Newborn Critical Care Center (NCCC) Clinical Guidelines

Neonatal Acute Symptomatic Seizures Antiseizure Medication Pathway

Seizures are one of the most distinctive signs of neurological dysfunction in neonates. Most neonatal seizures are subclinical, which makes identifying them an immense challenge for clinicians. Seizures affect up to 5 per 1000 term births, and even more frequently in premature infants as evidenced in population studies. Because improvements in technology and neonatal care have improved the morbidity and mortality of extremely premature infants, there is a growing need to identify and manage seizures in more premature infants. In addition, more evidence demonstrates that seizures exacerbate cerebral injury, suggesting that early treatment of neonatal seizures is important in reducing adverse long-term outcomes. Detrimental outcomes following seizures in preterm infants include death, neurological impairment, epilepsy, cerebral palsy, hearing and vision impairments.

The pathway below is established as a guideline for treatment of acute symptomatic seizures in neonates. Acute symptomatic seizures are defined as seizures occurring at the time of a systemic insult or in close temporal association with a documented brain insult.[1] The most common causes of acute symptomatic seizures in neonates are hypoxic-ischemic encephalopathy, ischemic stroke, intracranial hemorrhage, transient metabolic derangements and central nervous system infections.[2] It is important to differentiate these from neonatal-onset epilepsies, as this affects treatment.

There is limited data regarding management of neonatal seizures with antiseizure medications. Other sites have demonstrated improved care with implementation of neonatal seizure treatment algorithm (though with a small number of patients), with the thought that standardizing treatment decreases the probability of mistakes and delayed care.[3]

The available data regarding treatment of neonatal seizures includes a randomized controlled trial comparing phenobarbital and phenytoin, which showed that each achieved complete control of seizures in 43-45% of neonates. When used in combination, complete control was achieved in 57-62%. No difference was found in efficacy or side effects.[4] The preliminary data from an as-yet unpublished randomized controlled trial shows significantly better response to phenobarbital (80% seizure-free for 24 hours) compared to levetiracetam (28%).[5]

References:

1. Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, Tomson T, Hauser WA. Recommendation for a definition of acute symptomatic seizure. *Epilepsia*. 2010.
2. Soul JS. Acute symptomatic seizures in term neonates: Etiologies and treatments. *Semin Fetal Neonatal Med*. 2018.
3. Harris M, Malloy K, et al. Standardized Treatment of Neonatal Status Epilepticus Improves Outcome. *Journal of Child Neurology*. 2016.
4. Painter et al. Phenobarbital compared with phenytoin in the treatment of neonatal seizures. *NEJM*. 1999.
5. Sharpe C, Reiner GE, Davis SL, et al. NEOLEV2, A Randomized Controlled Trial of Levetiracetam Compared with Phenobarbital in the Treatment of Neonatal Seizures (June 17, 2019). Available at SSRN: https://ssrn.com/abstract=3405581

Additional references:

1. Glass H, Shellhaas R, Tsuchida T, et al. Seizures in preterm neonates: A multicenter observational cohort study. Pediatr Neurol, 2017 Jul;72(19-24).
2. Glass H, Shellhaas R, Wustoff C, et al. Contemporary profile of seizures in neonates: a prospective cohort study. J Pediatr, 2016 Jul;174 (98-103).
3. Pisani F and Spagnoli C. Acute symptomatic seizures in preterm neonates: etiologies and treatments. Semin Fetal Neonatal Med, 2018 Jun;23(3):191-196.
4. Pisani F and Spagnoli C. Outcome in preterm infants with seizures. Handb Clin Neurol, 2019;162:401-414.

UNC Neonatal Acute Symptomatic Seizures Antiseizure Medication Pathway

- Assess airway, breathing, and circulation
- Monitor vitals, treat as needed
- Initial labs should include blood glucose, Na, Ca, Mg, CBC, blood gas
- Treat underlying cause prior to antiseizure meds if immediate effect possible
- Initiate video EEG

This pathway is intended for acute symptomatic seizures. Recurrent seizures refractory to antiseizure meds and without a clear etiology should raise suspicion for an inborn error of metabolism, and trials of pyridoxine, biotin and folinic acid should be considered.

Seizures suspected, highly likely or confirmed with EEG and antiseizure medication determined to be required:

↓

IV Phenobarbital 20 mg/kg. If desired, obtain level after 2 hours.

Seizures Continue ← ***Reassess 20 minutes after load is complete*** → ***Seizures Stop***

IV Phenobarbital 20 mg/kg (total 40 mg/kg). Start maintenance 4 mg/kg/day divided BID. Obtain level 2 hours after load.

Consider maintenance dosing. If determined appropriate, start 4 mg/kg/day divided BID 12 hours after the load.

Seizures Continue ← ***Reassess 20 minutes after load is complete***

Second Line:
IV Fosphenytoin 20 mg/kg
OR
IV Keppra 60 mg/kg

→

Maintenance dosing can be considered pending response:
- Fosphenytoin 6 mg/kg/day divided BID
- Keppra 60 mg/kg/day divided TID, starting 12 hours after the load

Obtain free and total phenytoin levels 2 hours after fosphenytoin load.

Seizures Continue ← ***Reassess 20 minutes after load is complete***

Third Line:
IV Keppra or Fosphenytoin, whichever not used 2nd line.

→

Seizures Continue ← ***Reassess 20 minutes after load is complete***

Fourth Line:
Midazolam bolus 0.15 mg/kg
followed by infusion 0.06 mg/kg/hr.
Titrate up q5 min to effect.

Consider stopping antiseizure medications after acute symptomatic seizures resolve.