Neonatal Seizures – Neonatal – Impatient/Emergency Department Clinical Practice Guideline

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Content Expert:
Name: Monica Bogenschutz, PharmD, BCPPS, BCPS – Pharmacy
Phone Number: (608) 422-8164
Email Address: mbogenschutz@uwhealth.org

Contact for Changes:
Name: Philip Trapskin, PharmD, BCPS – Pharmacy
Phone Number: (608) 263-1328
Email Address: ptrapskin@uwhealth.org

Guideline Author:
Jenna Bender, PharmD, BCPPS – Pharmacy

Workgroup Members:
Jenna Bender, PharmD, BCPPS
Monica Bogenschutz, PharmD, BCPPS, BCPS
Joshua Vanderloo, PharmD, BCPS

Reviewers:
Andrew Knox, MD – Pediatric Neurology
Jamie Limjoco, MD – Neonatology
Adam Wallace, MD – Pediatric Neurology
David Yang, MD – Laboratory

Committee Approvals:
Pharmacy & Therapeutics Committee, July 2018

Introduction

The risk for seizures is highest in the neonatal period, occurring in 1.8 to 3.5/1,000 neonates.[1] There is growing evidence that neonatal seizures may contribute to adverse neurodevelopmental outcomes leading to the need for safe and effective treatment options.[2-4] Historical first-line treatment for neonatal seizures has been with phenobarbital.[5] However, data suggests phenobarbital efficacy in only 30% to 50% of neonates and a Cochrane Review concluded that there is little evidence to support the use of any antiepileptic drugs (AEDs) in the neonatal period.[6-8] With the lack of robust literature and the safety concerns associated with the use of phenobarbital, there has been a decrease in phenobarbital utilization and a significant increase in levetiracetam utilization.[5]

In humans, in utero exposure to phenytoin, phenobarbital, valproate, and/or carbamazepine has been shown to be associated with lower intellectual functioning, and children treated with phenobarbital for febrile seizures in the first three years of life years have decreased IQ compared to matched controls.[9-13] In multiple animal studies in both rats and primates, phenytoin and phenobarbital have been shown to cause neuronal apoptosis in the first weeks of life as well as affect other aspects of brain development such as synaptic maturation.[14] In contrast, levetiracetam has been shown not to lead to apoptosis in rats at any dose, nor has topiramate at therapeutic doses.[15,16] A recent study by Maitre and colleagues found that exposure to phenobarbital was associated with worse outcomes at two years of age and that levetiracetam may be associated with improved outcomes when compared to phenobarbital.[17]

The risk of morbidity from seizures, the risk of morbidity from a particular AED, and the expected efficacy of that AED must all be considered when treating neonatal seizures. There is not a large body of literature assessing levetiracetam as the first-line agent for the treatment of neonatal seizures, but there are multiple studies showing phenobarbital followed by levetiracetam is well tolerated and efficacious.[18-22] Based on this literature and our expert opinion, this guideline will focus on using levetiracetam as the first-line agent for the treatment of neonatal seizures.

Scope

Intended Users:

Pediatric physicians (residents, fellows, and attendings), Advanced Practice Providers, Nurses, Pharmacists, Respiratory Therapists

Objective:

To decrease unintended variability in caregiver practice and to minimize delays in providing care to neonatal patients with concern for seizures, by providing guidance and evidence-based recommendations for the acute evaluation and management of neonatal seizures.

Target Population:

This guideline targets neonatal patients with a PMA younger than 48 weeks presenting with concern for seizures or at high risk for seizures. For patients with a PMA greater than 48 weeks refer to Status Epilepticus – Pediatric – Emergency Department/Inpatient Clinical Practice Guideline.

Clinical Questions Considered:

- What is the initial medication strategy for neonates having seizure?
- What are the therapies for refractory seizure?
- How should neonates receiving therapy for seizure be monitored?

Definitions

1. **Neonatal seizures** should be defined as paroxysmal alterations in neurologic function (e.g. behavioral, motor, or autonomic function) due to abnormal excessive or synchronous neuronal activity in the brain.[23,24]
    a. While there is no standard definition for neonatal seizures, there is consensus that diagnosis relies on confirmatory EEG characteristics.

Recommendations

Goals of Treatment

1. The treatment of neonatal seizures should occur rapidly and continue sequentially until seizures are halted or there is a sustained response with less than a 10% seizure burden over a four-hour period. (*UW Health Conditional recommendation, very low quality evidence*)
2. Critical care treatment and monitoring should be started simultaneously with emergent initial therapy and continued until further therapy is successful or futile. (*UW Health Strong recommendation, very low quality evidence*)

General Initial Treatment Considerations

1. The etiology of neonatal seizures should be diagnosed and treated as soon as possible. (*UW Health Strong recommendation, very low quality evidence*)
2. Levetiracetam should be given as first-line therapy.[18,19,25] (*UW Health Conditional recommendation, low quality evidence*)
3. Pediatric Neurology should be consulted. (*UW Health Strong recommendation, very low quality evidence)*
4. Benzodiazepines should be the drug of choice in the instance that levetiracetam will not be available within the appropriate timeframe. (*UW Health Conditional recommendation, very low quality evidence*)
   4.1. Lorazepam is the drug of choice for intravenous administration. (*UW Health Conditional recommendation, very low quality evidence*)
5. Phenobarbital should be given as second-line therapy.[8,26] (*UW Health Strong recommendation, moderate quality evidence*)

Treatment Timeline

1. **Zero to 5 minutes** – Rapid assessment of neonate presenting with seizures by MD and RN
   1.1. Assess and support airway, breathing, and circulation and apply appropriate monitoring devices (continuous cardiac rhythm monitoring, continuous pulse oximetry, VEEG) *(UW Health Strong Recommendation, very low quality evidence)*
   1.2. Note time of seizure onset and clinical presentation through documentation as a progress note in the electronic medical record. *(UW Health Strong Recommendation, very low quality evidence)*
   1.3. Establish IV or IO access. *(UW Health Strong Recommendation, very low quality evidence)*
   1.4. Assess POC glucose and correct hypoglycemia if present.[27] *(UW Health Conditional Recommendation, moderate quality evidence)*
      1.4.1. For peripheral or central access: dextrose 10% intravenous 2 mL/kg over 5 minutes.[28] *(UW Health Conditional Recommendation, moderate quality evidence)*
   1.5. Assess electrolyte abnormalities and correct if necessary.[27] *(UW Health Conditional Recommendation, moderate quality evidence)*
      1.5.1. Most commonly contributing abnormalities in neonatal population include hypocalcemia, hypo- or hypernatremia, and hypomagnesemia.[23]
   1.6. Assess physical examination, including neurologic examination. *(UW Health Strong Recommendation, very low quality evidence)*
   1.7. Acquire laboratory samples, including, but not limited to *(UW Health Conditional recommendation, low quality evidence)*:
      - Serum electrolytes: sodium, potassium, chloride, bicarbonate, calcium (total and ionized), and magnesium
      - Blood urea nitrogen and creatinine
      - Complete blood count with differential
      - Antiepileptic drug concentrations, if deemed necessary by discussion with Pediatric Neurology and Pharmacy
      - Other labs that may be warranted depending on presentation include blood culture, urine culture, liver function tests, coagulation panels, genetic labs for assessment of inborn errors of metabolism, or toxicology screen.
   1.8. Consult Pediatric Neurology. *(UW Health Strong recommendation, very low quality evidence)*

2. **First-line treatment, after 5 minutes of seizure**
   - 2.1. The first drug administered should be levetiracetam.[18,19] *(UW Health Conditional recommendation, low quality evidence)*
     - 2.1.1. First intravenous loading dose: levetiracetam 50 mg/kg over 15 minutes.[20,29,30] *(UW Health Conditional Recommendation, low quality evidence)*
     - 2.1.2. If seizures are confirmed on EEG, a second loading dose of levetiracetam should be administered and maintenance levetiracetam should be initiated. (*UW Health Conditional recommendation, very low quality evidence)*
       - 2.1.2.1. Second intravenous loading dose: levetiracetam 50 mg/kg once over 15 minutes.[20,29,30]
       - 2.1.2.2. Intravenous or oral maintenance dose: levetiracetam 25 mg/kg twice daily. [29,30]
       - 2.1.2.3. Maintenance dose should start six to twelve hours after last intravenous loading dose.
   - 2.2. If levetiracetam is not available to administer within 10 minutes, may consider administration of lorazepam. (*UW Health Conditional recommendation, very low quality evidence)*
     - 2.2.1. Intravenous: lorazepam 0.1 mg/kg over 2 minutes, maximum of two doses. *(UW Health Conditional Recommendation, very low quality evidence)*

3. **Second-line treatment, allow 30 minutes after last levetiracetam loading dose**
   - 3.1. The next drug to be administered should be phenobarbital.[8,26] (*UW Health Strong recommendation, moderate quality evidence*)
     - 3.1.1. First intravenous loading dose: phenobarbital 20 mg/kg over 15-30 minutes.[31,32] (*UW Health Conditional recommendation, low quality evidence*)
       - 3.1.1.1. Adverse effects of phenobarbital include respiratory depression and hypotension and may necessitate airway and circulatory support.
   - 3.2. If seizures continue, may administer up to two further doses of 10 mg/kg (maximum of 40 mg/kg total).[31,32] (*UW Health Conditional recommendation, low quality evidence)*
     - 3.2.1. If improvement seen after an additional loading dose of phenobarbital, maintenance should be initiated. (*UW Health Conditional recommendation, very low quality evidence*)
       - 3.2.1.1. Intravenous or oral maintenance dose: phenobarbital 2.5 mg/kg twice daily.
       - 3.2.1.2. Maintenance dose should start twelve hours after last intravenous loading dose.

4. **Refractory treatment**
   - 4.1. The next drug administered may be fosphenytoin.[8,32] (*UW Health Conditional recommendation, very low quality evidence)*
     - 4.1.1. First intravenous loading dose: fosphenytoin 20 mg PE/kg given no faster than 2 mg PE/kg/min (maximum 150 mg PE/min; where PE is phenytoin equivalents).
     - 4.1.2. If seizures continue, may give another 10 mg PE/kg if seizures persist
     - 4.1.3. Monitor for adverse effects of fosphenytoin and phenytoin including cardiac arrhythmia and hypotension, as well as nystagmus and ataxia as these may be signs of supratherapeutic concentrations
   - 4.2. Other options to consider based on discussion with Pediatric Neurology include pyridoxine, midazolam continuous infusion, topiramate, or lidocaine infusion. (*UW Health Conditional recommendation, very low quality evidence)*

General Considerations Following Initial Seizure Management

1. Video EEG should be used to identify neonatal seizures as vEEG is able to discern true seizure activity from other clinical presentations which appear similar to seizures but are not seizures.[33] (*UW Health Strong recommendation, high quality evidence)*
2. In cases of renal insufficiency, dose adjustments for levetiracetam should be discussed with neonatologists, neurologists and pharmacists. (*UW Health Strong recommendation, very low quality evidence)*
3. Drug concentration monitoring
   - 3.1. Levetiracetam: there is insufficient data regarding clinical utility of these levels and dosing adjustments based upon therapeutic drug monitoring. Concentration reference ranges are not

adequately described in neonates to correlate with efficacy.[21,34] *(UW Health Conditional recommendation, low quality evidence)*

3.2. Phenobarbital: trough goal 15 to 40 mcg/mL.
   3.2.1. Consider obtaining prior to starting maintenance therapy.[8] *(UW Health Conditional Recommendation, low quality evidence)*
3.3. Free phenytoin: two-hour goal 1-2 mg/dL.
   3.3.1. Free phenytoin concentration is recommended in addition to total phenytoin concentration in the neonatal population as total phenytoin concentrations poorly predict free phenytoin concentrations in the critically ill pediatric patient.[35] *(UW Health Conditional Recommendation, low quality evidence)*

4. Continue EEG monitoring until seizure free for 24 hours (*UW Health Conditional recommendation, very low quality evidence)*
5. If etiology of seizures was hypoxic ischemic injury (HIE), consider discussing discontinuation of anti-epileptics (AEDs) after seven days if patient is free of seizures. (*UW Health Conditional recommendation, very low quality evidence)*
6. All patients with spells concerning of seizures should be evaluated with EEG until: (*UW Health Conditional recommendation, very low quality evidence)*
   - Patient is 24 hours seizure free; this may be extended at Neonatology or Pediatric Neurology discretion for patients at high risk for seizures based on history or EEG findings or when seizures may not be detected on clinical exam (i.e. paralyzed patients);
   - Events are shown not to be seizure;
   - Cooling protocol is completed for HIE patients

Disclaimer

Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Methodology

Development Process

Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Collect the Evidence:

The following criteria were used by the guideline author and workgroup members to conduct electronic database searches in the collection of evidence for review.

Literature Sources:

- Electronic database search (e.g., PubMed)
- Databases of systematic reviews (e.g., Cochrane Library)
- Hand-searching journals, external guidelines, and conference publications

Time Period: 1990 to 2018

Search Terms: The following is a list of various search terms that were used individually or in combination with each other for literature searches on PubMed: neonatal, neonates, seizures, phenobarbital, levetiracetam, neonatal seizures, pharmacokinetics, therapeutic drug monitoring.

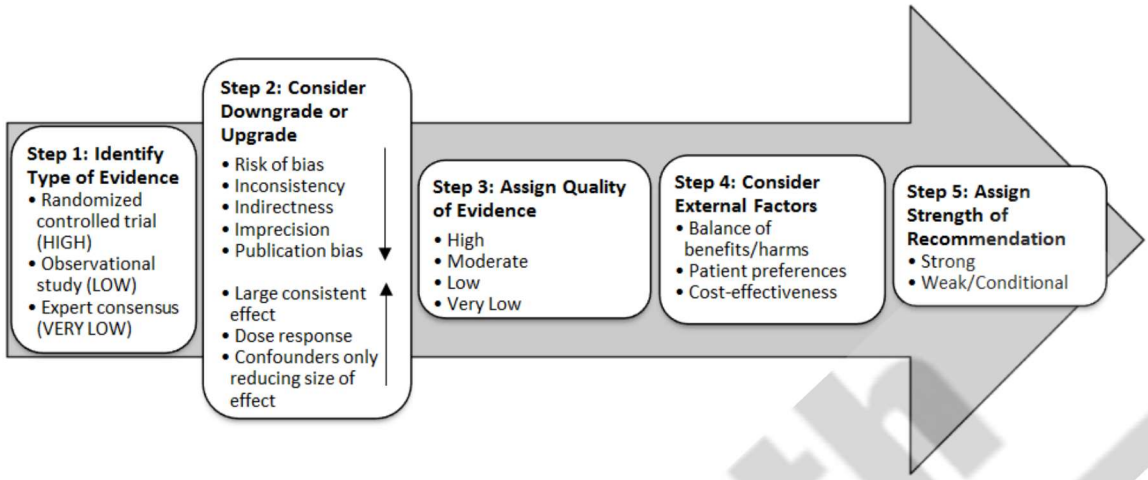
Methods to Select the Evidence:
Literary sources were selected with the following criteria in though: English language, publication in a MEDLINE core clinical journal, and strength of expert opinion.

Methods Used to Formulate the Recommendations:
The workgroup members created recommendations internally through a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:
Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see **Figure 1**).

Figure 1. GRADE Methodology adapted by UW Health



Rating Scheme for the Strength of the Evidence/Recommendations:

GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations For or Against Practice

Strong	The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.
Conditional	Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.

Recognition of Potential Health Care Disparities: None identified

Collateral Tools & Resources

Metrics

1. Time of onset of seizure to administration of levetiracetam
2. Number of patients receiving benzodiazepine prior to levetiracetam
3. Number of patients proceeding to receive phenobarbital
4. Documentation of seizure start time and duration in Health Link
5. Documentation of point-of-care glucose measurement

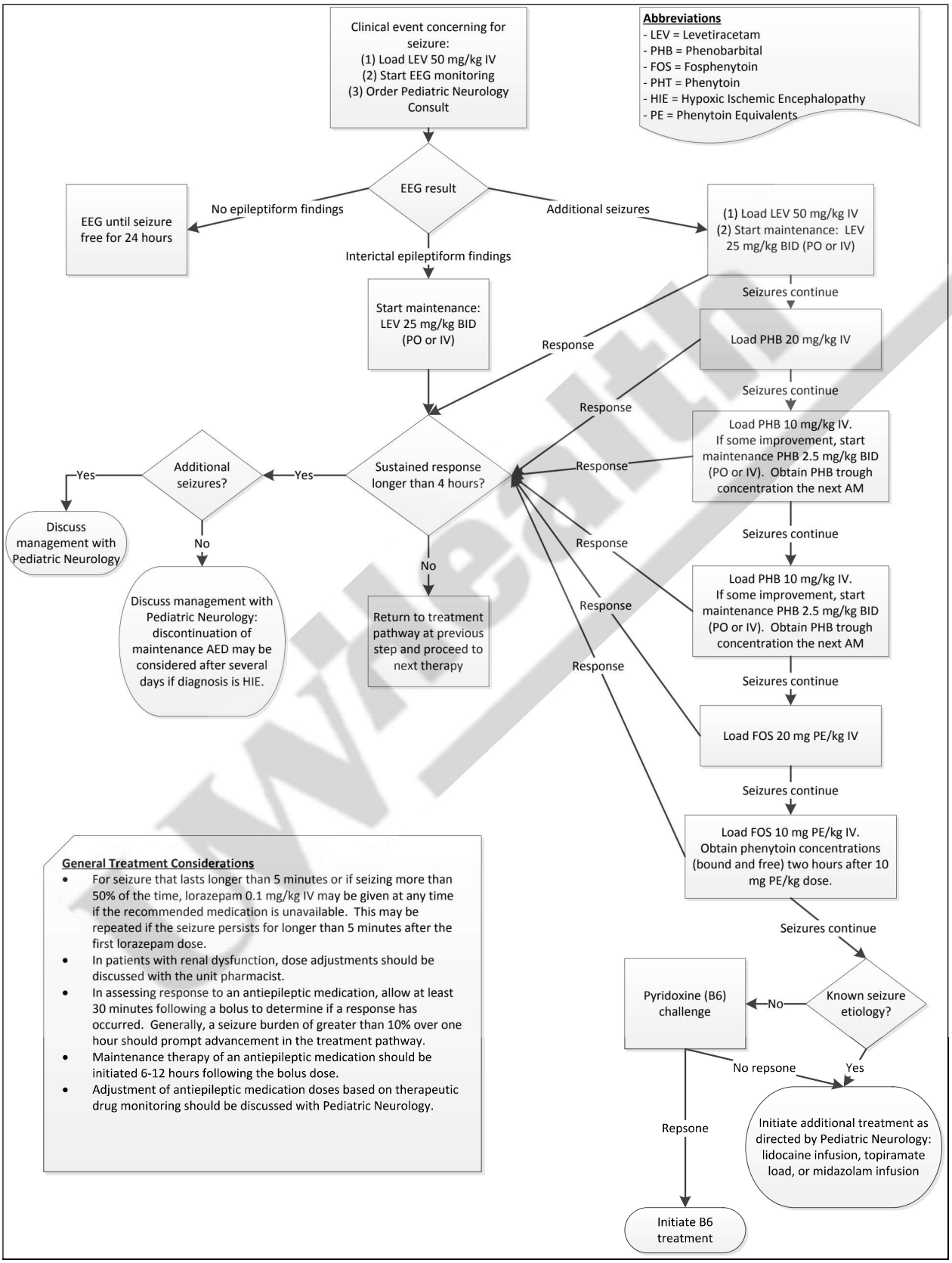
Patient Resources

1. Health Facts for You #7351 – Intranasal Midazolam to Treat Seizures in the Hospital
2. Health Facts for You #7358 – Intranasal Midazolam to Treat Seizures in the Hospital (Spanish)
3. Health Information: Seizures

Policies

1. UW Health Policy 6.10AP- Care of Patient With or at Risk For Seizure (Adult & Pediatric)

Appendix A. Management of Neonatal Seizure



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