PEDIATRIC NEWBORN MEDICINE CLINICAL PRACTICE GUIDELINES

Neonatal Seizures

Points of emphasis/Primary changes in practice:

1. Previous NICU policy on Neonatal Seizures did not exist.

2. Created new policy to document best practices.

3. Need to better capture subclinical seizure activity and intervene appropriately.

Rationale for change: Creation of new policy

Questions? Please contact: Pharmacy Department

Clinical Guideline Name	Neonatal Seizures
Implementation Date	May 15, 2015
Due for CPC Review	
Contact Person	Neonatal Clinical Pharmacist
Approved By	Dept of Pediatric Newborn Medicine Clinical Practice Council 2/12/15 CWN SPP 10/14/15 SPP Steering 10/21/15 Nurse Executive Board/CNO 10/26/15

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 2008).

- 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 4% to 48% (Vesoulis 2014).
- 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.
  - Paradoxic 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
- Laboratory tests

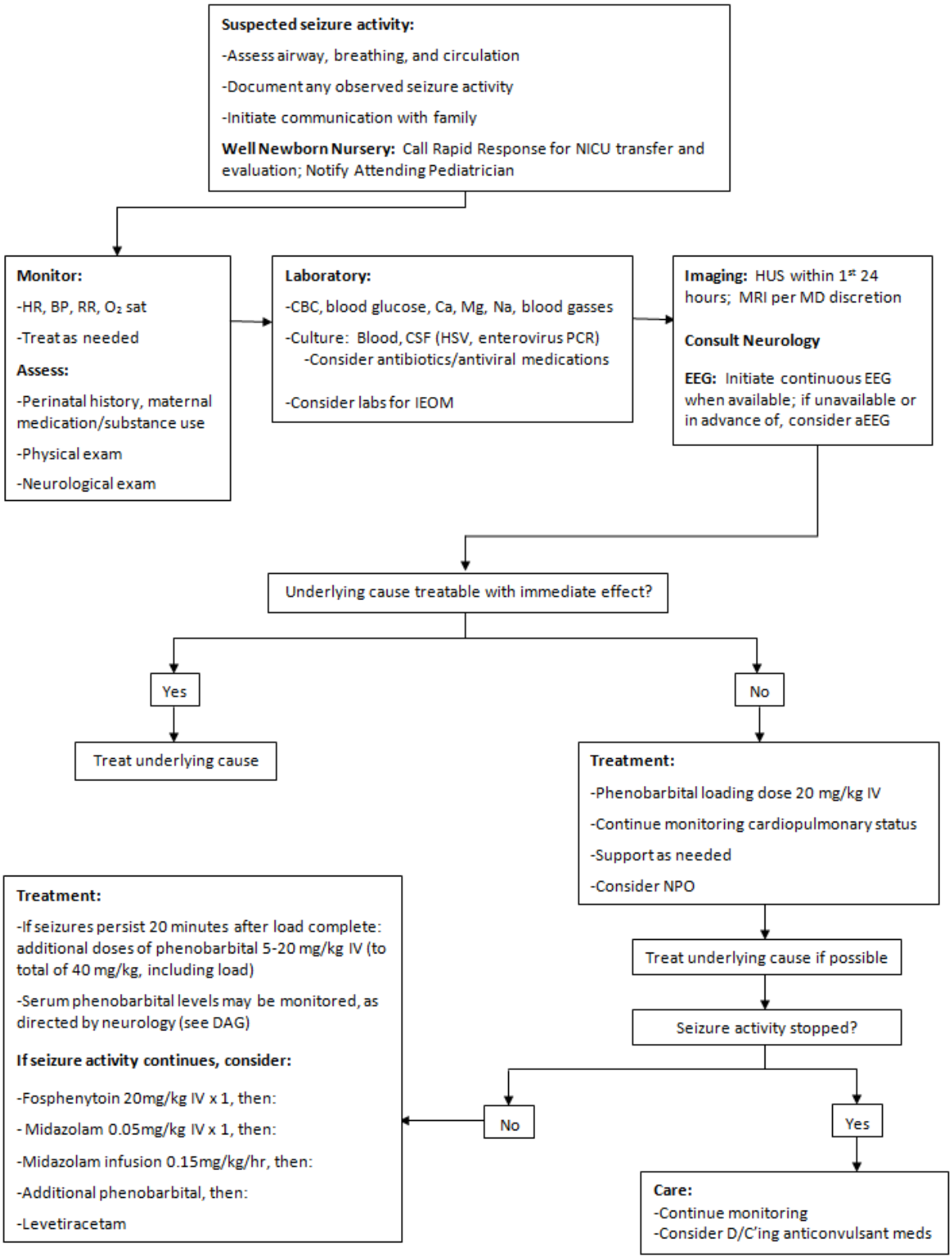
  NICU L.1 Assisting with Lumbar Puncture
    - Blood glucose level
    - Chemistries including calcium and magnesium
    - Consider liver transaminases
    - Complete blood count
    - Blood cultures
    - Serum ammonia
    - Arterial blood gases
    - Lumbar puncture
    - Additional tests depending on underlying condition, such as serum amino acids, urinary organic acids, serum pyridoxal 5-phosphate (PLP), and CSF PLP
- 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



Treatment

- 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 DAG: Pyridoxine
    - Pyridoxal 5'-phosphate BWH NICU DAG: Pyridoxal 5'-phosphate
    - Leucovorin calcium BWH NICU DAG: Leucovorin calcium

- **BWH NICU Therapeutic Algorithm:**
  - **First line:** Phenobarbital BWH NICU DAG: Phenobarbital
  - **Second line:** Fosphenytoin BWH NICU DAG: Fosphenytoin
  - **Third line:** Midazolam BWH NICU DAG: Midazolam
    - Bolus first
    - Then infusion if needed
  - **Fourth line:** Levetiracetam BWH NICU DAG: Levetiracetam

- **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 2008).
  - 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.
        - Despite this lack of efficacy and safety data, 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 DAG: Topiramate
  - 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 mental retardation (20%)
  - Epilepsy later in life (27%)

Family Support

- **Support and resources**
    - Family involvement
    - Family meetings
    - Social Work involvement

- **Communication**
    - Early and ongoing communication regarding:
        - Patient condition
        - Management and plan
        - Prognosis
    - Delivery:
        - Honest
        - Compassionate
        - Timely
    - Documentation of communication

- **Follow-up**
    - Discharge planning
    - Referrals
    - Seizure emergency management plan

BRIGHAM AND WOMEN'S HOSPITAL

Neonatal Intensive Care Unit

Parent Information Sheet: Neonatal Seizures in Full Term Infants

What is a seizure?

A seizure is a sudden, abnormal, and excessive electrical discharge in the brain's cells. Seizures in babies are very different than ones in adults. Infants can have "subtle" seizures which can be hard to diagnose as they are brief and, often times, difficult to see. Sometimes seizures in babies look very similar to normal infant behaviors and/or movements.

What causes seizures in full term babies?

The most common time to have a seizure is in the first week of life. Many things can cause seizures in babies, including:

- Low blood sugar
- Low blood calcium level
- Infection
- Bleeding in the brain
- Decreased oxygen delivery to the brain
- Abnormal formation/structure of the brain.
- Sometimes, the exact reason cannot be found

Are seizures serious?

Yes, seizures can be serious. This is why it is important to find the cause and to stop the seizures from continuing or being very frequent.

What tests are done when a baby has a seizure?

Many tests may be performed. An ultrasound or MRI of the brain is done to look for bleeding in or abnormal structure of the brain. Your baby will have an EEG, or electroencephalogram, done. This test measures the electrical waves of the brain by placing sticky leads on the head and recording the pattern. Sometimes, an EEG also involves videoing the baby's movements as well as monitoring the brain waves. Blood studies are also done. Many times, a spinal tap is necessary as well.

How are seizures treated?

It is important to find the cause of the seizure in order to treat it. For example, if the seizures are from an infection, antibiotics are needed. For many causes of seizures, specific medications (anti—seizure medicines) are given to help control and, hopefully, prevent future seizures. How long your baby will need the medication depends upon the reason for the seizures.

Some Seizure Signs

Frequent eye blinking

Staring

Lip smacking or chewing

Unusual pedaling movements of arms and/or legs

Tremors or shaking movements that do not stop when baby is touched

Pauses in breathing (apnea)

Rhythmic jerking movements of arms and/or legs

Neonatal Intensive Care Unit
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