a clinical test or on a research basis in high-resource settings.[24] Rapid identification of a specific genetic etiology may have treatment and prognostic implications, as discussed in the *Treatment* section later. If suspicion for a genetic/metabolic etiology is high, CSF lactate, pyruvate, amino acids, and neurotransmitters should be sent. A simultaneous serum glucose, lactate, pyruvate, and amino acids should be obtained at the same time as the CSF sample. Note that empiric trials of pyridoxine or other vitamins can alter results of CSF neurotransmitter studies. Consideration should be given to sending additional studies such as serum homocysteine, uric acid, very long chain fatty acids, pipecolic acid, carnitine, acylcarnitines, carbohydrate deficient transferrin, and a congenital disorders of glycosylation panel may be sent. Urine S-sulfocysteine can be sent if sulfite oxidase/molybdenum cofactor deficiency are suspected by severe encephalopathy, including refractory seizures, opisthotonos, axial and appendicular hypotonia, feeding difficulties, and apnea without acute provoked etiology, given that there is an FDA-approved treatment for a specific gene variant for molybdenum cofactor deficiency type A.

## MEDICAL/PHARMACOLOGIC MANAGEMENT

Neonatal seizures are a neurologic emergency and require prompt intervention and identification of potentially treatable etiologies to minimize brain injury and long-term sequelae. Seizure responsiveness to ASMs diminishes with prolonged seizures. In a study of 154 newborns with seizures, neonates treated with ASMs within 1 hour of seizure onset had a significantly lower seizure burden compared with those who received treatment two hours after seizure onset.[25] A minimum duration of 30 seconds per hour of seizure activity was proposed as the timepoint at which neonatal seizures should be treated in clinical trials, based on expert consensus opinion,[26] but this should not be construed as a guideline for clinical treatment, as the precise duration of seizure activity requiring treatment has not been definitely established. That said, neonatal units should have a treatment pathway that includes consultation with a Pediatric Neurologist, cvEEG monitoring, and prompt pharmacologic treatment.[27] Transfer to a tertiary care center should be considered if these resources are not available locally. Although cvEEG is required for a definite diagnosis of seizures, probable or possible seizures can be treated based on aEEG or observation by experienced clinicians, ideally followed by cvEEG initiation or transfer to a center with cvEEG.[27]

The initial management of a neonate with seizures involves immediate resuscitation and stabilization of cardiorespiratory status, while simultaneously investigating for reversible causes such as hypoglycemia, electrolyte disturbances, or infection. Seizures caused by hypoglycemia or electrolyte disturbances will not respond well to ASMs without treating the underlying etiology. Vitamin-dependent epilepsies, discussed later, are another seizure etiology that will not respond to traditional ASMs. Normothermia should be maintained as hyperthermia can lower the seizure threshold and potentially exacerbate brain injury with the exception being neonates who are undergoing therapeutic hypothermia.

As discussed later, in the *Prognosis* section, treatment to reduce the seizure burden may improve long-term outcome. ASMs should be administered promptly and titrated to achieve seizure freedom or therapeutic serum drug levels before sequentially

advancing to another ASM. Phenobarbital is the only ASM approved by the FDA to treat neonatal seizures; all other medications are used off-label. Unfortunately, currently available evidence to guide choice of ASM is limited. There are few randomized clinical trials (RCTs); the literature predominantly consists of retrospective studies that are hindered by their observational design, inability to control for confounding variables (such as comorbidities, illness severity, etiology, exposure to numerous ASMs, and timing of ASM administration), inconsistent definition of response to ASMs, and inconsistent quantification of seizure severity with and without cvEEG. The recommended dosing and most common adverse effects of ASMs used in neonates are summarized in **Table 1**.

First-line treatment of neonatal seizures is phenobarbital, based on data from 2 RCTs[28] and FDA approval. If a delay in administering phenobarbital is anticipated, or there are clinically suspected seizures without cvEEG confirmation, treatment with a benzodiazepine is an alternative. If there is a suspicion of self-limited (familial) neonatal epilepsy, or epilepsy caused by a pathogenic variant in KCNQ2, KCNQ3, or SCN2A (ie, by family history or clinical course), a sodium channel blocker (eg, fosphenytoin, phenytoin, carbamazepine, or oxcarbazepine) may be used first line.[34] In reality, in a neonate presenting emergently with seizures, they are often treated with phenobarbital initially, before this diagnosis is suspected.

The evidence for phenobarbital efficacy and safety is derived from 2 RCTs and extensive clinical use. In a randomized trial comparing intravenous (IV) phenobarbital and IV phenytoin in 59 neonates with EEG-confirmed seizures, the medications were equally effective in controlling seizures in less than half of the neonates. The response rate was 43% in the group treated with phenobarbital and 45% in the group treated with phenytoin.[28] Success rates were also similar when either ASM was added after the first one failed to control seizures; the response rate was 57% for phenobarbital followed by phenytoin, and 62% for phenytoin followed by phenobarbital. There were no significant adverse effects reported with either drug. The strongest predictor of treatment success was the severity of seizures, calculated as the duration of seizure activity in each channel that was active during a seizure. A more recent multicenter RCT compared phenobarbital with levetiracetam in 83 neonates with cvEEG-confirmed seizures.[29] A response was defined as 24 hours of seizure cessation determined by cvEEG. While 80% of neonates had seizure cessation with phenobarbital (20–40 mg/kg), just 28% had seizure cessation with levetiracetam (40–60 mg/kg). There were similarly large differences in secondary outcome measures of seizure cessation comparing phenobarbital with levetiracetam at 1 hour (93% vs 49%) and at 48 hours (64% vs 17%).[29]

The choice of second-line ASM is guided by limited evidence and should be determined on an individual basis, taking into consideration the drug's mechanism of action, potential adverse effects, and pharmacokinetics. Given the limited evidence, the ILAE could not reach consensus to recommend fosphenytoin, phenytoin or levetiracetam as second-line ASM. The evidence for these 2 ASMs includes data from the RCT comparing phenobarbital with phenytoin (phenytoin with seizure cessation in 45%), the RCT comparing phenobarbital with levetiracetam (levetiracetam with seizure cessation in 28% as first line, 17% as second line),[29] and a recent prospective study of levetiracetam as second line followed by phenytoin as third-line ASM.[36] In the latter study, levetiracetam controlled seizures in only 13.8% as second-line therapy, whereas phenytoin as third-line ASM was effective in 56.7%.[36] Since phenytoin was given later in the course of seizures, it was not shown to be superior to levetiracetam, but the efficacy of levetiracetam as second-line therapy was disappointing. That said, levetiracetam is well tolerated and has minimal adverse effects,[29] with possible

**Table 1**
**Pediatric weight-based loading and maintenance doses, and maximum dose for medications used in the treatment of neonatal status epilepticus**

| Drug | Dose and Route | Efficacy Data | Adverse Effects |
|---|---|---|---|
| Phenobarbital | Loading dose: 20 mg/kg IV/IO, followed by repeated boluses of 10–20 mg/kg as needed to target a serum level of 40–50 μg/mL<br>Maintenance dose: 4–6 mg/kg/day IV/PO divided BID or daily<br>Maximum dose: 40–50 mg/kg over 24 h | One RCT ($n$ = 59) demonstrated equal efficacy comparing phenobarbital (43%) vs phenytoin (45%) as a first-line or second-line ASM.[28]<br>One RCT ($n$ = 64) demonstrated superior efficacy of phenobarbital (80%) vs levetiracetam (28%) as a first-line ASM.[29] | Sedation, respiratory depression, apnea, hypotension.<br>Clearance may be reduced in hepatic impairment, renal impairment, or therapeutic hypothermia.<br>Longer half-life in premature neonates and the first week after birth. |
| Phenytoin, Fosphenytoin | Phenytoin loading dose: 20 mg/kg IV<br>Maintenance dose: 6–8 mg/kg/day IV/PO divided q8h, to target serum phenytoin level of 20 μg/mL<br>Fosphenytoin loading dose: 20 mg PE[a]/kg IM/IV/IO, followed by repeated boluses of 5 mg PE/kg as needed to target a serum level of 20 μg/mL<br>Maintenance dose: 6–8 mg PE/kg/day divided q8H | One RCT ($n$ = 59) demonstrated equal efficacy comparing phenobarbital (43%) vs phenytoin (45%) as a first-line or second-line ASM.[28] | Phenytoin: Infusion site irritation,purple glove syndrome, arrythmia, hypotension, respiratory depression, may worsen seizures due to toxins that also block sodium channels, may worsen seizures in patients with Dravet syndrome or other SCN1A-releated epilepsies.<br>Nonlinear pharmacokinetics, limited enteral absorption in newborns, variable hepatic metabolism, decreased elimination during the first weeks of life, variable bioavailability, highly protein bound.<br>Fosphenytoin:<br>Similar considerations to phenytoin with the exception of purple glove syndrome. Fosphenytoin is preferred to phenytoin due to improved safety profile and multple routes of administration. |

| | | | |
|---|---|---|---|
| Levetiracetam | Loading dose: 40 mg/kg IV followed by 20 mg/kg if needed<br>Maintenance dose: 40–60 mg/kg/day IV/PO divided BID or three times daily<br>Maximum dose: 60 mg/kg/d | One RCT ($n$ = 64) demonstrated superior efficacy of phenobarbital (80%) vs levetiracetam (28%).[29] | Sedation, irritability.<br>Preferred second-line ASM in neonates with cardiac disorders. |
| Midazolam | Loading dose: 0.05–0.15 mg/kg IV followed by a continuous infusion of 0.05–0.1 mg/kg/min which can be uptitrated in steps of 0.05 mg/kg/h q15–30 min to a maximum of 1 mg/kg/min<br>Maximum dose: 5 μg/kg/min | Limited efficacy data showing low efficacy in retrospective studies and very small RCTs.[30,31] | Sedation, respiratory depression. |
| Lidocaine | Loading dose: 2 mg/kg IV, followed by a continuous infusion of 7 mg/kg/h for 4 h, then decrease by 50% every 12 h for 24 h<br>Treat for 48 h maximum, <30 h preferable | One open label RCT ($n$ = 11) demonstrated efficacy of second-line lidocaine in 3 of 5 neonates,[31] but a large retrospective study showed lower second-line efficacy of 21%.[32] | Cardiac arrhythmia (contraindicated in congenital heart disease and patients who have received fosphenytoin or phenytoin), hypotension, methemoglobinemia.<br>Dose should be adjusted in prematurity, weight <2.5 kg, and therapeutic hypothermia. |
| Lacosamide | Loading dose: 5–10 mg/kg IV/PO<br>Maintenance dose: 5–10 mg/kg/day IV/PO divided BID | A retrospective study ($n$ = 47) demonstrated 29% with some seizure reduction.[33] | |
| Carbamazepine | Maintenance dose: 10–20 mg/kg/day PO divided BID<br>Maximum dose: 35 mg/kg/day | One retrospective study of patients with SLFNE ($n$ = 19) demonstrated good efficacy (88%) of carbamazepine or oxcarbazepine.[34]<br>One retrospective study of patients with KCNQ2 DEE ($n$ = 15) demonstrated good efficacy (40%).[35] | Sedation, gastrointestinal side effects, limited information regarding adverse events in neonates. Blood dyscrasias, hyponatremia, and rash/Stevens Johnson Syndrome in older patients. |

(*continued on next page*)

**Table 1**
**(*continued*)**

| Drug | Dose and Route | Efficacy Data | Adverse Effects |
|---|---|---|---|
| Oxcarbazepine | Maintenance dose: 10–60 mg/kg/day, divided BID<br>Maximum dose: 60 mg/kg/day | A retrospective study of neonatal SLFNE ($n$ = 19) demonstrated efficacy (88%) of carbamazepine or oxcarbazepine.[34] | Sedation, gastrointestinal side effects, limited information regarding adverse events in neonates. Blood dyscrasias, hyponatremia, and rash/ Stevens Johnson Syndrome in older patients. |
| Pyridoxine HCl (vitamin B6) | Loading dose: 100 mg IV x 1–2 doses<br>Maintenance dose: 15–30 mg/kg/day IV/ PO, divided BID | | Apnea, respiratory depression, hypotension, peripheral neuropathy. |
| Pyridoxal 5′-phosphate | Maintenance dose: 30–60 mg/kg/d PO divided q4–6h | | Respiratory depression, hepatotoxicity. |
| Folinic acid | Maintenance dose: 3–5 mg/kg/day divided q6–8h | | |
| Biotin | Maintenance dose: 5–10 mg daily | | |

*Abbreviations:* BID, twice daily; IM, intramuscular; IO, intraosseous; IV, intravenous; KCNQ2-DEE, KCNQ2-related developmental and epileptic encephalopathy; PO, oral; q, every; SLFNE, self-limited familial neonatal epilepsy.

[a] Fosphenytoin is a prodrug of phenytoin with a higher molecular weight than phenytoin, thus fosphenytoin is dosed in phenytoin equivalents (PE) to avoid confusion.

neuroprotective effects in some animal models. The ILAE guideline considers levetiracetam an acceptable option for neonates with cardiac disease in whom potentially arrhythmogenic fosphenytoin, phenytoin, and lidocaine might be avoided, hepatic dysfunction, or in neonates with significant hemodynamic instability.[37] Further data are needed to determine the comparative efficacy of these 2 ASMs or other potential ASMs before a strong recommendation can be given regarding choice of second-line ASM therapy.

Lidocaine was reported to have some efficacy in a retrospective study of 413 neonates with aEEG-confirmed seizures.[32] For 276 term neonates, there was a good effect (defined as cessation of seizure activity without recurrence for over 4 hours or with recurrence of short seizures that did not require further ASMs) in 21% as second-line ASM and 68% as third-line ASM. The authors reported that a further 51% of neonates responded to lidocaine as second-line or third-line ASM with an intermediate effect (defined as cessation of seizure activity with recurrence of repetitive seizures in 2–4 hours requiring the administration of rescue ASMs or cessation of seizure activity for over 4 hours but recurrence of repetitive seizures with 24 hours, requiring rescue ASMs). Notably, this intermediate effect was not a sustained effect on seizure cessation, given the need for further ASMs. Overall, lidocaine was significantly less effective in preterm than term neonates. This study was limited by retrospective design and use of aEEG to diagnose seizures rather than cvEEG, limiting the assessment of seizure burden and potentially either overdiagnosing or underdiagnosing seizures based on aEEG, as discussed in the *Diagnosis* section earlier. Lidocaine is arrhythmogenic and should be avoided in neonates with some cardiac disorders and those who have already been treated with fosphenytoin or phenytoin. Lidocaine also requires a dose adjustment in neonates less than 2.5 kg and those undergoing therapeutic hypothermia.

Midazolam causes minimal cardiovascular side effects but, as with other benzodiazepines, repeated doses or continuous infusions cause sedation and respiratory depression necessitating mechanical ventilation. A retrospective study of 13 neonates with EEG-confirmed seizures treated with midazolam after lack of response to phenobarbital and/or phenytoin reported that all 13 neonates responded to midazolam.[30] However, midazolam was given as a third-line ASM, and the seizures may have been resolving regardless of the midazolam infusion. In contrast, in a RCT of 11 neonates with EEG-confirmed seizures that did not respond to phenobarbital, 3 of 5 neonates in the lidocaine (lignocaine) group responded, compared with 0/3 in the midazolam group and 0/3 in the clonazepam group.[31] In the retrospective study of lidocaine and midazolam mentioned in the previous paragraph, midazolam had a good effect in 13% as second-line ASM and 57% as third-line ASM in term neonates, somewhat lower efficacy than for lidocaine. As for lidocaine, the apparent higher efficacy with later administration may reflect in part natural resolution of acute seizures, or the potential for synergistic effects.

Regarding lacosamide, a retrospective study demonstrated some degree of seizure reduction in 29% of 47 term neonates on days 1 to 2 as judged by qualitative evaluation of 3 days of cvEEG reports after lacosamide initiation; the other 71% showed no change or unknown effect. Lacosamide was typically administered after one or more ASMs had been tried, and had a relatively safe side effect profile.[33] Cardiac adverse effects, such as hypertension, hypotension, and cardiac arrest, were noted in 7 neonates, although 5 of those 7 had also received fosphenytoin prior to the cardiac event. PR interval prolongation is a known adverse effect of lacosamide in adults but was not seen in this study of neonates. RCTs are underway to demonstrate both the safety and efficacy of lacosamide for the treatment of neonatal seizures.[38]

Bumetanide is a diuretic that acts on the sodium-potassium-chloride transporter NKCC1, which is highly expressed in immature neurons compared with the low expression of potassium-chloride cotransporter KCC2 (KCC2 is predominant cotransporter at older ages). This expression pattern results in a reversed neuronal chloride gradient compared with mature neurons. In this setting, GABA-A receptor activation, (ie, with phenobarbital or benzodiazepines), can paradoxically depolarize the neuron, potentially explaining the relative inefficacy of GABAergic medications in neonates. Bumetanide received attention as a potential medication to be used in conjunction with phenobarbital with promising results in animal models.[39] A phase I/II open label trial of 14 neonates with HIE and cvEEG-confirmed seizures treated with a combination of phenobarbital and bumetanide was closed early due to safety concerns (hearing impairment in 3 of 14) and limited efficacy by predefined endpoint of achieving 80% seizure cessation in greater than 50% of subjects.[40] Of note, hearing impairment is a known sequelae of HIE, and this result must be interpreted with caution in this small sample size. In a double-blind, RCT of 43 neonates with cvEEG-confirmed seizures, neonates were randomized to receive phenobarbital with bumetanide (treatment) or phenobarbital and placebo (standard therapy control) if seizures persisted after initial treatment with phenobarbital. Hearing impairment occurred in 2 of 27 treated neonates, and one nonrandomized neonate; all 3 had HIE. The trial showed a reduction in seizure burden 4 hours after bumetanide administration compared with standard therapy controls, adjusted for seizure burden, as there was higher pretreatment and total seizure burden in bumetanide versus control subjects.[41] There was no difference in neurologic outcome between the bumetanide and control groups at 18 to 24 months, that is, no adverse effects and, as expected, no beneficial effects, as subjects received only a single dose of bumetanide.[42] Larger phase III trials are needed to establish safety, efficacy and to optimize dosing before bumetanide can be recommended for the treatment of neonatal seizures.

In a Phase II/III multicenter open-label single-arm study of brivaracetam in 6 neonates with persistent seizures after treatment with at least one appropriate ASM, brivaracetam 0.5 mg/kg IV BID was well-tolerated with a pharmacokinetic and safety profile consistent with prior adult and pediatric data, but there were very limited efficacy data.[43]

Topiramate is a promising ASM for neonates, because of multimodal mechanism of action and neuroprotective effects, but its use has been limited by the lack of an IV formulation. Retrospective studies of enteral topiramate to treat neonatal seizures have reported seizure reduction without significant side effects, such as in a study with reported efficacy in 46/75 neonates (61%) with refractory neonatal seizures.[44] Two prospective RCTs compared enteral topiramate for 3 or 5 days added to therapeutic hypothermia versus hypothermia alone to improve neurologic outcome in neonatal HIE.[45,46] These 2 trials showed that topiramate treatment was associated with lower rates of acute seizures or later epilepsy, but neither finding was statistically significant; larger trials are needed to test topiramate for treatment of neonatal seizures.

If seizures are unresponsive to first-line and second-line ASMs, particularly if there is not a suspicion for acute provoked seizures, a vitamin-responsive epileptic encephalopathy should be considered. In this situation, sequential trials of pyridoxine, pyridoxal-5-phosphate, folinic acid, and leucovorin should be performed with cvEEG monitoring to assess response to treatment, including changes in the EEG background. Trials of IV pyridoxine should be performed in an ICU setting with cardiorespiratory monitoring as apnea can occur with administration.

Once seizures have been controlled, medication regimens should be simplified to avoid polypharmacy, drug-drug interactions, and unnecessary adverse effects.

Medications that are ineffective should be discontinued. The duration of therapy with ASMs is largely dependent upon the etiology of the patient's seizures. Acute provoked seizures usually resolve within 72 to 96 hours,[6] and these patients are not considered to have epilepsy. Prolonged phenobarbital use is associated with negative neurocognitive side effects in older children and apoptotic neurodegeneration in animal models,[47] suggesting a risk of adverse neurodevelopmental effects.

Currently available ASMs have not yet been demonstrated to reduce rates of postneonatal epilepsy, thus is not an argument for maintaining patients on ASMs. Patients with a prolonged duration of neonatal seizures (3 or more days), a severely abnormal EEG background, and an abnormal neurologic examination at discharge are at an increased risk of postneonatal epilepsy, including infantile epileptic spasms syndrome (IESS). In addition, neonates with acute provoked seizures are often treated with phenobarbital, which is not the preferred ASM for postneonatal epilepsy or IESS. In a comparative effectiveness study of neonates with acute provoked seizures, there was no difference in neurodevelopmental outcome or the risk of epilepsy at 2 years of age when comparing patients maintained on ASMs for 2 to 4 months compared with those whose ASMs were discontinued prior to hospital discharge.[48] When weighing this finding with the risk of prolonged exposure to potentially harmful ASMs,[47] it is recommended that ASMs be discontinued prior to hospital discharge in neonates with acute provoked seizures regardless of MRI or EEG findings, as supported by the ILAE guideline.[37] We recommend close follow-up and counseling families for signs of seizures, particularly infantile spasms. Note that this approach to discontinuing ASMs by hospital discharge should not be applied to patients with neonatal-onset epilepsy.

Most neonates with neonatal-onset epilepsy syndromes have a chronic risk for recurrent unprovoked seizures and should be maintained on ASMs effective for their type of seizure(s) or epilepsy. Sodium channel blockers should be used for patients with a confirmed pathogenic variant in KCNQ2, KCNQ3, or SCN2A, or in whom this diagnosis is suspected on a clinical basis.

## PROGNOSIS

In a study of 144 children with acute provoked neonatal seizures managed by a neonatal neurocritical care service at a tertiary care center in the United States, 26% died before 1 year of age, 21% had cerebral palsy, and 9% had epilepsy.[49] In patients with perinatal arterial ischemic stroke, patients who present with seizures have 3 times the risk of subsequent epilepsy, with the highest risk of seizure recurrence in the first year of life. Observational data suggest that a higher seizure burden is associated with a higher risk of abnormal neurodevelopmental outcomes, brain injury on MRI, epilepsy, and death.[2,42,50–57] **Table 2** summarizes the literature regarding the relationship between neonatal seizure burden and neurologic outcome. In an observational study of 47 neonates with HIE, a total seizure burden of over 40 minutes was associated with a 9-fold increase in the odds of an abnormal outcome and a maximum hourly seizure burden of more than 13 minutes per hour was associated with an 8-fold increase in abnormal outcome at 24 to 48 months (cerebral palsy, epilepsy, developmental delay, or death).[58] Other studies have shown a relationship between neonatal seizure burden and later adverse outcome, but without a specific threshold of seizure burden.[42]

Despite strong evidence of the link between neonatal seizure burden and later epilepsy and disability, there is still debate regarding whether to treat electrographic-only seizures, which is best tested by randomized clinical trials. Commendable efforts have

**Table 2**
**Selected literature on the relationship between neonatal seizure burden and neurologic outcome**

| First Author, Year | |
|---|---|
| *Prospective and Retrospective Studies* | |
| Trowbridge et al,[42] 2023 | Outcome data from Boston Bumetanide Trial showed a significant association between higher neonatal seizure burden and worse outcome at 18–24 mo by Bayley scores (cognitive, language, motor) for 84 term neonates with HIE and stroke but not ICH. |
| Fitzgerald et al,[52] 2018 | Retrospective study of 116 term neonates with HIE treated with therapeutic hypothermia demonstrated that higher cvEEG-confirmed seizure burden was associated with worse motor and language outcomes at 13–36 mo and MRI injury. |
| Glass et al,[2] 2016 | Prospective observational study of 426 term and preterm neonates with seizures demonstrated that higher cvEEG-confirmed seizure burden was associated with length of hospital stay, abnormal neurologic examination at hospital discharge, and mortality. |
| Guidotti et al,[53] 2016 | Retrospective study of 79 neonates born at $\geq$36 weeks gestational age with moderate or severe HIE demonstrated that treatment with therapeutic hypothermia was associated with a lower seizure burden (verified by cvEEG) and better outcomes defined by a compound score including neurodevelopmental outcomes, epilepsy, and mortality. |
| Kharoshankaya et al,[58] 2016 | Retrospective study of 47 term neonates with HIE demonstrated that higher seizure burden (independent of HIE severity or treatment with therapeutic hypothermia) was associated with abnormal outcomes (defined as any of mortality, cerebral palsy, epilepsy, or developmental delay based on Griffiths assessments or Bayley scores at 24–48 mo). |
| Payne et al,[54] 2014 | Prospective observational study of 93 term neonates and children in the intensive care unit with cvEEG confirmed seizures demonstrated that higher seizure burden was associated with worse short-term neurologic outcome and mortality. |
| Glass et al,[50] 2009 | Retrospective study of 77 term neonates at risk for hypoxic ischemic injury demonstrated that the presence of cvEEG-confirmed seizures and seizure severity was associated with worse neurodevelopmental outcomes independent of the severity of hypoxic ischemic brain injury on MRI. |
| McBride et al,[57] 2000 | Prospective observational study of 68 term and preterm neonates undergoing cvEEG monitoring demonstrated that seizures were associated with worse outcomes (microcephaly, severe cerebral palsy). |
| *Randomized Controlled Trials* | |
| Srinivasakumar et al,[51] 2015 | RCT of 35 neonates born at $\geq$36 weeks gestational age with moderate to severe HIE and cvEEG-confirmed seizures, randomized to the treatment of electrographic seizures versus the treatment of clinical seizures only, demonstrated that higher seizure burden was associated with worse MRI injury and neurodevelopmental outcomes at 18–24 mo. |
| Van Rooij et al,[55] 2010 | RCT of 33 term neonates with moderate to severe HIE and aEEG-diagnosed subclinical seizures, randomized to treatment of both clinical and subclinical seizures versus the treatment of only clinical seizures demonstrated that higher seizure burden was associated with worse injury on MRI. |

been made to study this question; however, randomized trials have been limited by low enrollment. Two small prospective trials showed that treatment of electrographic seizures was associated with a reduction in neonatal seizure burden and with less severe brain injury by MRI and adverse cognitive outcome (see **Table 2**).[51,55]

For neonatal epilepsy syndromes, the prognosis is highly dependent upon etiology. Children with self limited (familial) neonatal epilepsy often have no further seizures and normal development, although some go on to develop generalized seizures later in life. Children with neonatal epileptic encephalopathy are likely to have intractable epilepsy, severe developmental disability, and early mortality. Vitamin-dependent epilepsies are highly responsive to their respective treatments. If untreated, these conditions result in progressive developmental impairment, however, appropriate treatment improves developmental outcome.

## SUMMARY

Neonatal seizures are a common emergency in neonatal neurocritical care due to their high incidence and association with long-term neurodevelopmental sequelae. This review highlights the importance of rapid and accurate diagnosis, the gestational age-dependent etiologies, and the complexities surrounding treatment. The prognosis for neonates with seizures varies widely, influenced by seizure etiology, severity, and timely and appropriate treatment. While some neonates may have favorable outcomes with appropriate treatment, particularly those with acute provoked seizures or benign epilepsies, others face significant risks of developmental impairments and postneonatal epilepsy. The goal of neonatal seizure treatment is to improve short-term outcomes and morbidity, reduce long-term neurocognitive sequalae, and reduce the risk of postneonatal epilepsy. There is a need for ongoing research into enhanced diagnostic capabilities, etiology-specific treatments and outcomes. Advances in quantitative EEG analysis hold promise for improving seizure detection and prognostication. Finally, large-scale, multicenter RCTs are necessary to establish evidence-based guidelines for the use of newer ASMs in neonates.

***Best Practices***

***What is the current practice for Neonatal Seizures***

*Best Practice/Guideline/Care Path Objective(s):*

- Rapid and accurate diagnosis with cvEEG monitoring
- Prompt treatment with phenobarbital (FDA-approved) and other ASMs as needed
- Consideration of sodium channel blocker for suspected self-limited (familial) neonatal epilepsy
- Establish etiology by history, laboratory, neuroimaging, and genetic/ metabolic tests as needed

***What changes in current practice are likely to improve outcomes?***

- Implementation of pathway to manage neonatal seizures at local institutions
- Advances in artificial intelligence and machine learning to improve real-time seizure detection and prognostication
- Large-scale, multicenter RCTs are needed to test efficacy and safety of newer ASMs in neonates

***Is there a Clinical Algorithm?***

- Compilation of algorithms from 11 large US Academic Centers[59]

## DISCLOSURE

Dr J.V. Gettings receives research funding from NIH. Dr J. Soul conducted an investigator-initiated research study of lacosamide with funding from UCB, Belgium that ended in December 2022.

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# A Clinical Review of Perinatal Stroke

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**KEYWORDS**

• Perinatal stroke • Neonatal stroke • Perinatal arterial ischemic stroke
• Neonatal hemorrhagic stroke

**KEY POINTS**

- Perinatal stroke is a focal vascular brain injury around birth. Stroke types are defined by clinical and neuroimaging features and classified by type of injury and vessel involvement.
- Pathophysiology is multifactorial and there are no clear strategies for prevention.
- Careful management can improve outcomes including neuroprotection, rehabilitation, and care of the entire family.
- Perinatal stroke is the leading cause of hemiparetic cerebral palsy. Nonmotor complications include language, cognitive, and visual deficits, epilepsy, and mental health burdens on the family.
- This article will discuss perinatal stroke diagnosis, investigations, and management using clinical case examples.

## INTRODUCTION

Perinatal stroke is a focal vascular brain injury that often presents acutely in the neonatal period near term. Classification by vessel involvement (arterial or venous), type of injury (ischemic or hemorrhagic), and timing of presentation defines specific perinatal stroke disease states.[1,2] Perinatal stroke is common, occurring in about 1:1000 live births,[3] and will be encountered regularly by any neonatal practitioner. Proper diagnosis and management carry lifelong implications for the child and their family.

We present a practical summary of the clinical features, diagnosis, management, and prognosis required to optimize the care of a neonate with stroke. The most common scenario of acute perinatal arterial ischemic stroke (PAIS) is presented

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| Abbreviations | |
|---|---|
| CSVT | cerebral sinovenous thrombosis |
| DWI | diffusion-weighted imaging |
| HIE | hypoxic-ischemic encephalopathy |
| NHS | neonatal hemorrhagic stroke |
| PAIS | perinatal arterial ischemic stroke |
| PPAIS | presumed perinatal arterial ischemic stroke |
| PVI | periventricular venous infarction |

first, followed by the less common stroke diseases of cerebral sinovenous thrombosis (CSVT) and neonatal hemorrhagic stroke (NHS). Finally, common issues including neuroprotective care and prognostication of long-term outcomes are discussed.

Family perspectives are prioritized whenever possible, including the most common questions encountered by health care professionals in the acute setting: Why did this happen to our baby? What can we do to help them? What does this mean for their future?

## ACUTE PERINATAL ARTERIAL ISCHEMIC STROKE

Case: Baby M was born at 39 weeks gestation via spontaneous vaginal delivery after an unremarkable pregnancy. Apgar scores were 9, 9 at 1 and 5 minutes respectively. At 14 hours of age, she began having apneas and rhythmic clonic movements of her left arm and leg. MRI brain demonstrated a focal area of acute ischemia in the territory of the right middle cerebral artery (**Fig. 1**).

Acute PAIS typically presents with focal motor seizures, usually at 12 to 72 hours of age.[4] Most neonates are otherwise neurologically normal though neonatal encephalopathy may be present, making distinction from hypoxic-ischemic encephalopathy (HIE) more challenging. The 2 conditions are not mutually exclusive and may share common risk factors. Neuroimaging with MRI is required to differentiate the acute stroke from HIE, particularly if seizures are hemifocal and noted after 12 hours of age[5,6]

MRI with diffusion-weighted imaging (DWI) is required for accurate diagnosis of acute PAIS.[6] This confirms that ischemia is recent (within 7–10 days) and focal, in the form of restricted diffusion within one or more arterial territories.[7] MR angiography may confirm persistent arterial occlusion but rarely shows any other arterial abnormalities. In the unstable neonate, or when MRI is not available, cranial ultrasound or computed tomography (CT) has some utility in diagnosing larger PAIS.

Definitive proof of the mechanism by which a cerebral artery became occluded near birth is often difficult to obtain at this age. Understanding the underlying pathophysiology is essential for accurate diagnosis, investigation, and targeted management including the education of the family. Many case-controlled studies, described below, have sought to provide evidence-based information by examining clinical factors of the mother, pregnancy, placenta, delivery, and newborn.[8–11] These have been supplemented in recent years with much larger samples[12] and advanced methodologies[13] as well as several systematic reviews and meta-analyses,[14] though the latter may risk confusing complex associations with possible causation.

Placental thromboembolism likely accounts for the vast majority of PAIS. Pathologically proven placental diseases resulting in thrombosis and leading to thromboembolism to the fetal brain are well established.[15–19] This mechanism is further supported by indirect observations including overlap in time windows of placental disease in late

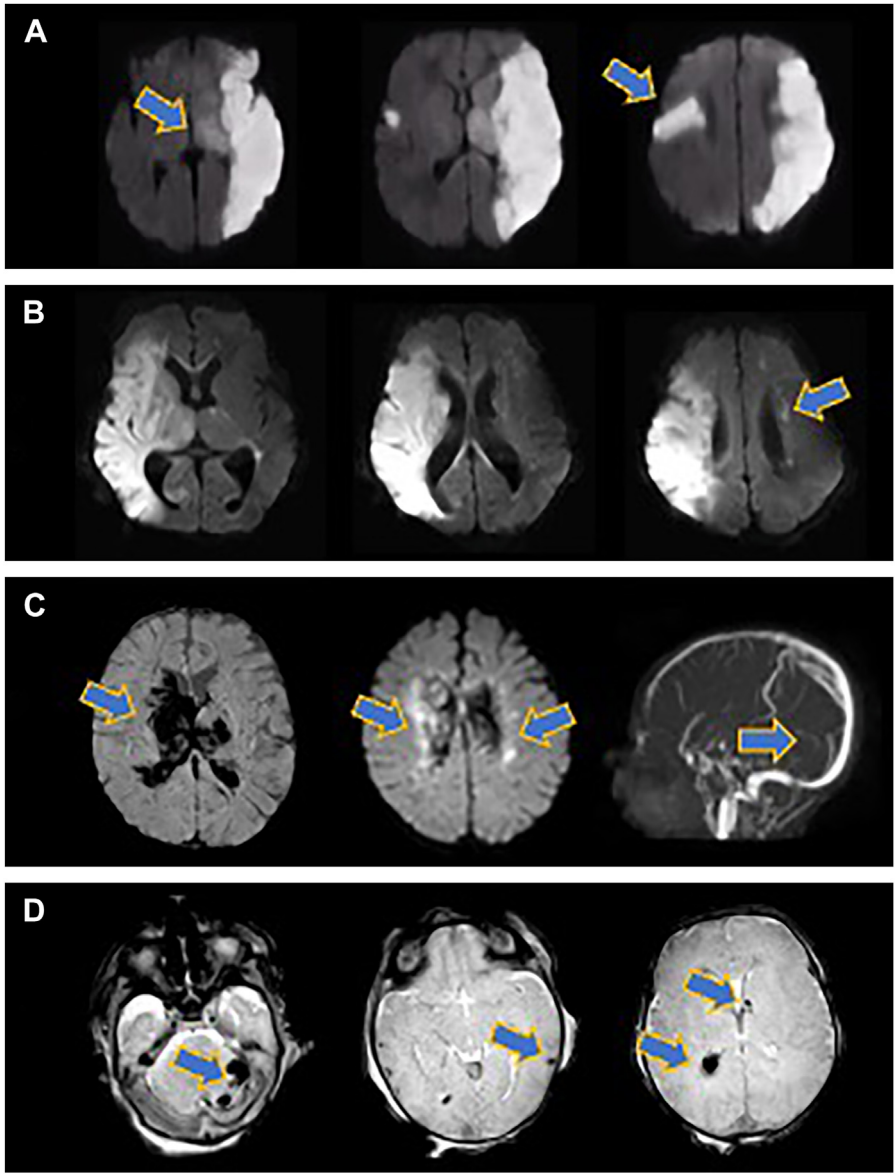


**Fig. 1.** MRI patterns of perinatal stroke. (*A*) PAIS of the left middle cerebral artery (MCA) and a distal branch of the right MCA (*A3, arrow*). Thalamic diaschisis is also noted (*A1, arrow*). (*B*) PAIS of the right MCA, Small DWI lesions in the left hemisphere may represent small embolic PAIS or concomitant watershed global hypoxia-ischemia (*B3, arrow*). (*C*) CSVT shows bilateral thalamic hemorrhage (*C1, arrow pointing to black*) and venous ischemia without hemorrhage (*C2, arrows pointing to bright*), all within the deep venous system. magnetic resonance venography (MRV) shows an absent straight sinus (*C3, arrow*). (*D*) Multifocal hemorrhagic stroke in the cerebellum (*D1, arrow*), temporal cortex (*D2, arrow*), basal ganglia and choroid plexus (*D3, arrows*) of a neonate with severe thrombocytopenia.

pregnancy, bilateral strokes in ~30% suggesting a proximal embolic source, and a recurrence rate of lesser than 1% after delivery. Other probable etiologies may include complex congenital cardiac disease[20] or bacterial meningitis,[21] both of which are usually overt clinical diagnoses with obvious mechanisms leading to cerebral arterial occlusion (though additional contributing factors may still be present).

Several risk factors have been inconsistently associated with acute PAIS, and their lack of direct biological plausibility suggest they may be related to multifactorial mechanisms (such as through placental disease or infection) rather than primarily causative mechanisms. These include primiparity, chorioamnionitis, oligohydramnios, premature rupture of membranes, emergency caesarean section, preeclampsia, poor neonatal transition, intrauterine growth restriction, infertility, and male sex. A high proportion of cases will have no identifiable risk factors[4] and speculating to assign causation to apparent factors should be carefully avoided. There is no increase in prothrombotic conditions when survivors of perinatal stroke are tested during childhood.[22] That there is no association between PAIS and objective measures of birth *trauma* or the mechanical forces of delivery[23] should be emphasized to the parents who often fear such causation as there is concern for potential long-term consequences for family mental health.[24]

Identifying the underlying cause of perinatal stroke involves a specific, targeted evaluation. An echocardiogram should be completed to exclude a cardiac source as this may change management, though the yield in neonates with a normal cardiac examination is low.[4] Bacterial meningitis needs to be excluded in any neonate with clinical signs of infection or those demonstrating associated imaging patterns such as multifocal perforating artery strokes.[21] Pathologic examination of the placenta is indicated in all cases when possible. As only a small area of placental disease may be required to generate thromboembolism, a negative evaluation does not exclude this mechanism. Identification of placental disease does not usually change management but may provide a valuable causative explanation to families. Thrombophilia or genetic testing may be considered in rare cases particularly when there is a family history of hypercoagulability.

## NEONATAL CEREBRAL SINOVENOUS THROMBOSIS

CSVT occurs when thrombosis occurs in the cerebral venous sinuses or veins and presents within 28 days after birth. CSVT also occurs in utero and in delivered preterm infants.[25] CSVT often leads to cerebral venous congestion and edema and eventually venous infarction, often with hemorrhagic transformation.[26] Clinical presentations of CSVT may mimic other perinatal strokes but can also be protean including lethargy, irritability, poor feeding, encephalopathy, or signs of increased intracranial pressure.[27]

Prompt imaging, ideally with MRI including MR venography, and a high index of suspicion are required to ensure cases of CSVT are not missed. Deep system CSVT can be particularly challenging where thrombus is often not directly visible but must be implied by specific patterns for ischemia within the corresponding venous territory. In a term infant with intraventricular hemorrhage, extension from a deep CSVT is the presumed diagnosis until proven otherwise.[28]

Controlled studies are lacking but probable risk factors for neonatal CSVT include infections, most notably bacterial meningitis. Dehydration may be a common trigger, particularly in a newborn who has failed to feed well in the first week of life. Additional possible associations include congenital cardiac disease, cardiac surgery, coagulopathy, and mechanical compression of the venous sinuses.[26,27,29]

## NEONATAL HEMORRHAGIC STROKE

Defined here as a focal accumulation of blood within the brain parenchyma, NHS includes both primary hemorrhage and hemorrhagic transformation of ischemic injuries. This definition does not include extra-axial bleeding such as subarachnoid, subdural, or epidural hemorrhage, which is common in normal newborns. NHS is less common than PAIS and also typically presents with seizures, but larger hemorrhages may produce decreased level of consciousness and signs of increased intracranial pressure.[30]

Risk factors and possible pathophysiology are defined mostly by case series and limited controlled studies.[6,30] NHS can be caused by bleeding diatheses such as hemophilia or neonatal thrombocytopenia, structural lesions like vascular malformations, or hemorrhagic transformation of arterial or venous infarcts.[30] Accordingly, neonates with NHS require hematological evaluations (complete blood count [CBC], partial thromboplastin time [PTT], and international normalized ratio [INR]) and cerebral vascular imaging. The most common scenario is a single, isolated intraparenchymal hemorrhage without any risk factors identified. In this case, the rupture of a small vascular anomaly during the transition to extrauterine life, which is then obliterated, is favored as a common mechanism. Multiple, objective, controlled studies have found no association between the physical forces imparted to the fetal head during delivery and NHS.[23,30] As this may contrast with common perceptions that bleeding is usually due to trauma, careful counseling should be provided to parents to clarify the mechanism.

## NEUROPROTECTIVE CARE AND SPECIFIC TREATMENTS

Initial management of all acute neonatal stroke syndromes focuses on neuroprotective care to minimize ultimate brain injury. Supportive care is always indicated for acute presentations of perinatal stroke, with seizure detection and management being key components of treatment. electroencephalogram (EEG) is required for accurate diagnosis of neonatal seizures and long-term monitoring plays an increasing role during the first days when seizure risk is highest. As there are no antiseizure medication trials specific to stroke, best practices for neonatal seizures should be followed including medication choices based on randomized controlled trials when possible.[31,32] Empiric seizure prophylaxis is not recommended in infants with perinatal stroke in the absence of clinical or electrographic seizures. Seizures secondary to perinatal stroke almost always resolve within the first week with a very low early recurrence rate, and antiseizure medication should not be continued at discharge.[33]

The proven efficacy of therapeutic hypothermia for global hypoxic-ischemic injury does not apply to perinatal stroke for many reasons including unknown time of onset.[34] However, hyperthermia likely worsens acute brain injury; so normothermia and prompt diagnosis and treatment of infection is important. Additional neuroprotective interventions include maintaining normal fluid volume status, blood pressures, and euglycemia. Early novel neuroprotection trials in perinatal stroke are underway.[35,36]

Specific treatments must also be considered for each perinatal stroke disease. For PAIS, the only indication for acute anticoagulation is detection of a cardiac source with ongoing risk.[6] PAIS cases associated with bacterial meningitis require antibiotics, and corticosteroids might be considered for presumed, secondary perforating artery vasculitis.[21] Mechanical thrombectomy is not indicated for PAIS for many reasons including unknown timing of stroke and risk of iatrogenic complications.[37]

For neonates with CSVT, anticoagulation has been shown to be safe and probably effective[6,38] and is employed broadly around the world.[29] If contraindications exist, or relative concerns such as large hemorrhage are present, and the clinical team decides

not to anticoagulate, imaging should be repeated within 5 to 7 days to exclude clot propagation, which may occur in up to 30% of cases.[38] Mechanical compression of the superior sagittal sinus is an additional risk that may be relieved by simple infant positioning to improve venous drainage.[39]

Neonates with NHS require neurosurgical consultation though surgery is not often required except in cases of large volume hematomas or hydrocephalus.[30] A bleeding diathesis with high risk of ongoing or recurrent bleeding requires correction of underlying deficiencies such as platelet transfusions or factor replacements where the help of hematology experts is invaluable.

A practical overall approach to the recognition, diagnosis, investigation and management of term newborns with each of the different acute stroke syndromes is provided in **Fig. 2**. This is presented only as suggested considerations and does not constitute guidelines or specific recommendations for care. All final clinical and treatment decisions rest with the primary physician and the consulting neurologist.

## PRESUMED PERINATAL STROKE: REMOTE PRESENTATIONS

In addition to the acute syndromes described above, nearly half of all perinatal stroke patients are asymptomatic at birth.[40,41] They instead present later in childhood, most commonly with an early hand preference and motor asymmetry first noticed at 4 to 6 months.[42] This eventually leads to concern of hemiparetic cerebral palsy and neuroimaging ,which reveals a remote stroke. These are collectively termed presumed perinatal strokes with 2 specific disease states defined by neuroimaging.

In children with early motor asymmetry, MRI will often reveal a remote infarct in an arterial territory. These are indistinguishable from the chronic appearance of PAIS cases and may well represent the same disease, differing only in the timing of symptomatic presentation. This has been termed presumed perinatal arterial ischemic stroke (PPAIS) and may represent up to 50% of perinatal arterial ischemic strokes.[1]

A second late-presenting perinatal stroke is called periventricular venous infarction (PVI). The mechanism is presumed to be in utero germinal matrix hemorrhage during midgestation with secondary venous infarction.[41] MRI reveals a well-circumscribed lesion of the white matter that spares the cortex and deep gray matter, and hemorrhage-sensitive sequences may still show residual hemosiderin deposition.[43] Clinically distinguishing PVI and PPAIS is difficult, although PVI is more likely to demonstrate lower limb impairment while seizures are more common in PPAIS.[42] A recent controlled analysis of 141 PVI cases found no relationship to peripartum factors but possible associations with primiparity, maternal age, gestational diabetes, and small for gestational age.[44] Genetic conditions can also create PVI-like lesions, most notably collagen type IV alpha 1-related where the presence of bilateral lesions with concomitant hemorrhage and/or family history should prompt genetic testing.

Outcomes and management for presumed perinatal stroke are similar to acute perinatal strokes. Due to the selection bias of their late presentation, most children will have significant motor disability.

## OUTCOMES

Prognosticating outcomes after perinatal stroke is challenging due to the variable presentation and the evolving nature of neurodevelopment. While many children achieve favorable outcomes, lifelong neurologic disabilities often persist. The initial diagnosis of perinatal stroke can be devastating to families and the communication of lifelong outcomes must be fully communicated, including the fact that many children will be able to live happy and productive lives and achieve their own goals.

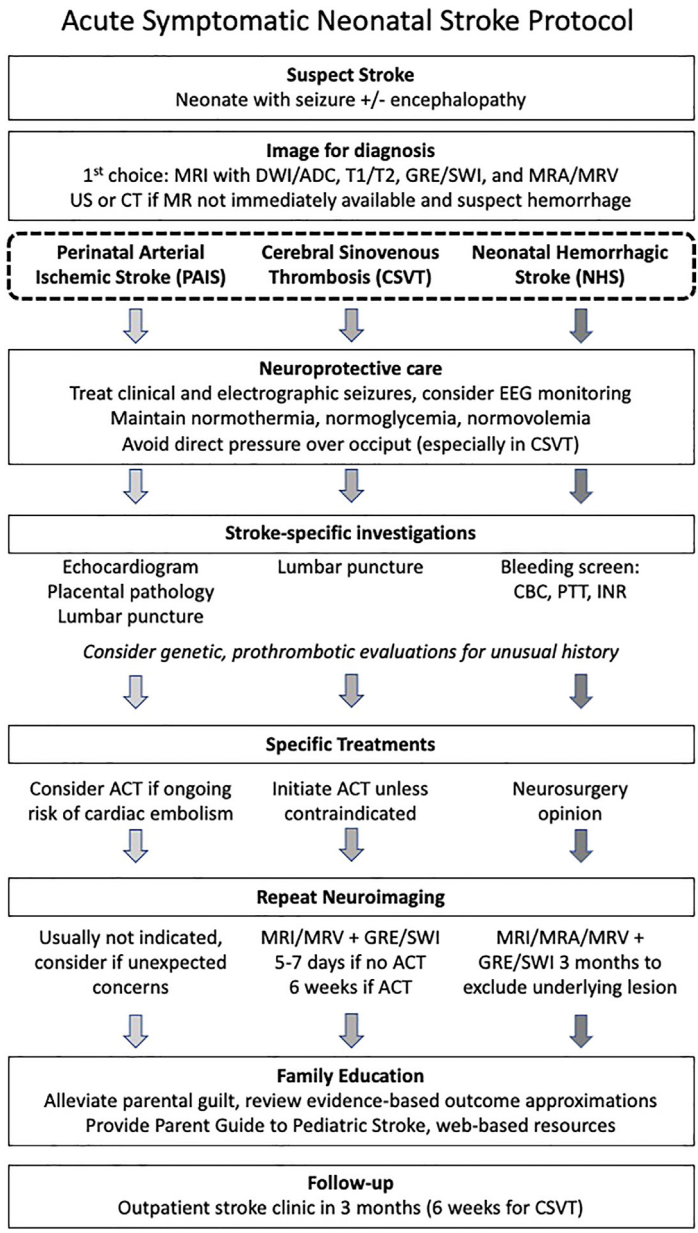


**Fig. 2.** Example of an approach to acute symptomatic neonatal stroke. ACT, anticoagulation treatment; ADC, apparent diffusion coefficient; GRE, gradient echo; SWI, susceptibility-weighted imaging; US, ultrasound.

Hemiparetic cerebral palsy is the most common consequence of perinatal stroke, resulting in unilateral motor impairment of variable severity. Motor outcome can be accurately predicted on acute neuroimaging including basal ganglia and corticospinal tract involvement and diffusion biomarkers of early degeneration or

"diaschisis".[7,45–47] Multidisciplinary care teams, including physiotherapy and occupational therapists play a crucial role in supporting children with perinatal stroke and their families with a focus on life participation. Prognostication and counseling should include descriptions of what life often looks like with chronic hemiparesis, including challenges but also realistic hopes such as walking in nearly all cases with little or no delay, ability to participate in most normal childhood activities with minor modifications and some limitations, and independence in activities of daily living for the vast majority.

Although most children with perinatal stroke will have average intelligence and participate in normal school, injury can impact cognitive and behavioral domains, including attention, processing speed, and verbal memory.[48] Cognitive/behavioral issues often emerge when a child with perinatal stroke starts school. This may present with inattention, disinhibition, or abnormalities of processing speed, verbal or visual memory, and intellectual function. Formal neuropsychologic testing is recommended for any child encountering school difficulties. Language is remarkably plastic and the vast majority of children, even those with large left hemisphere lesions, will have normal language function.[49,50]

Remote symptomatic epilepsy will occur in 25%-30% of perinatal stroke survivors.[51] Predicting epilepsy is difficult; so, education and passive ongoing surveillance is required. Epileptic encephalopathy, such as continuous spike and wave in sleep, can significantly impair cognitive function and is treatable, highlighting the need for early detection and intervention.[52] Accordingly, any child with perinatal stroke and nonmotor delays, particularly if there is regression and regardless of daytime seizures, requires sleep EEG to exclude this diagnosis.

Providing adequate support and education to families is essential for promoting resilience and coping mechanisms. This includes avoidance of misinformation and connecting families with supports as needed to avoid common mental health morbidities including depression and posttraumatic stress disorder.[24] Parental engagement in the child's care and rehabilitation process can facilitate adjustment and improve outcomes. The risk of stroke recurrence in both the child and subsequent pregnancies (<1%) must be communicated to the parents.

## SUMMARY

Perinatal stroke represents a complex clinical entity with diverse types, mechanisms, manifestations, and long-term implications for neurodevelopment. A multidisciplinary approach encompassing early diagnosis and targeted interventions in the acute setting is essential for optimizing outcomes and promoting the well-being of affected children and their families.

## TAKE-HOME POINTS

- In a term neonate with unexplained focal seizures, stroke must be investigated.
- Prompt neuroimaging with MRI is crucial for diagnosing specific perinatal stroke types.
- Neuroprotective care forms the foundation of management for newborns with acute stroke, focusing on seizure management and supportive measures.
- Infants with perinatal stroke have diverse outcomes, emphasizing the importance of individualized prognostication and family-centered care.
- Careful counseling of parents regarding causation, misplaced guilt and blame, and hope for the future must occur early and repeatedly to optimize mental health outcomes.

***Best Practices***

Timely diangosis of perinatal stroke is required to guide management and provide optimal care for patients and families.

## DISCLOSURES

The authors have nothing to disclose.

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# Hypotonia in the Neonatal Intensive Care Unit

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**KEYWORDS**

• Neonate • Hypotonia • Abnormal tone • Peripheral nervous system
• Central nervous system • Neonatal intensive care • Diagnostic evaluation

**KEY POINTS**

- Care of the neonate with hypotonia requiring neonatal intensive care unit (NICU) care is challenging due to a broad differential.
- Evaluation for a potentially treatable and time sensitive systemic etiology including infection or acute metabolic derangement remains the most emergent consideration.
- Emerging treatments for multiple genetic conditions have increased the urgency of evaluation for primary hypotonia.
- Updated consensus guidelines recommend rapid exome/genome testing as first-line genetic testing for the newborn requiring intensive care unit level care with primary hypotonia.

## INTRODUCTION AND DEFINITIONS

Neonatal hypotonia is one of the most common neurologic conditions in the neonatal intensive care unit (NICU), occurring in over 1% of NICU admissions[1] and yet one of the most challenging to clinicians due to the broad spectrum of causes. Neonatal hypotonia is defined as diminished resistance to passive movement,[2] which may or may not be associated with weakness. Neurologic weakness is defined as a reduction in the maximum voluntary power of the muscles.[3] Neonatal hypotonia may be secondary to systemic illnesses or related to either central nervous system (CNS) or peripheral nervous system (PNS) causes. Secondary causes of hypotonia may be systemic in origin, or sequelae from neurologic injury. Primary causes of hypotonia are those

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| Abbreviations | |
|---|---|
| CNS | central nervous system |
| CSVT | cerebral sinus venous thrombosis |
| EEG | electroencephalogram |
| EMG | electromyography |
| HIE | hypoxic ischemic encephalopathy |
| NICU | neonatal intensive care unit |
| PNS | peripheral nervous system |
| rNCS | repetitive nerve stimulation |
| SMA | spinal muscular atrophy |

due to genetic or structural causes. Rapid diagnosis has become ever more important with targeted care decisions and treatments either available or in development for multiple conditions including Prader-Willi syndrome,[4] spinal muscular atrophy (SMA),[5] metachromatic leukodystrophy,[6] congenital myopathies,[7] and congenital myasthenic syndromes[8] although treatment remains primarily supportive for most conditions. Fortunately, the last 5 years had seen tremendous progress in both the availability and diagnostic yield of genetic testing with continuously decreasing turn-around times, often in less than 1 week. Rapid genetic analysis in form of exome and short-read genome testing is commercially available and now considered the first-line diagnostic approach for many neonates with concern for a primary genetic hypotonia.[9] This article focuses on the evaluation of the hypotonic infant in the NICU including relevant history and examination findings as well as the recommended diagnostic approach, with an emphasis on rapid identification of treatable conditions and updated recommendations on the utilization of genetic testing in the genomic era.

## EXAMINATION OF THE NEWBORN WITH HYPOTONIA

A thorough examination is an essential first step in the diagnosis of the newborn with low tone. The exam of a neonate with hypotonia ideally includes a thorough general and neurologic examination, including a thorough evaluation for dysmorphologies that may provide diagnostic clues. This should include an assessment of whether developmental features including primitive reflexes are consistent with the stated gestational age. In addition, a focused parental examination can provide helpful information. Parental exam classically includes a handshake, with maternal inability to release a handshake suggestive of myotonic dystrophy. Examination of parental facial features may also suggest familial syndromic or genetic etiologies or conversely suggest that distinctive neonatal facial features are likely benign familial traits.[10] Examination of the neonate should start with a head-to-toe evaluation for dysmorphic features including an evaluation of relative macro/microcephaly. Key components of the nonneurologic neonatal examination include evaluation of respiratory status such as signs of respiratory insufficiency, cardiac size, and function. A comprehensive neonatal neurologic examination includes an assessment of mental status, cranial nerves, movement patterns relative to expected gestational age,[11] and reflexes.[12] The evaluation of tone includes examination of limb positioning in a quiet awake state, head position on pull to sit, and an evaluation of trunk and limb positioning during vertical and horizontal suspension,[13] whereas an evaluation of strength includes assessing the maximal power that the neonate can generate with stimulation. Assessment of deep tendon and primitive reflexes are imperative in the newborn with hypotonia.

## FOCUSED HISTORY IN NEONATAL HYPOTONIA

A thorough review of maternal, fetal/neonatal, and family history along with the targeted examination of both mother and infant can provide important clues to guide the diagnostic workup (**Table 1**) and suggests the diagnosis in up to 50% of neonates.[14]

Maternal and neonatal history should include a pregnancy history incorporating certainty of gestational age, as expected neonatal tone evolves with age and any prenatal pharmacologic or drug exposures. Prenatal infectious screening and exposures are important as prenatal infection with cytomegalovirus, Zika virus, rubella virus, and others may result in CNS injury and malformations manifesting as neonatal hypotonia.[15] Prenatal concerns for polyhydramnios can suggest the presence a CNS or genetic etiology that results in abnormal fetal swallowing, maternal diabetes, or prenatal infection.[16] An expanded maternal and family health history that includes known or suspected diagnosis of myasthenia gravis (which can result in transient neonatal myasthenia), a history of seizures (as many causes of genetic seizures are associated with hypotonia, and some maternal antiseizure medications can contribute to neonatal hypotonia), and maternal myotonic dystrophy, among others can assist with narrowing the broad differential. A fetal movement history is key as decreased movement throughout the latter part of pregnancy increases the chance of a chronic or genetic etiology versus a history of late and sudden decreased movement may suggest a perinatal insult or injury. Particular attention to birth history includes if there were any events concerning for neonatal hypoxic injury, perinatal chorioamnionitis or a traumatic birth with risk for a brachial plexus or cervical spine injury, as well as the fetal presentation at delivery. The onset and evolution of neonatal hypotonia and attention to static versus progressive course is important for discerning perinatal injury vs concern for developing sepsis or evolving evidence of inborn errors of metabolism; for example, presence from birth with associated low Apgar scores with improvement may suggest the former, while progressive hypotonia over the first few days of life raises concern for the latter.

The family history can also shed light on the potential underlying etiology of hypotonia. Reported familial history typically includes known or suspected neuromuscular disease, hypotonia, and myotonia. It is also important to include the presence or absence of consanguinity, any history of recurrent miscarriages, infantile deaths, and developmental delay as these can suggest the presence of a familial inherited etiology.[9] Many causes of neurodevelopmental delay include neonatal hypotonia within the spectrum of potential presentation and other effected family members may have had less prominent hypotonia.

## DIFFERENTIAL DIAGNOSIS AND SUGGESTED APPROACH

The differential diagnosis of neonatal hypotonia is extensive (**Box 1**), and the initial challenge for NICU clinicians is categorizing the likely reason for hypotonia using the history and examination to prioritize the workup appropriately. Prior studies have suggested that approximately 70% to 80% of neonates have systemic or CNS etiologies with 15% to 20% having PNS causes and the balance without a diagnosed cause.[13,14,17] Pragmatically, one often must consider these possibilities simultaneously, with broad initial evaluation as the most urgent need is to rule out time sensitive treatable systemic causes and then evaluate for CNS or PNS etiologies. Initially, CNS or systemic etiologies can have overlapping clinical features with accompanying neonatal encephalopathy, microcephaly or macrocephaly, or dysmorphic features. Additional evidence of other organ involvement such as enlarged cardiac silhouette,

**Table 1**
**Focused history and exam for evaluation of neonatal hypotonia**

*History*

*Maternal Medical History with attention to the following:*
- Myotonic dystrophy
- Seizures/Epilepsy
- Myasthenia Gravis
- Systemic Lupus Erythematosus

*Pregnancy and Delivery History:*
- Pregnancy losses
- Certainty of gestational age
- Fetal movement
- Teratogen and maternal medication \ substance exposure
- Infection concerns, particularly for pre and perinatal infections associated with neonatal brain involvement or Group B Streptococcus, concern for chorioamnionitis
- Concerns for hypoxic sentinel events or birth trauma

*Neonatal History*
- Timing of concern for hypotonia: notable from birth, vs development in the first few days
- Progression: static since noted, vs progressive
- Additional medical concerns

*Family history*
- Attention to familial hypotonia, neuromuscular disease, developmental delay, early infantile deaths
- History of consanguinity

*Examination*

*Parental examination*: assess for distinctive facial features, handshake with inability to let go suggestive of myotonic dystrophy or myotonia on brachioradialis percussion

*General exam:*
*Head, Eyes, Ears, Nose, Throat*: Orbitofrontal circumference, fontanelle, presence of distinctive or dysmorphic facial features
*Respiratory*: Attention to chest shape, need for respiratory support, and ability to stimulate breaths
*Cardiac*: Associated congenital abnormalities including cardiac size and function
*Liver*: Hepatosplenomegaly and/or evidence of liver dysfunction
*Musculoskeletal*: Presence of contractures or arthrogryposis with attention to distribution if present
*Skin*: Evidence of jaundice, nevi, and vesicular lesions

*Neurologic examination:*
*Mental status*: Response to tactile stimulation, spontaneous eye opening
*Cranial nerves*: Attention to extraocular movements, facial grimace, ability to fully bury eyelashes as evidence of facial hypotonia or weakness. Presence and quality of suck/swallow and cry strength
*Motor:*
*Posture at rest*: evidence of "frog-legged position"
*Tone/Tone Maneuvers:*
- Ventral suspension assessing for ability to elevate head above neutral and bring legs under hips
- Vertical suspension assessing for shoulder girdle tone
- Pull-to-sit: assessing degree of head lag. At term, anticipate some head lag, <30°
- Arm recoil/"scarf sign": drawing of arm across body with monitoring of how easily it draws back when letting go
- Leg recoil: Flexion of leg toward hip with monitoring of how easily to return when letting go

*Strength and Movement patterns:*
- Degree of spontaneous movements, symmetric frequency of movements
- Movements in plane of bed, vs antigravity

*Reflexes*: Deep Tendon Reflexes: hyporeflexia or areflexia raises suspicion for PNS involvement, presence and quality of primitive reflexes: Moro, plantar and palmar grasp, suck and root
*Sensory*: Response to touch: motoric, changes in vital signs

**Box 1**
**Localization based differential diagnosis**

Systemic causes
- Sepsis
- Severe hypoglycemia
- Severe hepatic dysfunction
- TORCH infections
- In-utero/perinatal drug exposures
- Hypothyroidism
- Acute Bilirubin Encephalopathy
- Genetic
  - Chromosomal abnormalities including Trisomy 21
  - Prader-Willi
  - A broad range of monogenic disorders include hypotonia in the phenotypic spectrum
- Metabolic
  - Hypotonia is frequently observed in neonatal onset metabolic diseases including disorders of glycogen metabolism, disorders of carnitine metabolism, disorders of amino acid metabolism, peroxisomal disorders, organic acidemias, and urea cycle defects

CNS
- Acute hypoxic injury/hypoxic ischemic encephalopathy
- Intraparenchymal hemorrhage
- Perinatal stroke (arterial or venous)
- Brain malformations
- Spinal injury or malformation
- Syringomyelia

PNS
- *Anterior Horn cell*
  - Spinal Muscular Atrophy (SMA) non-5q- SMA
- *Congenital neuropathies*
  - Charcot-Marie-Tooth disease
    - Dejerine-Sottas disease
    - Hypomyelinating neuropathy
  - Hereditary sensory and autonomic neuropathy
- *Neuromuscular junction abnormalities*
  - Transient neonatal myasthenia
  - Congenital myasthenia syndrome
  - Infantile Botulism
  - Aminoglycoside toxicity
  - Magnesium toxicity
- *Congenital myopathies*
  - Nemaline myopathy
  - Central core disease
  - Myotubular myopathy
  - Mitochondrial myopathy
- *Muscular dystrophies*
  - Dystrophinopathies
  - Congenital muscular dystrophies
  - Muscle-Eye-Brain disease
  - Early infantile facioscapulohumeral dystrophy
  - Congenital myotonic dystrophy

concern for hepatomegaly, jaundice, or cataracts may clue the clinician into systemic causes.[2] Features that suggest a PNS etiology include an intact, alert mental status with cranial nerve involvement and severely hypoactive or absent deep tendon reflexes such as absent patellar or Achilles tendon reflex.

### *Initial and Time Sensitive Evaluations for Systemic Etiologies*

Of utmost importance in the NICU is ensuring that hypotonia is not secondary to an acute, potentially treatable and time sensitive etiology (Fig. 1). To this end, essentially all neonates with concern for hypotonia requiring NICU evaluation should undergo assessment for systemic infection with rapid evaluation and strong consideration for concurrent treatment. Presence of hypoglycemia or other severe electrolyte derangements, maternal medication exposure to magnesium sulfate, or general anesthesia should also be evaluated. Particularly within the first 6 hours of life, any possibility of hypoxic ischemic encephalopathy (HIE) and attendant potential qualification for therapeutic hypothermia should be considered.[18] Infants should be evaluated for hyperbilirubinemia as acute bilirubin encephalopathy can initially present with poor feeding and hypotonia. Urgent but less emergent secondary causes of neonatal hypotonia to be considered during initial evaluation may include congenital heart disease, congenital diaphragmatic hernia, primary pulmonary disease,[19] or neonatal liver failure,[20] particularly if there is limited access to prenatal care. Additionally, asymptomatic or minor findings may clue the clinician toward the search for a unifying genetic cause. Many metabolic conditions also present with hypotonia, and those with treatments available are being continually added to the recommended newborn screening panel in the United States.[21] An initial screen with blood gas, glucose, lactate, and ammonia should be considered, as abnormalities may quickly raise suspicion for inborn errors of metabolism. In addition, ensuring the newborn screening is sent promptly and undergoes expedited evaluation is an effective initial screen for rare but treatable neurometabolic disorders while more in-depth evaluation is ongoing.

### *Central Nervous System Etiologies*

CNS causes of hypotonia occur more common than those of the PNS. The etiology for hypotonia in the setting of encephalopathy is broad and includes HIE, perinatal stroke, intraparenchymal hemorrhage, cerebral sinus venous thrombosis (CSVT), infectious, metabolic, and structural and other genetic causes. In CNS injury such as HIE, stroke or hemorrhage, tone may evolve from initially hypotonic in the acute phase to hypertonic in the chronic phase and this transition may be heralded by evidence of hyperreflexia, defined as spread of deep tendon reflexes beyond the tested tendon, or sustained clonus. CSVT can present secondary to prolonged compression occurring during labor or after dehydration and/or poor feeding; it is crucial to differentiate whether hypotonia was present early in the course and the cause of poor feeding and subsequent dehydration.

Congenital brain malformations may also result in neonatal hypotonia. While some may be diagnosed prenatally, such as ventriculomegaly, holoprosencephaly, pontocerebellar hypoplasia, or Dandy-Walker syndrome, varied access to prenatal testing and care remains, and thus a consideration postnatally. Lissencephaly and polymicrogyria can present first with hypotonia and may not be detected on prenatal imaging depending on the time obtained.

Spinal injury or malformation should be considered in the setting of an examination with significantly decreased lower extremity tone versus upper extremity tone or diffusely decreased tone with preserved mentation and difficult birth. Spinal injury may be quite challenging to distinguish from PNS etiologies in the acute phase but will typically develop increased tone and reflexes over time.

Beyond this, there are numerous monogenic causes of neonatal hypotonia, with ever-expanding knowledge of disorders that can present in the neonatal period with hypotonia as a predominant feature.[9]

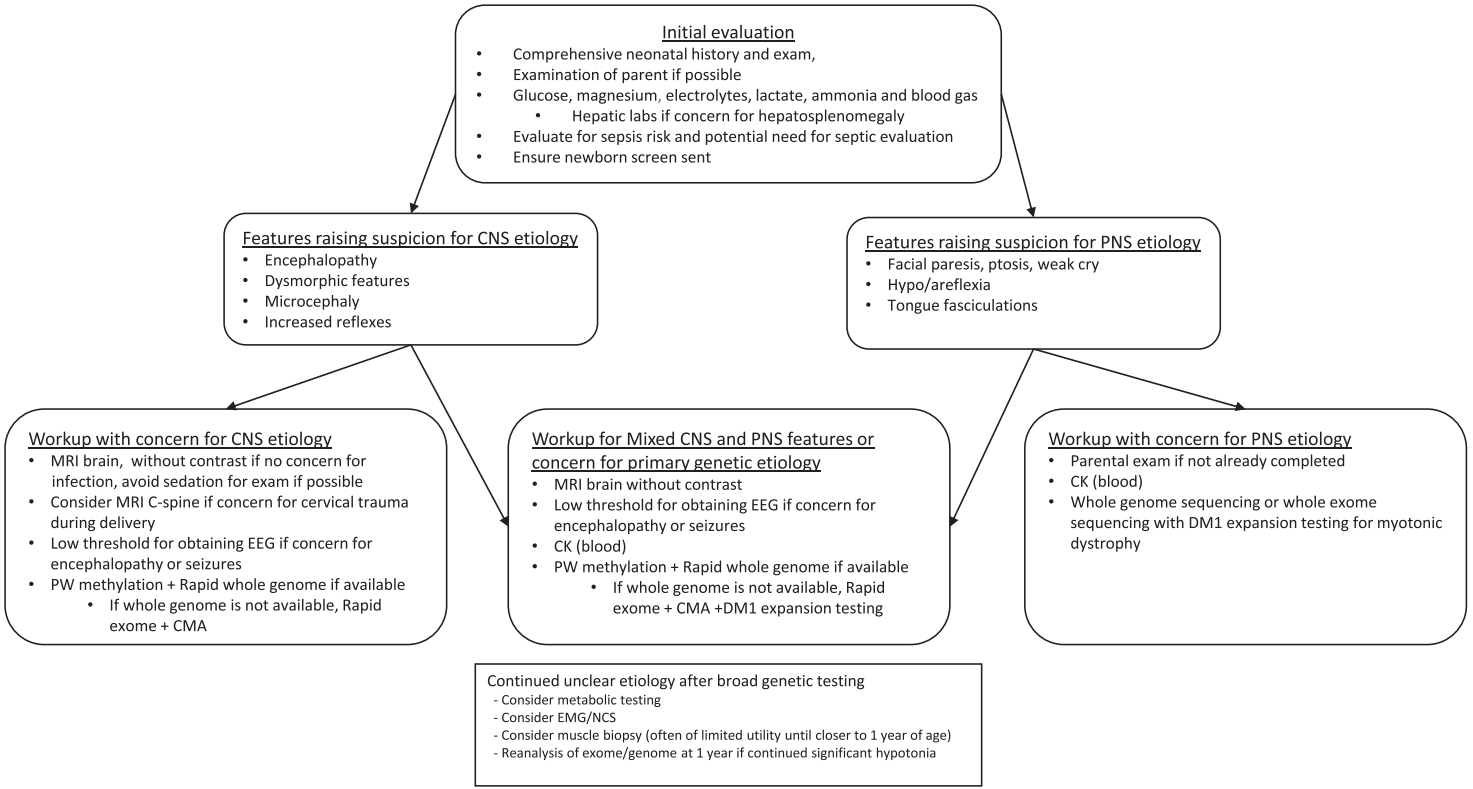


**Fig. 1.** An updated approach to hypotonia. Proposed flowchart for the evaluation of neonatal hypotonia presenting in the NICU.

### *Workup with concern for central nervous system etiology*

When clinical features suggest a CNS or genetic etiology, recent changes in cost and clinical availability have significantly altered the diagnostic approach, although heterogeneity in available diagnostic resources remains. If clinical features suggest a specific genetic etiology, classically trisomy 21, then targeted testing is a reasonable first step. However, most CNS causes of neonatal hypotonia are difficult to diagnose based on clinical examination alone. For the encephalopathic hypotonic infant, a MRI of the brain should be considered early in the diagnostic process (see **Fig. 1**). If there is no concurrent concern for infection, a noncontrasted study is sufficient. It is advised to complete this study without sedation after feeding and bundling the neonate where feasible,[22] which decreases the risk of harm to the neonate, particularly if there are concomitant concerns for airway tone in the setting of anesthetics. Interpretation of neonatal brain imaging, especially when assessing subtle congenital brain malformations, can be challenging and is best interpreted by pediatric neuroradiologists. If there is a history concerning potential spinal involvement, then additional MRI spinal imaging should be considered. While an electroencephalogram (EEG) is not indicated for every hypotonic neonate, neonatal seizures can be challenging to detect clinically[23] and there should be a low threshold to obtain an EEG in an encephalopathic hypotonic neonate, or when the presence of encephalopathy is uncertain. Rarely, the EEG background activity can provide valuable diagnostic information particularly with regard to metabolic diseases, such as comb-like pattern in maple syrup urine disease,[24] and more commonly can aid the clinician in determining the degree of encephalopathy.

## *Peripheral Nervous System Etiologies*

Peripheral causes of neonatal hypotonia occur less commonly but are important to consider in the newborn. These encompass disorders of the anterior horn cell, nerve, neuromuscular junction, and muscle. Neonates with a PNS etiology may exhibit an alert mental status and severely hypoactive or absent reflexes. Often, features such as facial weakness or abnormal eye movements may be present. Tongue fasciculations raise suspicion for SMA, a disorder of the anterior horn cell. Hypotonia related to PNS disease can be associated with respiratory insufficiency. While nonencephalopathic neonates with PNS disease are often able to initiate breathing, muscle weakness impairs the ability to take adequate breaths, which may result in transitory or permanent need for ventilatory support. Examination often demonstrates a newborn with a paucity of movement, and in most severe cases the neonate may not be able to generate adequate strength to react to examination even with stimulation.

Muscle disorders affecting the newborn are classified into 2 broad categories, congenital myopathies and congenital muscular dystrophies. Congenital muscular dystrophies demonstrate dystrophic changes on muscle biopsy, that is, injury to the muscle structure and architecture; in general, these disorders tend to be progressive. Congenital myopathies do not have dystrophic changes on muscle biopsy and tend to have a slowly progressive or nonprogressive course. Numerous genes have been associated with both congenital myopathies and muscular dystrophies and are reviewed elsewhere.[25]

Although primarily a neuromuscular condition, several congenital muscular dystrophies also result in brain abnormalities.[26] Muscle-Eye-Brain disease and its most severe form, known by the eponym Walker-Warburg syndrome, are forms of muscular dystrophies called dystroglycanopathies with associated brain malformation that often includes cobblestone lissencephaly and abnormal brainstem formation and eye involvement. Laminin $\alpha 2$ related disorder affects the white of the brain.[27]

Congenital myotonic dystrophy, a form of congenital muscular dystrophy, requires specific diagnostic consideration as this often has medical implications for both the

newborn and parent, as this is inherited with anticipation of CTG repeats in the dystrophia myotonica protein kinse (*DMPK*) gene, and high clinical suspicion with parental examination as previously discussed may quickly steer the clinician to the diagnosis.

Congenital myasthenic syndromes can have variable fatigability, and classically required repetitive nerve stimulation for consideration[8] although they are typically diagnosed with genetic testing currently. Transient neonatal myasthenia gravis can occur in newborns born to mothers with myasthenia gravis. Congenital neuropathies are rare and affected neonates may have worsened distal weakness over proximal involvement, although this can be challenging to discriminate on examination.[2]

***Workup with concern for peripheral nervous system etiology***

Historically, evaluation for PNS disorders required both a high degree of clinical suspicion as well as testing with laboratory testing of creatine kinase (typically avoided in the first few days of life secondary to elevations related to birthing process), electromyography (EMG), repetitive nerve stimulation (rNCS) and even muscle biopsy in the newborn, after which further genetic studies were pursued. However, in the genomic era, it is clear there is pleiotropy in the presentation of neonatal neuromuscular diseases, with a broad spectrum of phenotypes present with pathogenic variants in a single gene. This, coupled with the technical challenges associated with EMG and muscle biopsy in the newborn and potentially uncomfortable nature of this testing, has led to changes in the recommendations of evaluation for PNS etiology. Early use of rapid exome or clinical genome sequencing is often pursued first, with subsequent use of EMG/rNCS or muscle biopsy when diagnostic uncertainty remains.

## GENETIC TESTING IN THE EVALUATION OF THE HYPOTONIC NEONATE

The era of rapid genomic testing has changed the approach to genetic testing of the hypotonic neonate. Genetic causes can include aneuploidies and copy number variants,[28,29] changes in DNA methylation of uniparental disomy (such as Prader-Willi Syndrome),[4] repeat expansions (such as CTG repeats in the DMPK gene in congenital myotonic dystrophy),[30] and a multitude of single-nucleotide variates or small insertion/deletion variants in either the nuclear or mitochondrial genome.[9] While clinically available short-read genome testing can often assess for large copy number variants and repeat expansions, this may not be detected with exome sequencing.[31] If high suspicion for congenital myotonic dystrophy, *DMPK* CTG repeat testing is currently recommended; however, long-read genome sequencing is emerging as testing method, which has the ability to identify short tandem repeats[32,33] as well as methylation changes[34] The strengths and limitations of genetic testing available in the NICU is reviewed elsewhere, but multiple trials have now demonstrated that broad, rapid testing, ideally with clinical exome or clinical genome evaluation is cost-effective[35–37] and has a diagnostic yield up to 50%.[9] Given this, new consensus recommendations suggest broad genetic testing as first-line testing once secondary causes of hypotonia are ruled out[9] (see **Fig. 1**).

## TREATMENT CONSIDERATIONS

Once a treatable secondary cause of neonatal hypotonia such as sepsis, hypoglycemia, or electrolyte abnormalities has been ruled out, treatment options are limited to supportive care with some key exceptions. The most dramatic change in diagnostic urgency is prompt diagnosis of SMA. This has become a *do not miss* diagnosis as treatment with either antisense oligonucleotides (nusinersen and risdiplam)[38] or gene therapy with

onasemnogene abeparvovec[5] make striking, time sensitive differences in motor outcomes for affected children. Accordingly, SMA has been rapidly added to the newborn screen across the United States, with 34 programs fully implemented by June 2021[39] and 50 states screening as of January 2024.[40] Other important, treatable causes of neonatal hypotonia included in newborn screening in the United States include Pompe disease, for which enzyme replacement therapy is available and additional treatments are being developed,[41] several diet treatable organic acidemias[42] and fatty acid disorders,[42] congenital hypothyroidism, and biotinidase deficiency,[42] though tests vary by state. The number of urgently treatable causes for neonatal hypotonia will likely rise soon, as gene therapy approaches are well underway in metachromatic leukodystrophy[6] and several of the congenital myopathies.[7] Even without curative treatments available, early genetic diagnosis of congenital myasthenic syndromes is essential to optimize medication therapies[8] and early diagnosis of Prader-Willi Syndrome helps avoid unnecessary gastrostomy tube placement.[4]

In areas with limited access to genetic testing, the approach to neonatal hypotonia may be more incremental. The initial and emergent workup should still focus on ruling out infection and other treatable causes of secondary neonatal hypotonia with emergent transfer if this evaluation cannot be accomplished. For mild hypotonia in a US based setting where the availability of imaging, genetic testing, and neuromuscular testing is limited, an expedited newborn screen review may be sufficient to rule out urgently treatable causes of neonatal hypotonia. Of note, newborn screening for SMA carries limitations, as approximately 5% of patients with SMA can have a compound heterozygote state causing a false negative result.[43] In areas where newborn screening is not available or does not include SMA, or when high clinical suspicion for SMA exists, *SMN1* and *SMN2* copy number testing is recommended, or transfer to an institution where this can be obtained, particularly if treatment is available in these regions. If hypotonia does not limit respiratory status or oral feeding, referral for outpatient evaluation at a tertiary or quaternary pediatric center is reasonable. If neonatal hypotonia is profound enough to limit home-going, opportunities for telehealth consultation with neonatal neurology are rapidly emerging. Such consultations can assist with further workup recommendations and facilitate transfer to a specialized center.

## SUMMARY

Neonatal hypotonia is a common occurrence in the NICU and requires consideration of a broad spectrum of etiologies. Initial evaluation is geared to assessment of treatable and urgent causes. Physical examination can help distinguish central versus peripheral origin. CNS causes for hypotonia are more common in the neonate than peripheral causes. Early consideration of broad genetic testing in the form of rapid whole exome or short-read whole genome sequencing is both comprehensive and cost-effective, and currently recommended as standard of care, although knowledge of its limitations is necessary.

***Best Practices***

***Best Practice Objective(s)***

Streamline evaluation of neonatal hypotonia in the ICU.

***What changes in current practice are likely to improve outcomes?***

New advances in genetic testing will expedite the evaluation of primary hypotonia, with new recommendations suggesting clinical exome/genome testing as the first-line of genetic testing.

***Is there a Clinical Algorithm?***

Please refer to **Fig. 1**.

***Pearls/Pitfalls at the point-of-care***

It is essential that initial testing focus on rapidly evaluating for acutely actionable etiologies of hypotonia in the ICU including sepsis, metabolic/electrolyte derangements, and hypoxic-ischemic encephalopathy within the first 6 hours of life.

***Major Recommendations***

Once acute, actionable etiologies of neonatal hypotonia have been ruled out, subsequent evaluation should be driven by clinical concern for a central versus PNS etiology. Etiologic evaluation, including genetic evaluation, is increasingly urgent to complete promptly as there are emerging treatments for multiple genetic etiologies. Updated consensus guidelines recommend rapid clinical exome/genome testing as the recommended first-line testing for newborns requiring ICU care with concern for primary genetic hypotonia.

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## DISCLOSURE

None.

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# Neonatal Neurocardiac Care

## Strategies to Optimize Neurodevelopmental Outcomes in Congenital Heart Disease

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**KEYWORDS**

• Congenital heart disease (CHD) • Brain injury • Neurodevelopmental outcomes
• Critical care

**KEY POINTS**

- Long-term neurodevelopmental outcomes and risk for brain injury in critical congenital heart disease (CHD) are influenced by a myriad of factors beginning in the fetal period and spanning the preoperative, perioperative, and postoperative periods and beyond.
- Understanding and mitigating risk factors for brain injury in CHD may improve long-term outcomes.
- There are no clear guidelines for routine neuromonitoring and neuroimaging in CHD, but implementation of routine genetic testing, postoperative electroencephalogram monitoring, neuroimaging, and neurology consultation may provide important data regarding neurologic risk and prognosis and may help guide management.
- Individualized developmental care, support of parental mental health, and long-term neurodevelopmental follow-up are also critical components of optimal neurologic care for neonatal CHD.

## INTRODUCTION: NEUROLOGIC AND DEVELOPMENTAL OUTCOMES IN CONGENITAL HEART DISEASE

In recent decades, advances in neonatal cardiovascular surgery have dramatically improved the survival of patients with critical congenital heart disease (CHD). However, a significant number (25%–90%) of survivors of CHD experience neurodevelopmental

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| Abbreviations | |
|---|---|
| 2V | Two ventricle |
| AHA | American Heart Association |
| CHD | Congenital heart disease |
| ECMO | Extracorporeal membrane oxygenation |
| EEG | Electroencephalogram |
| HLHS | Hypoplastic left heart syndrome |
| ICU | Intensive care unit |
| IVH | Intraventricular hemorrhage |
| NDD | Neurodevelopmental disabilities |
| NIRS | Near-infrared spectroscopy |
| SV | Single ventricle |
| TGA | Transposition of the great arteries |
| WMI | White matter injuries |

impairment[1,2] that may significantly impact quality of life.[3–7] Brain injuries, particularly white matter injuries (WMI) and strokes, are common.[3–7] Despite improvements in both surgical technique and survival over recent years, neurodevelopmental morbidity among survivors has not improved.[1] Here, this article discusses the neurologic evaluation, management, and outcomes of infants with critical CHD, focusing on those infants requiring bypass repair or palliation in the neonatal period.

## *Neurologic and Developmental Sequelae in Congenital Heart Disease*

Neurodevelopmental and neurobehavioral differences have been noted even preoperatively in infants and neonates with CHD.[8–10] Feeding difficulties are common, and device-assisted feeding at 3 months is associated with worse psychomotor development at 6 months.[11] Seizures are a frequent complication during the postoperative period and have been reported in 5% to 26% of neonates status post bypass surgery, depending on the study.[12–16] More recent studies report an incidence of approximately 11%, typically within the first 48 hours after bypass surgery.[13,14,16–18]

Long-term survivors of critical CHD requiring neonatal repair or palliation, particularly those with single-ventricle (SV) physiology, transposition of the great arteries (TGA), and cyanotic heart disease (regardless of whether neonatal repair/palliation is required), are at exceptionally high risk for neurodevelopmental disabilities (NDD).[19] NDD, microcephaly, and abnormalities on brain MRI occur with high frequency (>40% in some studies) in neonates with SV physiology, specifically, hypoplastic left heart syndrome (HLHS) and its variants.[4–7,20,21] Lower academic achievement, deficits in expressive and receptive language skills, as well as working memory and attention, and high rates of gross and fine motor dysfunction (>20%) have been reported in preschool and school-aged survivors of TGA after arterial switch operation.[22–27] Neuromotor deficits persisted into school age in a cohort of survivors with various SV and two-ventricle (2V) physiology heart defects.[28]

Although early research focused on the role of surgical and intraoperative factors in determining long-term neurodevelopmental outcomes, more recent studies have shown that intraoperative factors account for only about 5% of the variance in neurodevelopmental outcomes.[29] Fetal and neonatal factors play an equal, if not greater, role in determining developmental outcomes in CHD.[21,30,31] The impact of NDD on survivors of CHD has been widely recognized, and the American Heart Association (AHA) recommends long-term neurodevelopmental surveillance and follow-up through school age in high-risk patients with CHD.[2]

## BRAIN DEVELOPMENT IN CONGENITAL HEART DISEASE

Fetuses and neonates with critical CHD are known to have delayed brain development,[32] reduced brain volumes/growth,[33,34] and altered brain metabolism.[34] Differences in brain development begin to manifest in the third trimester in fetal CHD, possibly secondary to impaired brain perfusion and oxygenation in this population.[34–36] On average, term neonates with critical CHD have brains that are approximately 4 weeks immature[1,2,6,37] and display changes in brain microstructure.[5,33] Delayed fetal brain development correlates with abnormal postnatal brain development and preoperative and postoperative brain injury in neonates with CHD.[38–42] In a population of survivors of critical CHD in which both SV and 2V physiology were included, brain immaturity on an MRI at age 3 months was associated with lower motor, language, and cognitive scores at age 2.[39] Small fetal and neonatal brain volumes seem to correlate with neurodevelopmental outcomes between 9 and 24 months.[43,44]

## BRAIN INJURY IN CONGENITAL HEART DISEASE

Brain injury is common in neonates with CHD. Preoperative brain injury rates in this population range between 10% and 35%,[36,41,45] whereas newly acquired postoperative brain injury rates range between 33% and 75%.[39,46,47] WMI and strokes are particularly prevalent,[3–7,43] although the rate of postoperative (but not preoperative) WMI in neonates does appear to be declining with more recent advancements in critical care.[48]

Neonates with CHD commonly develop a pattern of WMI similar to periventricular leukomalacia.[49] The predisposition to WMI in critical CHD is thought to be related to the immaturity of the white matter, even in term neonates, and the fact that the immature, premyelinating oligodendrocytes may be more susceptible to hypoxia, ischemia, inflammation, and oxidative stress.[5,6] There is mounting evidence that WMI impacts neurodevelopmental outcomes. Neonatal WMI involving the posterior limb of the internal capsule is associated with more severe neurodevelopmental outcomes, including lower IQ, motor scores, and attention difficulties at school age,[50] and moderate to severe preoperative or postoperative WMI is associated with lower motor scores at age 2.5 years.[51]

Ischemic injury is common in the CHD population owing to inherent changes in vasculature, hemodynamic flow, and the need for bypass during surgical intervention.[52] Injury can take the form of hypoxia-ischemia, reperfusion injury, or embolic stroke.[53] Up to 10% of neonates undergoing CHD surgery develop ischemic stroke, with approximately 50% of strokes identified preoperatively.[53] Chen and colleagues[53] demonstrated that strokes varied in anatomic distribution and age in the neonatal CHD population, suggesting multiple time points for injury. Most strokes were clinically silent in neonates and, therefore, were undetectable without the routine use of brain imaging.[53] Although one group found that small, clinically silent neonatal strokes were not associated with adverse neurodevelopmental outcomes in infants with TGA,[51] acute ischemic stroke in the corticospinal tract does appear to be associated with abnormalities of muscle tone and gross motor delay.[43] Severe ischemic brain injury is associated with a diagnosis of cerebral palsy in CHD.[43]

Hemorrhages, including intraventricular hemorrhages (IVH), microhemorrhages, and intraparenchymal hemorrhages, are other common neurologic complications for neonates with CHD. IVH may be found in 2% to 23% of neonates with CHD and may impact neurodevelopmental outcomes.[54] Most of the IVH are low grade and associated with lower gestational age.[54] Neonates with CHD are subject to several factors, including impaired circulation and developmental immaturity, that may impact the germinal matrix and increase susceptibility to IVH.[54] Microhemorrhages are

nonspecific, scattered hemosiderin deposits in the brain parenchyma frequently found in postoperative neonates with CHD. Although the precise cause is unknown, it is thought that microhemorrhages may be secondary to emboli from catheterization or the use of bypass.[55] The association between microhemorrhages and developmental outcomes is an area of active research, but one study found some association with psychomotor outcomes at age 1 year.[55]

### *Brain Injury Risk Factors*

Fig. 1 summarizes known factors associated with brain injury in CHD. A prenatal (rather than a postnatal) diagnosis of SV heart disease or TGA may be protective.[37] Cardiac physiology is an important consideration when assessing an infant's risk for brain injury. Neonates with SV physiology and TGA are at very high risk for preoperative and postoperative brain injury.[8,39,46,56,57]

During the neonatal period, a multitude of physiologic risk factors for brain injury exist. More severe preoperative brain injury is associated with hypoxemia,[36,41,58] hypotension,[41] and worse autonomic function.[59] Balloon atrial septostomy is associated with preoperative stroke.[41,58,60,61] Longer times between birth and surgery have been associated with preoperative[36] and postoperative[62] WMI, which may be related to a progressive decline in cerebral oxygenation over time before surgery.[63] Postoperative brain injury is associated with hypotension in the first 24 to 48 hours following surgery,[41,46,64] lower postoperative oxygen saturation,[64] and decreased cerebral $rso_2$ (regional cerebral oxygenation).[46,65] Prolonged cardiopulmonary bypass and circulatory arrest times are associated with new postoperative WMI.[39]

## SEIZURES IN CONGENITAL HEART DISEASE

Neonates with CHD undergoing bypass surgery have a high risk for postoperative electrographic seizures within the first 2 postoperative days, with reported incidence

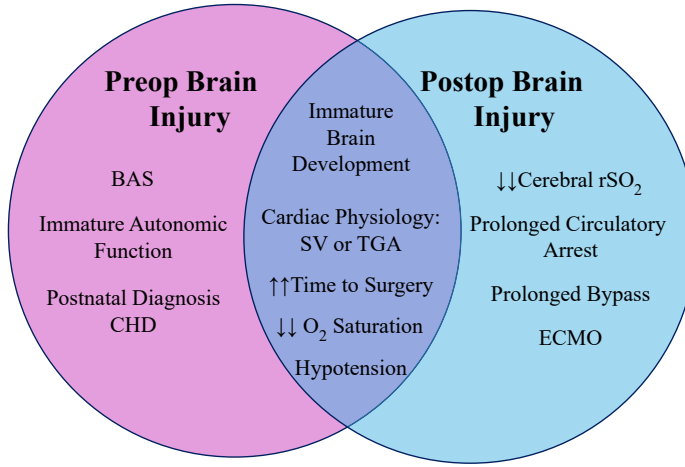


**Fig. 1.** Risk factors for preoperative and postoperative brain injury in neonatal CHD. Factors associated with preoperative brain injury are listed in the pink circle, and factors associated with postoperative brain injury are listed in the blue circle on the Venn diagram. Factors associated with both preoperative and postoperative brain injury are listed in the middle section of the Venn diagram. ↑↑, "increased"; ↓↓, "decreased"; BAS, balloon atrial septostomy; $o_2$, oxygen; Postop, postoperative; Preop, preoperative; $rso_2$, regional cerebral oxygenation.

of 5% to 26%, depending on the study.[13,14,16,18,66,67] The highest risk for seizure onset seems to be within 4 to 36 hours after surgery.[13,68] Postoperative electrographic seizures are highly correlated with brain injury.[13,69] Most (85%–100%, depending on the report) postoperative seizures are subclinical, electrographic only,[17,70] so they may only be detected by continuous electroencephalogram (EEG) monitoring. Factors associated with developing postoperative seizure include longer operating times with longer cooling on deep hypothermic circulatory arrest, HLHS cardiac physiology, the presence of a genetic disorder, and underlying brain injury.[1,14,18,66] Postoperative seizures are associated with longer intensive care unit (ICU) and hospital stays, increased risk for epilepsy, and, significantly, worse long-term neurodevelopmental outcomes and abnormal neurologic examinations at follow-up.[7,24,71–75]

## EVALUATION AND ASSESSMENT OF RISK FACTORS FOR NEURODEVELOPMENTAL IMPAIRMENTS

Evaluation of any child with CHD should take into consideration the clinical history of risk factors for long-term neurodevelopmental delays and disabilities. Factors influencing neurodevelopmental impairments in CHD are numerous and cumulative, beginning in the fetal period and spanning the preoperative, perioperative, and postoperative period throughout the lifetime (**Table 1**).[8–10,56]

### *Intrinsic/Patient-Specific Factors*

Patient-specific and preoperative factors account for 25% of the variance in neurodevelopmental outcomes in CHD, whereas intraoperative and postoperative medical risk factors account for less than 5% of the variance in outcomes.[76] Cardiovascular physiology is a significant risk factor for poor long-term developmental outcomes. As outlined above, patients at the highest risk include those with SV physiology, particularly HLHS, and those with TGA physiology.

Social and family environment is another critical determinant of long-term outcomes. Lower maternal educational level is associated with lower mental development

**Table 1**
**Factors associated with high risk for neurodevelopmental disorders and disabilities in congenital heart disease**

| Category | Risk Factors |
|---|---|
| Intrinsic/patient specific | Cardiac physiology: SV, cyanotic lesion, or TGA<br>Genetic abnormality or syndrome<br>Family socioeconomic status<br>Parental (maternal) stress/mental health |
| Prenatal | Delayed/immature brain development |
| Neonatal | Low birth weight (<2.7 kg)<br>Microcephaly<br>GA at birth <38 wk |
| Medical | Longer ICU LOS<br>Higher cumulative anesthetic exposure<br>Significant brain injury<br>Seizures<br>ECMO<br>Cardiac arrest |

Intrinsic/patient-specific, prenatal, neonatal, and medical risk factors are listed.
*Abbreviations:* GA, gestational age; LOS, length of stay.

index scores on the Bayley Scales of Infant Development-II at 14 months in patients with HLHS and variants.[77] Psychological distress is highly prevalent among parents of children with CHD, and there is mounting evidence suggesting that many of the long-term difficulties faced by children with CHD may be partially related to parental mental health. Psychosocial adjustment and behavior problems in children with CHD have been linked with maternal stress, in particular.[78,79] Up to 30% of parents of children with CHD have symptoms consistent with posttraumatic stress disorder; 90% have clinically significant symptoms of trauma; 25% to 50% have depression and/or anxiety, and 30% to 80% have severe psychological distress.[80] Maternal psychological distress in the prenatal period is associated with poorer fetal brain growth, metabolism, and cortical maturation.[81] Prenatal maternal stress is also associated with poorer 18-month cognitive performance and social-emotional performance in infants and parenting stress at 18 months.[82]

Genetic abnormalities are found in up to 10% of sporadic cases and up to 50% of syndromic cases of critical CHD.[83] Aneuploidies, copy number variants, and de novo single-nucleotide variants have all been reported,[84] and numerous genes have been associated with CHD and neurodevelopmental delays. Although the association between specific aneuploidies and CHD is widely known, more recent work has found that up to 20% of subjects with CHD and neurodevelopmental delays have de novo genetic variants.[83] The presence of a genetic syndrome or extracardiac anomaly has significant implications for long-term neurodevelopmental outcomes in CHD, independent of cardiac physiology or type of repair.[20,21,30,77,85,86] Early detection of genetic disorders is critical to adequately assessing neurodevelopmental risk. Detailed clinical recommendations for genetic testing in CHD, including karyotyping, chromosomal microarray, targeted testing, and ethical considerations, are beyond the scope of this article but are outlined in a scientific statement from the AHA.[87]

### *Neonatal Factors*

Prematurity increases the risk for adverse neurodevelopmental outcomes even in the absence of CHD. Gestational age of less than 38 weeks at the time of delivery has a significant negative effect on neurodevelopmental outcomes in both SV and 2V CHD.[20,88] Low birth weight (<2.7 kg) is associated with an increased risk for adverse neurodevelopmental outcomes at 12 to 14 months.[21,30,77,86] Microcephaly at birth is common[8,89] and persists into infancy in many children with CHD.[90–92] Microcephaly at the time of initial surgery predicts poorer neuromotor outcomes at age 5[28] and correlates with poorer cognitive development during adolescence.[93]

### *Medical Risk Factors*

Factors associated with increased length of ICU stay[94] and increased cumulative anesthetic exposure[95] are associated with worse neurodevelopmental outcomes in CHD. Such factors include the need for temporary pacing, the number of days requiring inotropes after surgery, the number of days to enteral feeding, infection, and the presence of residual cardiac/hemodynamic abnormalities.[96] Higher volatile anesthetic exposure is associated with lower cognitive scores at age 12 months.[47]

### *Cerebral Oxygenation*

Cerebral near-infrared spectroscopy (NIRS) is a commonly used neuromonitoring tool in the ICU setting, but data relating regional cerebral oxygen saturation ($rcSO_2$) values to outcomes and brain injury are highly variable. Some studies suggest that postoperative NIRS values less than certain thresholds ($rcSO_2$ of 45%–56%) at different time points may be associated with adverse events in the ICU and with

adverse neurodevelopmental outcomes, but it is unclear whether interventions in response to subthreshold $rcSO_2$ improve these outcomes.[97]

### *Extracorporeal Membrane Oxygenation*

The use of extracorporeal membrane oxygenation (ECMO) comes with its own set of risks, morbidity, and mortality. In studies of neonates who underwent ECMO for cardiac or respiratory indications, up to 50% had abnormal neuroimaging studies,[98,99] and up to 13% had severe acute clinical neurologic findings.[98] Prematurity, acidosis, coagulopathy, the use of anticoagulation, hypotension, impaired cerebral autoregulation, and neck cannulation all increase the risk of intracranial hemorrhage while on ECMO.[98] Studies indicate that 20% to 73% of children with cardiac disease who undergo ECMO have some type of long-term neurologic disability.[100]

## MANAGEMENT AND MITIGATION OF RISK

There are no standardized guidelines for ICU neuromonitoring practices for neonates and infants with CHD. Survey studies of institutions in North America[101] and Europe[102] reveal significant variation in the utilization of preoperative and postoperative neuromonitoring practices, including various brain imaging modalities (head ultrasound, MRI, computed tomography scan), EEG, and cerebral NIRS. Developing strategies for optimizing neurologic and developmental outcomes in CHD is an area of active focus in the CHD community. However, there remains debate about best practices, particularly regarding ICU neuromonitoring. Any strategy will require a multipronged approach, beginning in the fetal period and continuing throughout the neonatal transition, perioperative and intraoperative management, and beyond the ICU period with long-term developmental follow-up.[103–105] In later discussion, several practical strategies are outlined to optimize neurodevelopmental outcomes in CHD beginning in the prenatal period. **Fig. 2** summarizes a proposed clinical algorithm for neurocardiac care.

### *Prenatal Diagnosis of Congenital Heart Disease*

Infants who are prenatally (rather than postnatally) diagnosed with CHD have improved microstructural brain development and reduced brain injury.[37] Prenatal diagnosis allows optimal delivery planning and management, particularly for ductal-dependent lesions.

### *Optimize Delivery Planning*

Even early-term delivery may negatively impact developmental outcomes in CHD. Optimizing the timing of delivery for greater than 38 weeks, when feasible, and advanced planning for immediate intervention for CHD types that may result in hemodynamic instability shortly after birth may minimize any additive effect of prematurity and immature brain development.[105]

### *Identify Genetic Syndromes and Extracardiac Anomalies*

Given the significant impact of genetic factors on neurodevelopmental outcomes in CHD, early identification of genetic disorders is critical for assessing neurodevelopmental risk and optimizing opportunities for intervention.[103] Genetic testing, including karyotype and microarray versus targeted genetic testing, is recommended prenatally or postnatally.[103] Children identified as having genetic syndromes should have routine neurodevelopmental surveillance.[103]

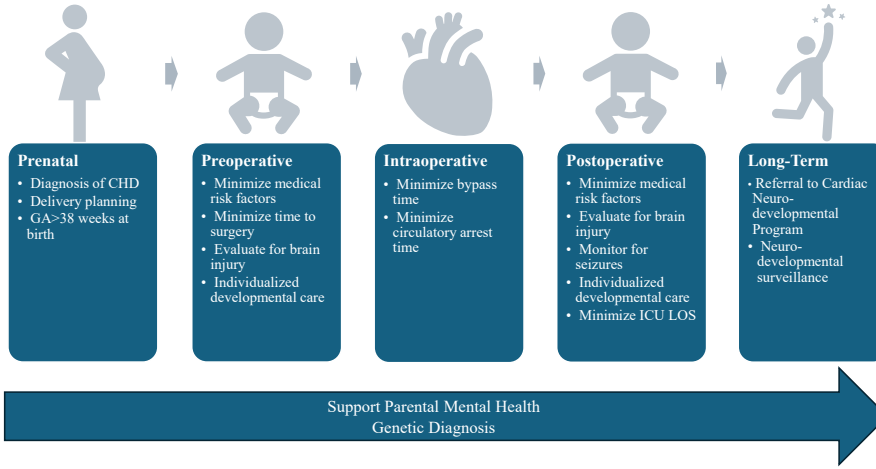


**Fig. 2.** Clinical algorithm for neurocardiac care. Time points and opportunities for intervention. Prenatal diagnosis and planning for delivery at greater than 38 weeks' gestational age reduces brain injury and lowers risk for NDD. In the perioperative period, minimizing medical risk factors listed in Fig. 1 and Table 1 may improve outcomes. Screening for brain injury with the assistance of neurology/neurocritical care consultants and imaging allows for early diagnosis and appropriate counseling of families, as well as early referral to appropriate therapeutic and developmental follow-up. Individualized developmental care improves outcomes in other high-risk neonatal populations. Parental stress has been shown to impact offspring brain development beginning in the fetal period and is linked with long-term neurobehavioral outcomes. Addressing parental mental health concerns should be an ongoing part of care to improve neurodevelopmental outcomes in offspring with CHD. Genetic disorders significantly impact neurodevelopmental outcomes in CHD, and screening for genetic disorders should occur as early as possible. Providers should be aware of any genetic diagnosis, and children with CHD and a genetic diagnosis should have close neurodevelopmental surveillance throughout their lifetime. GA, gestational age; LOS, length of stay.

### *Monitor for Brain Injury*

Although specific guidelines for neuroimaging are lacking in the CHD community, brain injury is highly prevalent in this population and, in several studies, is associated with long-term outcomes.[43,50,51,55] The clinical utility of neuroimaging in CHD remains a hotly debated topic. Head ultrasound is a valuable tool to identify major intracranial hemorrhages or structural anomalies and should be considered a screening tool for all neonates with CHD, but data show that MRI is superior to head ultrasound in detecting nonhemorrhagic intracranial pathologic conditions, such as WMI and stroke or another ischemic injury.[106] In the absence of clear guidelines regarding the timing and type of routine neuroimaging to perform in neonates with CHD, detailed neurologic examinations preoperatively and postoperatively and consultation with neurology and/or neurocritical care should be considered to assist providers in determining the need for and type of neuroimaging.[103]

### *Monitor for Postoperative Seizures*

As detailed above, neonates with CHD are at high risk for seizures occurring most frequently within the first 4 to 36 hours postoperatively.[13,14,18,66,68] Given the association of seizures with brain injury and worse neurodevelopmental outcomes[7,13,24,69,71–75] and the fact that most postoperative seizures are subclinical and electrographic

only,[17,70] the American Clinical Neurophysiology Society guidelines state that high-risk neonates should receive at least 24 hours of continuous EEG monitoring after cardiac surgery.[68] Other modalities, such as amplitude-integrated EEG, may be considered when continuous EEG monitoring is not feasible or available.

### *Minimize Preoperative, Intraoperative, and Postoperative Medical Risk Factors*

As outlined above and in **Fig. 1** and **Table 1**, a myriad of preoperative, intraoperative, and postoperative factors are associated with brain injury and worse neurodevelopmental outcomes. Careful medical management and minimizing these risk factors may improve long-term outcomes and reduce brain injury.

### *Support Parental Mental Health*

Parents of children with CHD experience significant psychological trauma related to their child's diagnosis of CHD. Parental mental health and long-term behavioral, developmental, and social outcomes of their offspring are intrinsically linked. Although these associations are an area of active study, current evidence suggests that offering mental health support to parents of children with CHD may lead to better outcomes in children.

### *Individualized Developmental Care*

Because infants with CHD undergo surgical interventions and intensive medical care during periods of developmental and brain immaturity, developmental and behavioral care is crucial, in addition to optimal medical care. Individualized developmental care in the ICU improves neurobehavioral functioning and structural brain development in preterm infants.[107] Elements that should be included in individualized developmental care programs include providing a supportive hospital environment, including attention to circadian rhythms, appropriate noise and light levels, developmentally appropriate approaches to medical procedures, nonpharmacologic comfort measures, and opportunities for social interaction/play.[103] Infant holding and kangaroo care, specifically, have been associated with improved autonomic function in preterm infants, accelerated brain maturation, fewer stress behaviors, better long-term cognitive function, reduced pain responses, and improved feeding.[108] Kangaroo care has been shown to be safe and feasible in the CHD population preoperatively and postoperatively.[108] Attention to parental engagement and an individualized, cue-based plan are additional components of a well-rounded individualized care plan.[109]

### *Referral to Cardiac Neurodevelopmental Program After Discharge*

Although the focus of this article is on neurocardiac critical care, one cannot consider recommendations complete for children with CHD without emphasizing the importance of long-term neurodevelopmental care in this population. The 2012 AHA/American Academy of Pediatrics Scientific Statement provides guidelines for neurodevelopmental care and evaluation in CHD and proposes a medical home model.[2] All children with CHD should be assessed for neurodevelopmental delays. Those with high risk should be referred for formal developmental evaluations, and evaluation is recommended between 12 and 24 months, 3 and 5 years, and 11 and 12 years.[2] Families and parents should be aware of these recommendations, and referrals to cardiac neurodevelopmental programs (if available) should be made at the time of discharge.

## SUMMARY

Neurocardiac care is a developing field, and there are currently no standardized practices or guidelines for neuromonitoring in the ICU setting. In addition to performing

thorough preoperative and postoperative neurologic examinations, clinicians must understand and evaluate for risk factors for brain injury and poor neurodevelopmental outcome in neonates with CHD as part of their neurologic evaluation. Although neurocardiac care is still an area of active investigation, current evidence suggests that optimization of the hospital environment to include individualized developmental care practices; support of parental mental health; early detection of genetic disorders, brain injury, and seizures; and reduction of medical risk factors may improve neurologic and developmental outcomes in neonates with CHD.

***Best Practices***

***What is the current practice for Neurocardiac Care in Neonatal CHD?***

Current guidelines focus on long-term neurodevelopmental surveillance with a medical home model. Neurologic and developmental care in the hospital setting varies widely between centers, and there is currently no standardized practice or guideline for neurocardiac care or neuromonitoring.

***Care Path Objective(s):***

The objective is to provide evidence-based suggestions for clinical neurologic care of neonates with CHD to improve neurodevelopmental outcomes by optimizing delivery planning and management, identifying and minimizing risk factors, preventing brain injury and seizures, detecting brain injury and seizures when they occur, optimizing the hospital environment through individualized developmental care, and supporting parental mental health.

***What changes in current practice are likely to improve outcomes?***

- Development of clear guidelines for ICU neuromonitoring and perioperative neuroimaging
- Understanding risk factors for poor neurodevelopmental outcomes and brain injury
- Implementation of individualized developmental care in the hospital setting and support of parental mental health

***Is there a Clinical Algorithm?***

See **Fig. 2**.

***Major Recommendations:***

- Prenatal Diagnosis of CHD
- Optimize Delivery Planning
- Identify Genetic Syndromes and Extracardiac Anomalies
- Monitor for Brain Injury
- Monitor for Postoperative Seizures
- Minimize Preoperative, Intraoperative, and Postoperative Medical Risk Factors
- Support Parental Mental Health
- Individualized Developmental Care
- Referral to a Cardiac Neurodevelopmental Program after Discharge

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# Ethical Complexities of Neonatal Neurocritical Care

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**KEYWORDS**

• Genetic • Prematurity • Intraventricular hemorrhage
• Hypoxic-ischemic encephalopathy • Ethics

**KEY POINTS**

- Social and political trends impact neonatal neurocritical care.
- Uncertainty and bias can undermine counseling about neurologic prognosis.
- Time pressures intensify need for careful ethical reasoning and family counseling.

## INTRODUCTION

Neurologic interventions for infants and bioethical approaches to complex clinical situations have been evolving side by side. The 1970s saw the first advances in antiepileptics beyond phenobarbital for seizures, the most common neurologic symptom in infants.[1] Ventriculoperitoneal shunts for neonatal hydrocephalus became routinely available in the 1980s.[2] Therapeutic hypothermia for hypoxic-ischemic encephalopathy (HIE) has only been widely used since the late 2000s.[3]

This timeline mirrors advances in neuroethics and neonatologists' access to bioethics resources. The earliest hospital ethics committees began in the 1970s and focused on end-of-life decisions for adults, with particular attention to neurologic status; the first ethics committee in New Jersey, where the Karen Ann Quinlan case went to the Supreme Court, was called a "prognosis committee" and its sole members were neurologists and neurosurgeons.[4] In the 1980s and in response to the Baby Doe regulations, the American Academy of Pediatrics recommended that hospitals with a neonatal intensive care unit (NICU) should have ethics committees.[5] It was not until the 1990s that the Joint Commission on Accreditation of Healthcare Organizations required all hospitals to have ethics committees.[6] The first professional neuroethics conference, with scholarly collaboration in neuroscience, bioethics, philosophy, and law, occurred in 2002.[7]

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| Abbreviations | |
|---|---|
| HIE | hypoxic-ischemic encephalopathy |
| IVH | Intraventricular hemorrhage |
| LST | life-sustaining therapies |
| NICU | neonatal intensive care unit |
| PHVD | posthemorrhagic ventricular dilation |

Innovations in neonatal neurocritical care and the associated ethical complexities will undoubtedly continue to evolve alongside novel therapies and long-term outcome data. In this article, we review 3 neonatal neurologic conditions and highlight ethical challenges that currently occur within and across those conditions (Table 1).

## DISCUSSION

### *Evolving Social Values About Cognitive Disability*

#### *Example, genetic conditions*

Medical approaches to genetic conditions involving cognitive impairment were at the core of the earliest ethical complexities in neonatology. Trisomy 21 and the Baby Doe controversy triggered public discussion—and professional conflict—about whether and when cognitive impairment is a morally valid reason to withhold life-sustaining treatment. The Baby Doe regulations, and the confusion and fear they provoked in hospitals, likely prompted clinical innovation for Trisomy 21. Before the 1980s, the average lifespan for persons with Trisomy 21 was 10 years; today it is closer to 50 years.[8] We have learned that, on average, when infants with Trisomy 21 receive standard medical interventions and care, they may live for decades. Cognitive disability remains ubiquitous to the diagnosis and intensifies throughout the lifespan.[9] Yet educational and community resources now support individuals with Trisomy 21 and studies confirm a valuable quality of life for them and their families.[10,11] With community supports like adult day programs, persons with Trisomy 21 can achieve some independence,[12] reinforcing the perspective cognitive disability is not so much medical pathology as social diversity. Today, withholding even resource-intensive, scarce therapies like organ transplant from individuals with Trisomy 21, solely based on cognitive disability, is considered ethically untenable.[13,14]

Similar clinical and bioethical transformation is occurring for other genetic conditions involving neurologic impairment, such as Trisomy 13 and 18. Infants with these diagnoses who survive the neonatal period have more severe cognitive disability than individuals with Trisomy 21. Most persons with Trisomy 21 communicate with speech; few with Trisomy 13 or 18 do.[15,16] Both because of this cognitive disability and serious

**Table 1**
**Neonatal neurocritical care: example conditions and ethical challenges**

| Genetic Conditions | Intraventricular Hemorrhage /PHVD | Neonatal Encephalopathy |
|---|---|---|
| Evolving values about neurodiversity | Prognostic uncertainty | Time pressures |
| Combined death/disability research outcomes | Delayed outcomes evaluations | Intense emotion during decision-making period |
| Sociopolitical forces | Adverse social context reduces child outcomes | Religious/Spiritual guidelines about withdrawing therapies |

multiorgan abnormalities, comfort care alone is often offered to many families whose infant has Trisomy 13 or 18.

There is, however, an important distinction between the Baby Doe era and current times, which is access to the Internet and social media. The information shaping parent decisions often now expands beyond medical research to include family testimonials, publications from national/international foundations, and connections with advocacy groups. These sources may have participation bias (eg, families who chose pregnancy termination, or whose infant died, may be less likely to post experiences and photos), yet family stories share detailed, compelling information that most clinicians cannot: what it is like to raise a medically complex child who communicates and forms relationships in atypical—but valued—ways. The growth of groups like the National Organization for Rare Diseases, the many disease-focused social media sites, and rapidly expanding genetic testing will predictably strengthen advocacy for medical interventions in these conditions.

Changing national and state politics are also shaping medical approaches to genetic conditions involving cognitive impairment. Limited access to pregnancy termination increases the population born with these conditions: 2023 US data confirmed that the number of children born with Trisomy 21 increased in states with 20-week abortion bans.[17] Locales with 6-week abortion bans essentially eliminate prenatal genetic testing, since maternal serum-testing and cell-free DNA screening are inaccurate until closer to the second trimester. This means that expectant parents will not learn of genetic diagnoses until there is no (local) option for termination. In addition, obstetricians and neonatologists in these locales may worry about associated legal risk from providing palliative and comfort care at birth for such infants, feeling legally obligated to provide intensive interventions. These political trends mean that more hospitals will be caring for more newborns with serious genetic conditions involving cognitive impairment. It is unclear how this will impact family and community outcomes, including limited services like pediatric home health care.

For neurocritical care researchers, it is increasingly important to question the utility of primary outcomes that combine "death and disability." Major randomized trials for neonatal neurocritical care interventions, for example, therapeutic hypothermia, have often employed such composite outcomes. But the relevance to patients, families, and society of death versus disability may separate further and further as neurodiversity is held in greater value. A research emphasis on patient-reported and family-reported outcomes is essential, given the well-documented gap between how medical professionals versus families value cognitive and functional differences in children. Research ethics will also need to evolve to support neurodiversity, for example, to evolve the concepts of informed assent and consent.

For neurocritical care clinicians caring for infants with known or suspected genetic conditions, many considerations must inform our decision-making. First: scientific considerations. What are the outcomes data, and if mortality is high, does that reflect natural disease course or actively limiting treatment? Are there enough data to reliably prognosticate? Second: considerations for the child. How severely impacted might they be in the short-term and long-term? Will they need surgery or chronic medical technology to survive? What are the risks for suffering? Third: considerations for the family. Do the potential neurologic outcomes distress them, or are they accepting of blindness, deafness, cognitive impairment, and cerebral palsy? What community supports could help them care for the child? Fourth: sociopolitical considerations. Do local laws constrain medical options? If yes, could the family relocate? What advocacy groups exist and what can be learned from others living with the condition? And finally: ethical considerations. As social values evolve about neurologic disability, how can

clinicians prioritize beneficence, nonmaleficence, and justice for patients who may never be able to contribute to decisions made on their behalf?

### *Prognostic Uncertainty*

#### *Example, intraventricular hemorrhage and posthemorrhagic ventricular dilation*

When an infant's prognosis includes the potential for both typical and severely-affected neurologic outcomes, the range of ethically-permissible treatment options may be wide.[18] Clinicians may feel it is wrong to obligate or deny specific treatments in the face of prognostic uncertainty and so choose to share treatment decisions with families. Families' goals and values may or may not align with their capacity to care for a child with substantial medical needs. When they do not align, this adds pressure to the need for prognostic information.

Intraventricular hemorrhage (IVH) is an example of a neonatal diagnosis with uncertain prognosis. In one study, 1% and 4% of infants with Grades 1 and 2 IVH developed posthemorrhagic ventricular dilation (PHVD), compared to 25% and 28% of infants with Grades 3 and 4.[19] The cognitive disability associated with IVH/PHVD varies with severity of bleeding and ventricular dilation, white matter injury, parenchymal infarctions, and the overall clinical course.[20] Infants who have IVH/PHVD are also typically premature and have additive neurologic risks: infection, hemodynamic instability, hypoxia, malnutrition. It is important to note the significant variations even in outcomes from severe IVH, with rates of cerebral palsy ranging from 10% to 42%.[21]

The American Academy of Pediatrics recommends that counseling about extreme prematurity should clarify that prediction of long-term neurologic outcomes remains limited.[22] Adding to the potential confusion for stressed families is the fact that they receive a large amount of complex information: what physicians think parents understand about neurologic prognosis may differ from what they actually do. Not being able to more clearly predict neurologic outcome from IVH/PHVD can make it difficult for clinicians to both counsel and form therapeutic relationships with families. Clinicians may struggle to both articulate their worries about adverse outcomes while making room for hope. It is not uncommon for clinicians to adopt a "we will have to wait and see" approach.[23]

But delaying challenging conversations about neurologic prognosis can have detrimental impact. If the infant becomes acutely symptomatic from PHVD, their parents may face urgent surgical decisions without time to discuss their values related to neurologic outcomes. Some infants with IVH/PHVD have other life-threatening comorbidities, for example, necrotizing enterocolitis or severe lung disease. Clarifying the neurologic prognosis may be the key as teams and families consider decisions about life-sustaining therapies and chronic medical technologies related to those conditions. Acknowledging that an infant will likely have both lifelong total parenteral nutrition (TPN)-dependence and severe neurologic impairment, for example, can help a family assess their ability to care for a child with these needs.

In most situations, NICU counseling about IVH/PHVD is not urgent and is more about preparing a family for the possibility of future impairments. Our tools for monitoring neurodevelopmental risk are imperfect and work best late in a hospitalization. In one study, about 25% of infants who had normal head ultrasounds went on to have cognitive or motor impairment; many of these families may have felt falsely reassured by normal early screening.[24] Term-corrected MRI showing moderate to severe white matter abnormalities is better—though still limited—at predicting cerebral palsy/motor disability and global cognitive disability.[24] A normal MRI has a sensitivity of 45% and specificity of 61% for typical neurodevelopment, and a sensitivity of 17% and specificity of 94% for a typical motor outcome at 20 months of age.[25] But MRIs are not

without risks: they may require anesthesia/sedation, may be costly for the family, and may increase the infant's length of stay. It is also unclear how much prognostic certainty an MRI adds for infants with prior abnormal ultrasounds. Data suggest that some NICU parents become more anxious when testing enhances uncertainty about neurologic prognosis and sometimes prefer that testing not occur.[26]

It is important to note multiple studies suggesting that neurologic outcomes from prematurity, IVH, and PHVD are associated with family social context. Higher maternal education tracks with better infant/child neurodevelopmental outcomes; lower maternal education and socioeconomic status are linked to worse cognitive function for extremely preterm infants and lower academic achievement at school-age and adolescence.[27] Folger and colleagues showed that adverse childhood experiences of parents, including physical, sexual, and emotional abuse, neglect, household violence, or substance abuse, directly correlated to negative impact on child development in multiple domains.[28,29] Maternal stress and/or depression can also impact the developmental trajectories of preterm infants that can extend through childhood.[29]

Some of these social risk factors are nonmodifiable—particularly if medical teams do not identify or attempt to address them. Data suggest that, when counseling parents about serious decisions for extremely premature infants, neonatologists ask few lifestyle or psychosocial questions.[23,30] Yet exploring a family's social context helps inform discussions about what a family would need in order to be able to care for a child with intense medical needs. Detailed discussions about family structure, housing security, mental health, financial vulnerability, etc, can help identify what community supports should be secured to build a family's capacity to care for their child. These supports include publicly funded early intervention therapy programs. Studies dating back nearly 40 years show a positive effect of early intervention for young children with developmental delays.[31] A more recent meta-analysis confirmed early intervention successes with improved cognitive and motor outcomes in infancy and at preschool age.[32]

The fact that social risk factors impact neurodevelopmental outcomes raises additional ethical complexities and communication challenges. Should family circumstances be integrated into prognostic counseling? If multiple social risk factors are present, does the "best case" outcome change for an infant and should this be relayed to the family? How is bias kept out of these decisions? These are important questions that deserve dedicated study.

## *Withdrawing Life-Sustaining Therapies*

### *Example, hypoxic-ischemic encephalopathy*

Most infant deaths in the NICU occur following withholding/withdrawal of life-sustaining therapies (LST). Neonatal encephalopathy, and specifically hypoxic-ischemic encephalopathy (HIE), presents unique ethical complexity to decisions about LST because of the added pressure of time. While families of infants born with genetic conditions or prematurity often receive some prenatal counseling, parents of infants born with neonatal encephalopathy receive none. They transition from a healthy pregnancy to having an infant with neurologic injury in a matter of minutes. In the trauma of an emergent delivery, parents must process complex information from the NICU team; the mother may be critically ill herself and the infant may be quickly transported for therapeutic hypothermia or other critical care supports.

The scenario is particularly complicated after a planned home birth. The American Academy of Pediatrics has a policy statement recommending against planned home birth.[33] Yet the number of out-of-hospital births nearly doubled from 2004 to 2017; during this period, home births increased by 77%.[34] Compared with planned in-

hospital birth, planned out-of-hospital birth is associated with perinatal death, neonatal seizures, and NICU admission.[35] All of these factors contribute to the challenges of caring for infants with neonatal encephalopathy and possible HIE following home birth. Clinicians may struggle with feelings of blame, since they may see HIE as a preventable occurrence. Biases may creep into clinical care and prevent truly aligning with the family.

Wilkinson describes a "window of opportunity" in HIE, an initial period of physiologic instability and multiorgan dysfunction.[36] During this "window," if the parents agree with removal of the endotracheal tube or vasopressors due to neurologic prognosis, the infant will likely die quickly. If LST is not stopped, physiologic instability usually improves within a few days and most infants, aside from the most severely-affected ones, will begin to breathe on their own. Once the "window" closes, often the only remaining LST is medically-provided nutrition and hydration. Wilkinson considers whether prognostic testing such as MRI should be done early so as to optimize decision-making about LST during the acute "window" of HIE. Delaying testing until after therapeutic hypothermia yields more accurate results but may narrow the options for withdrawing LST. Delaying prognostic testing does give the family time: time to be reunited if the infant was transferred after birth, time to process what is happening, time to get to be parents, time for family members to meet the infant, and time for religious, cultural, and memory-making activities. It also gives the medical team time to build a relationship with the family and help them consider potential neurologic impairment from their social, cultural, and religious contexts.

Wilkinson's 2009 discussion about limiting treatment after the window of opportunity closes highlighted withdrawal of medically provided nutrition and hydration as a contentious topic. This remains true. In 2021, Saoud and colleagues reported that approximately one-third of surveyed North American NICUs do not offer withholding/discontinuing medically provided nutrition or hydration for any patient.[37] The American Academy of Pediatrics states that medically provided nutrition and hydration can be withheld in specific situations in which the treatment's burdens outweigh the benefits. One such scenario is "children who are rendered comatose from a severe central nervous system injury or whose disease may transition to a persistent vegetative state." A second scenario is children with "prenatal injury who never possessed the capacity to feed orally."[38] Either scenario may apply to severely affected infants with HIE. In a retrospective cohort study of 150 infants with HIE, 8/23 infants with severe encephalopathy were discharged with some form of medically provided nutrition and hydration.[39] Families and clinicians may worry that an infant will suffer when feeds/hydration stop. While pediatric data are limited, one study found that fewer than 10% of children were reported by physicians to have any increase in distressing symptoms (aside from dry lips/mouth) during the process.[40] Nevertheless, some families and some clinicians will not consider this option for withdrawing LST for any infant who is otherwise clinically stable.

Some families may not wish to consider withdrawal of LST in any form. Families facing a child's serious illness often draw on their religious and spiritual beliefs to make decisions. For some religions, withdrawal of LST is not acceptable or is only acceptable in certain situations. Most religions do support withdraw of LST when a patient is actively dying, as in the most critical period of instability with HIE. Most religions also allow for withdrawal of LST in patients with brain death.[41] But brain death is a rare scenario in HIE since an open fontanelle and unfused sutures can mitigate brain herniation during increased intracranial pressure.[42] Brain death evaluations of infants less than 37 weeks corrected gestational age are also not reliable and are not recommended per 2023 guidelines.[42] Infants with HIE who are not actively dying and do not progress to brain

death (eg, infants with serious neurologic injury and chronic ventilator needs) may fall outside acceptable scenarios for withdrawal of LST for some family's religious beliefs.

The element of time makes withdrawing LST challenging even for those families who elect to move down this path. Families may not be united during the initial phase of critical instability. Mothers may still be recovering, leaving family members splitting time between the infant's and mother's hospital bedside. Additionally, clinicians care for many patients at once and do not have unlimited time with families during the critical phase. As most NICUs function on a shift schedule, there are handoffs between clinicians who may have different views on withdrawing LST. Oncoming clinicians may be uncomfortable proceeding with withdrawing LST during their shift if they do not have a relationship with the family. This can further delay the "window of opportunity."

Families need to feel as confident as possible when making these complex decisions and this may not be achievable during a short time. Withdrawing LST during the period of clinical instability and withdrawing medically provided nutrition and hydration later on are 2 possibilities for redirection of care, but they are not the only choices. Another option is nonescalation. If the infant becomes sicker later in the hospitalization or during a readmission, the team and family could choose to limit treatment escalation. They may decide to use no more than noninvasive ventilation for a viral illness, or to decline a surgical feeding tube and allow the infant to orally feed less than typical daily goals. Rushing families to make a decision risks harming the therapeutic relationship and risks a decision the family may regret.

## SUMMARY

Even as care improves for infants with neurologic conditions, there will continue to be challenging clinical and ethical questions about what can and should be done. The 3 clinical examples in this article—genetic conditions, IVH/PHVD, and HIE—raise both distinct and overlapping challenges and highlight how important it is for clinicians to hone both their clinical and ethical skills to provide optimal care for this group of patients and families.

***Best Practices***

Ethical complexities continue to evolve alongside neurologic interventions. As clinicians, we must take steps to recognize these complexities, address them, and better support our team members and families.

***What changes in current practice are likely to improve outcomes?***

- Awareness of and attention to these ethical complexities can aid clinicians in providing wraparound neurocritical care for infants.
- Recognizing the ethical implications of new therapies can help avoid conflict.
- If there is any conflict among team members or with families, recommend an ethics consult.

***Pearls/Pitfalls at the point-of-care:***

- Awareness of ethical complexities does not necessarily mean that these complex clinical situations will be easier to manage or that there will be an obvious right answer.

***Major Recommendations:***

- Communicating with the medical team and with families about goals and values can address many ethical complexities in neurocritical care.
- Consult ethics if there is any conflict among team or family members.

## DISCLOSURE

The authors have nothing to disclose.

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