



PEDIATRIC NEWBORN MEDICINE CLINICAL PRACTICE GUIDELINES

Neonatal Seizures





Points of emphasis/Primary changes in practice:

1. Immediate initiation of aEEG.
2. Defined seizure burden that warrants treatment.
3. Defined underlying causes that may result in immediate seizure resolution if treated.
4. Added typical therapeutic range of phenobarbital.
5. Streamlined maintenance phenobarbital dose.
6. Added additional fosphenytoin bolus doses.
7. Updated fosphenytoin maintenance dose with acceptable range.
8. Added phenytoin level timing and goal.
9. Updated phenytoin maintenance dose.
10. Updated midazolam infusion dose.
11. Added levetiracetam loading dose with additional boluses.
12. Updated levetiracetam maintenance dose and daily maximum.
13. Updated topiramate load and maintenance dose.
14. Reorganized parent handout for etiology prevalence.

Rationale for change:

- Improve timing of aEEG placement.
- Streamlined CPG to coincide with Neurology consult service practices.
- Availability of new evidence and references for seizure medications.
- Optimize therapeutic drug monitoring.
- Improve communication with parents/caregivers.

Questions? Please contact: Neonatal Neurocritical Care Program, Department of Pediatric Newborn Medicine



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| Clinical Guideline Name | Neonatal Seizures |
| Implementation Date | May 15, 2015; updated June 29, 2020 |
| Due for CPC Review | |
| Contact Person | Neonatal Neurocritical Care Program |
| Approved By | Dept of Pediatric Newborn Medicine Clinical Practice Council <u>2/12/15</u> CWN SPP <u>10/14/15</u> SPP Steering <u>10/21/15</u> Nurse Executive Board/CNO <u>10/26/15</u> |

This is a clinical practice guideline. While the guideline is useful in approaching the care of the neonate with neonatal seizures, clinical judgment and / or new evidence may favor an alternative plan of care, the rationale for which should be documented in the medical record.

I. Purpose

The purpose of this clinical practice guideline is to establish standard practices for the care of infants being evaluated, monitored, and/or treated for neonatal seizures. These guidelines have been developed to ensure that infants receive consistent and optimal care for neonatal seizures.

II. All CPGs will relay on the [NICU Nursing Standards of Care](#). All relevant nursing PPGs are listed below.

[NICU M.2 Monitoring](#)

[NICU T.4 Transfer from an Outside Hospital](#)

III. Scope

These guidelines apply to infants in the neonatal intensive care unit (NICU) and the Well Newborn Nursery. The scope of this guideline includes the identification, evaluation, monitoring, diagnosis, treatment, and care of infants and their families, who are being evaluated for neonatal seizures in the NICU or identified in the Well Newborn Nursery.

III. Guidelines

Definition

- A seizure is the result of the excessive electrical discharge of neurons in a synchronous fashion in the central nervous system (Volpe 2018).

- This electrical discharge is initiated by the depolarization of neurons, produced by an influx of sodium. Repolarization of the neurons occurs by an efflux of potassium. The membrane potential is governed by an ATP-dependent Na⁺/K⁺ pump.

Incidence

- Retrospective review of documented clinical seizures reported incidence of 6% of preterm infants (Davis 2010).
- Reported incidence of electrographic seizures in preterm infants varies from 5% to 48% (Vesoulis 2014, Lloyd 2017).
- The overall incidence in full term infants is not known.

Pathophysiology

- The neonatal brain is hyperexcitable compared to the more mature brain (Glass 2014):
 - High rate of synaptogenesis and peak synapse and dendritic density.
 - Overabundant glutamate receptors.
 - Paradoxical excitatory GABA receptor response.
- Decreased GABA receptors and decreased sensitivity to benzodiazepines (Glass 2014).

Etiology

- Common causes:
 - Neonatal encephalopathy (NE)
 - 40-42% of neonatal seizures followed NE (Tekgul 2006, Van Rooij 2013)
 - Intracranial hemorrhage and stroke
 - CNS infections
 - Congenital malformations
 - Inborn errors of metabolism (IEOMs)
 - Transient metabolic disturbances
 - Acidosis
 - Hypocalcemia, hypomagnesemia, hypoglycemia, hyponatremia, hypernatremia
 - Pyridoxine-dependent epilepsy (PDE)
 - Pyridoxine phosphate oxidase deficiency (PNPO)
 - Folinic acid-responsive seizures
 - Maternal drug use
 - Neonatal epilepsy syndromes



Assessment and Monitoring

- Perinatal history
- Physical exam
- Neurological exam
- Clinical observation
 - Clinical seizures versus electrographic seizures
- Cardiorespiratory monitoring
 - HR, RR, BP, O2 sat
- Electrographic monitoring
 - Recommended to confirm clinical seizures
 - Conventional continuous video EEG
 - Gold standard
 - aEEG
 - Lower sensitivity and specificity than cEEG
 - However, should be initiated while waiting for cEEG
- Laboratory tests

[NICU L.1 Assisting with Lumbar Puncture](#)

- Blood glucose level
 - Chemistries including calcium and magnesium
 - Consider liver transaminases
 - Complete blood count
 - Blood cultures
 - Serum ammonia
 - Arterial blood gases
 - Lumbar puncture (as clinically indicated)
 - Additional tests depending on underlying condition, such as serum amino acids, urinary organic acids, serum pyridoxal 5-phosphate (PLP), CSF PLP, toxicology screen, placenta pathology
- Neuroimaging
 - [Newborn MRI Protocol](#)
 - Cranial ultrasound: recommended to rule-out intracranial hemorrhage
 - MRI: recommended to help determine etiology, diagnosis, and prognosis

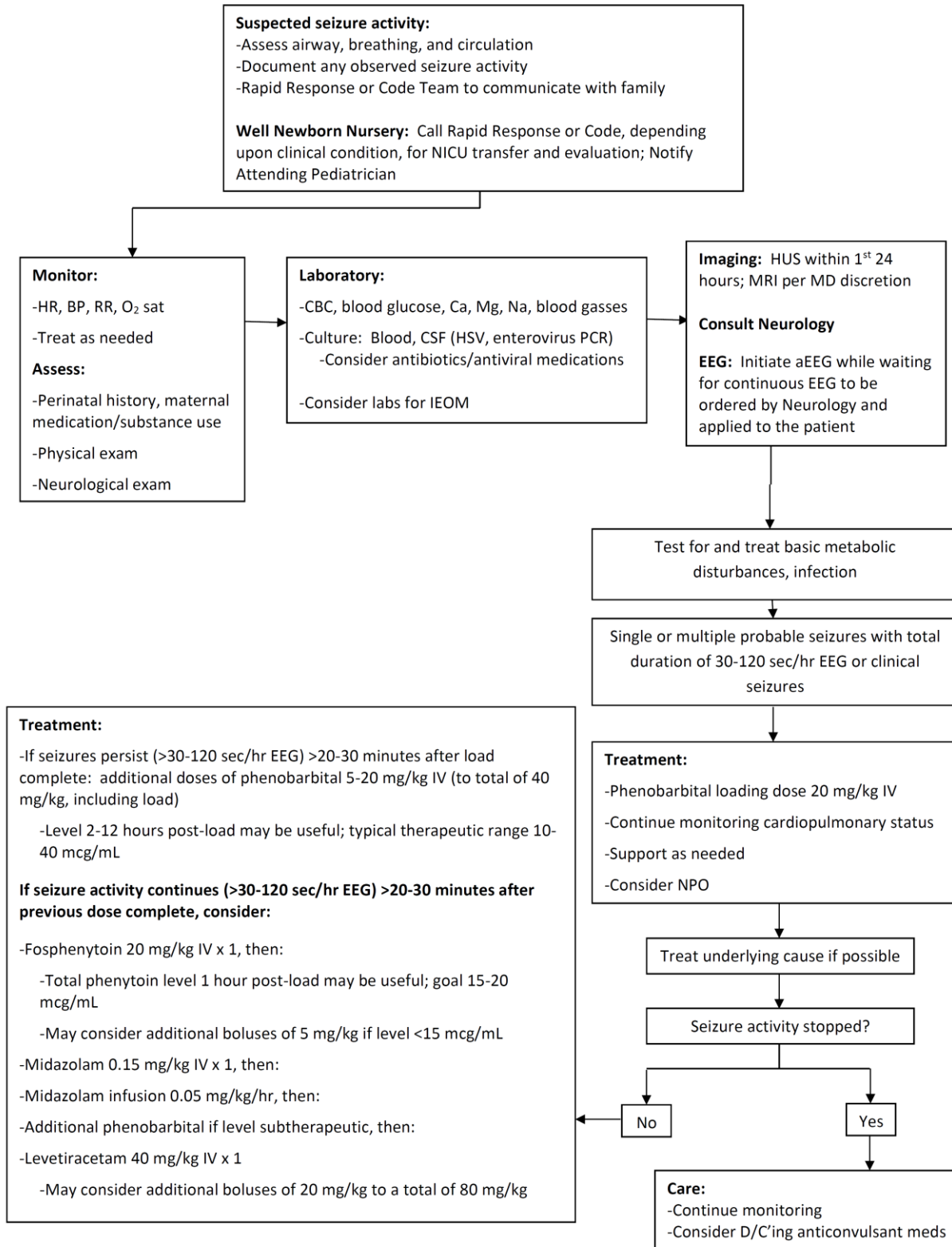


Diagnosis

- Differential diagnosis
 - Normal infant behavior versus seizure activity
 - Normal infant behavior
 - Seizure activity—clinical presentation:
 - Subtle: The clinical manifestations of subtle seizures can be easily overlooked, especially when they mimic normal behaviors and reactions. These include the following:
 - Repetitive sucking
 - Repeated extending of the tongue
 - Continuous chewing
 - Continuous drooling
 - Apnea
 - Atypical respiration
 - Rapid eye movements
 - Blinking or fluttering of the eyes
 - Fixation of gaze to one side
 - Body aligned to one side
 - Pedaling or stepping movements of the legs
 - Paddling or rowing movements of the arms
 - Complex purposeless movements
 - Rapid muscle jerks
 - Clonic
 - Tonic
 - Myoclonic
- Documentation of suspected seizure activity
 - Date, start time, end time, observations of signs and symptoms



Treatment Flow Chart





Management

- Limited evidence in neonates for optimal agents, doses, and serum levels (Maitre 2013).
 - Best therapeutic regimen for neonatal seizures has not been established.
- General principles: IV route, obtain high therapeutic range, max out doses before adding another agent.
- Observations suggest, depending on etiology but especially for HIE and stroke, seizures may be the most severe during the first week of life and may subside regardless of treatment (Painter 1999).

- Identify and correct treatable metabolic and symptomatic causes.
 - Transient metabolic disturbances: hypocalcemia, hypomagnesemia, hypoglycemia, hyponatremia
 - Infection
 - PDE, PNPO, folinic acid-responsive seizures
 - Pyridoxine: [BWH NICU Drug Administration Guidelines \(DAGs\)](#)
 - Pyridoxal 5'-phosphate: [BWH NICU DAGs](#)
 - Leucovorin calcium: [BWH NICU DAGs](#)

- **BWH NICU Therapeutic Algorithm:**
 - **First line:** Phenobarbital: [BWH NICU DAGs](#)
 - **Second line:** Fosphenytoin: [BWH NICU DAGs](#)
 - **Third line:** Midazolam: [BWH NICU DAGs](#)
 - Bolus first
 - Then infusion if needed
 - **Fourth line:** Levetiracetam: [BWH NICU DAGs](#)

- **Initiation of treatment**
 - Consider anticonvulsant drugs when seizures are confirmed by EEG or by clinical exam are prolonged, frequent, or disrupt ventilation or hemodynamics.

- **Duration of treatment**
 - Need for maintenance therapy not well defined.
 - 10-30% recurrence following initial neonatal seizure (Volpe 2018).

- Appropriate duration of therapy not well defined.
- Shorter treatment durations may be warranted.
 - This is due to the potentially neurotoxic effects of AEDs (Van Rooij 2013) and the understanding that seizure control is commonly obtained within days of starting therapy (van Rooij 2013).
- Wean infants from medication upon cessation of seizures. Prolonged treatment may be warranted with clear focal structural abnormality or persisting seizures or EEG abnormalities after 1 week of life (Vento 2010).
- **Discontinuation of treatment**
 - Consider risk of recurrence
 - Consider discontinuation once seizures have abated and neurological exam normal.
 - If continued abnormal neurological exam, consider discontinuation if EEG normal.
- **Therapeutic choices and clinical data** (see BWH DAGs for additional data)
 - A survey of randomly selected NICUs in Europe found phenobarbital to be the most common first-line agent, with benzodiazepines (midazolam or clonazepam) being second-line. For continuous infusion medications, lidocaine was preferred with midazolam or fosphenytoin being second or third choices. (Vento 2010).
 - Most infants receive phenobarbital as first line treatment, according to a retrospective study of 6099 infants from 31 pediatric hospitals (Blume 2009).
 - Despite negative effects on brain growth and experimental evidence of apoptotic neurodegeneration (Vento 2010) (Bittigau 2002) (Kim 2007).
 - Shown to interfere with the maturation of synaptic connections (Forcelli 2012).
 - Retrospective cohort analysis showed poorer motor and cognitive scores at 12 months with phenobarbital versus levetiracetam. Phenobarbital was also associated with an increase in cerebral palsy rates at two years, where levetiracetam was not (Maitre 2013).
 - Phenobarbital and phenytoin were found to be equally, yet poorly effective, with a control rate of 59% and the probability of control increasing with a decreasing severity of the seizure (Painter 1999).
 - Levetiracetam lacks prospective, randomized controlled trial data supporting efficacy and safety in neonates.
 - A multicenter, randomized, blinded, controlled phase IIb study evaluated levetiracetam compared with phenobarbital for first-line treatment of seizures in 106 term neonates. More infants in the phenobarbital group remained seizure free for 24 hours as compared to the levetiracetam group (80% versus 28%, $p < 0.001$). Phenobarbital was also superior at 1 and 48 hours. Similar efficacy seen in HIE sub-group undergoing cooling. More adverse effects were seen in the phenobarbital group, including hypotension,



- respiratory suppression and sedation. 24% of infants failed to respond to both drugs (Haas 2019).
- Despite a lack of robust data supporting efficacy and safety, 73% of pediatric neurologists recommend treatment of neonatal seizures with levetiracetam and/or topiramate (Silverstein 2008).
 - Levetiracetam has been shown to reduce neuronal apoptosis after hypoxic injury and exhibit anti-inflammatory effects (Kilicdag 2013) (Stienen 2010).
 - Receptors that bind levetiracetam are in the human brain as early as 26 weeks gestation, and reach close to adult levels by 37 weeks (Talos 2012).
 - In-utero exposure to levetiracetam lead to higher developmental scores as compared to in-utero exposure to sodium valproate. The levetiracetam group did not differ from control children in overall development at 24 months. (Shallcross 2011).
- Topiramate: [BWH NICU DAGs](#)
 - Multiple mechanisms of action, including AMPA antagonism, voltage-gated sodium and calcium activity, and GABA_A potentiation (Glier 2004).
 - AMPA antagonism does not cause apoptotic neurodegeneration in rat models (Ikonomidou 1999).
 - May have neuroprotective effects along with promoting neural recovery of function after injury (Glier 2004) (Smith-Swintosky 2001).
 - Topiramate may have a neurotoxicity risk if excessive doses used above the normal therapeutic range (Glier 2004).

Prognosis

- Prognosis depends on specific etiology and severity of neurologic injury.
- Animal models suggest seizures themselves are harmful to the development of the immature brain (Holmes 1998) (Wasterlain 1997).
- Seizures during the neonatal period may impair learning and memory and increase susceptibility to epilepsy later in life (Holmes 2009).
- Mortality of less than 20% (Ronen 2007).
- Prolonged neonatal seizures can have long-term effects in a third of survivors (Ronen 2007):
 - Learning disability (27%)
 - Developmental delay and intellectual disability (20%)
 - Epilepsy later in life (27%)

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