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Guidelines for the Management of Seizures in Late Preterm and Term Neonates

(Gestational age ≥ 34 weeks AND Postmenstrual age < 44 weeks)

These guidelines will use the available evidence to guide medical teams in the management of seizures exclusively in late-preterm and term neonates.

Background

- The neonatal period carries the highest lifetime risk for seizures, and seizures are the most common manifestation of brain injury in neonates.[1,2]
- The majority of neonatal seizures are acute symptomatic seizures due to early brain injuries such as hypoxic ischemic injury, stroke and intracranial hemorrhage.[1,3]
- Untreated seizures have been shown to cause neuronal apoptosis and adverse neurodevelopmental outcomes in animal and human studies.[3-6]

Neurophysiologic Monitoring

- Clinical diagnosis of seizures is challenging and many paroxysmal behaviors in neonates are not seizures, so clinical assessment of seizures can result in both over- and underdiagnosis.[2,7]
- Majority of neonatal seizures are subclinical and accurate diagnosis of seizures can only be made by electroencephalography (EEG).[1,8]
- The gold standard for neonatal seizure diagnosis is continuous video EEG (cEEG) monitoring with a conventional 10–20 montage modified for neonates.[8]
- If cEEG is not available, amplitude integrated EEG (aEEG) can be used for cerebral function monitoring; however, aEEG is known to have lower sensitivity and specificity in detecting seizures.[9,10]
- In infants with neonatal seizures, cEEG monitoring should be continued until at least 24 hours after the last electrographic seizure.[8]
- In infants with HIE who undergo cEEG monitoring, cEEG can be discontinued after 24 hours of recording if no seizure is detected.[11] In these infants, aEEG monitoring should be continued throughout cooling and rewarming phases of the hypothermia protocol.

Goals of Treatment

- The overall seizure burden is associated with death and long-term disability.[3-5,12-14]
- It is essential to establish and communicate the goals of treatment for each neonate while weighing benefits of each medication against its potential risks.[1,15]
- The initial goal of treatment should be complete resolution of all clinical as well as subclinical seizures when treating acute symptomatic seizures.[1,2,12,16]
- In cases when seizures are symptomatic of underlying brain malformation or neonatal-onset epilepsy, the goal of treatment is to reduce seizure burden as much as possible.[1,12]
- Symptoms of anxiety and depression are common in parents of infants with neonatal seizures, and poorer parental quality of life and family well-being can also affect long-term outcomes.[17] Therefore, facilitating parent involvement and ongoing support to maintain well-being of the parents are encouraged throughout the neonatal intensive care unit stay.[17,18]

Overview of Acute Treatment

- The initial step is securing the neonate's airway, and maintaining adequate ventilation and circulation.[1,2,19]
- Electrolytes and glucose should be rapidly obtained and any disturbance should be corrected accordingly. Infants without a clear etiology should also be assessed with lumbar puncture when stable and empirical antimicrobial treatment should be initiated as per the institutional protocol for meningitis and/or encephalitis pending results.[1,2,19]
- In infants with hypoxic ischemic encephalopathy (HIE), due to its seizure-suppressive effect, therapeutic hypothermia should be initiated within the critical 6-hour window, when clinically indicated.[20]
- All neonates with a suspicion of seizures should receive aEEG monitoring for initial assessment.
- After risk stratification based on history, neurologic examination and aEEG assessment, if further cEEG monitoring is deemed necessary, Neurology Service consult should be done for consideration of video cEEG monitoring. This decision is to be made after Neonatology and Neurology staff to staff physician conversation.
- Due to its rapid onset of action and ease of administration, lorazepam is commonly used for abortion of brief clinical and/or subclinical seizures.[21] No further treatment was required in

around a quarter of the infants who received lorazepam in our cohort of 286 neonates between July 2017 and January 2020 (unpublished data).

- World Health Organization (WHO) and International League Against Epilepsy (ILAE) recommend phenobarbital as the first-line agent for the treatment of neonatal seizures.[19,22] In a recent multicenter, randomized, controlled trial, phenobarbital was more effective than levetiracetam as a first-line treatment of neonatal seizures.[23] Although the only randomized controlled trial comparing the efficacy of phenobarbital versus phenytoin showed similar results, phenytoin's less predictable pharmacokinetics, poor enteral absorption and shorter half-life makes phenobarbital a safer choice as the first-line treatment.[24] Therefore, phenobarbital remains the first-line medication in this updated protocol.
- Currently, there is no evidence to support efficacy of any one of the second-line therapies over the others. A systematic review showed no evidence that phenytoin/fosphenytoin is superior or inferior to other second-line medications.[25] WHO guidelines also recommend phenytoin after phenobarbital as a potential second-line treatment.[19] The secondary efficacies were 27% for phenytoin and 17% for levetiracetam in the previous randomized controlled studies.[23,24] Because the response rate to levetiracetam as a second-line treatment was only around 30%, and response to fosphenytoin, without levetiracetam, was 72% in our unit (unpublished data), fosphenytoin is substituted for levetiracetam in the main pathway; however, levetiracetam remains as an alternative to fosphenytoin, if there is any contraindication to fosphenytoin use.
- Currently, there is no evidence to support efficacy of any one of the third-line therapies over the others and treatment is guided by limited data. Given the potential effects of respiratory depression, hypotension and subsequent cerebral hypoperfusion, midazolam is recommended as a third-line treatment and several small studies showed its high efficacy to abort seizures when used as an add-on treatment.[26-29] We, therefore, keep midazolam as the third-line treatment in this updated protocol, until data from high-quality randomized controlled trials are available.
- For neonates with refractory seizures of unknown etiology, Metabolism/Genetics Service consult should be done for an empirical trial of vitamin supplementation (pyridoxine, pyridoxal-5-phosphate, folinic acid and biotin).[30] This step should be considered earlier in the pathway should the history and neuroimaging do not suggest any specific etiology.

- Despite all of the above steps, in neonates with refractory seizures, especially those with a positive family history, burst-suppression pattern in cEEG, asymmetric tonic posturing as the seizure semiology and in atypical cases when history does not point to a specific etiology, neonatal genetic epilepsy syndromes (e.g. KCNQ2, KCNQ3, SCN2A) should be included in the differential diagnosis and carbamazepine is warranted following a Neurology consult.[30]

Overview of Maintenance Treatment

- There is a wide variability among physicians regarding the decision of maintenance treatment.[31] The 2015 ILAE Task Force Report does not provide recommendations on the initiation and duration of maintenance treatment, given there is no clear evidence in the literature.[22] Therefore, the likelihood of seizure recurrence for each individual case should be weighed against possible adverse effects of antiseizure medications on brain growth.[32]
- Based on expert opinion, it is recommended to start phenobarbital maintenance treatment 12 hours after the last loading dose to maintain therapeutic plasma concentrations.[1,2,16] In the absence of further evidence, additional maintenance therapies beyond phenobarbital should only be started after Neurology Service consult.
- The ideal duration of antiseizure medications in neonates with acute symptomatic seizures is not known.[31] The WHO guidelines, based on expert opinion in the absence of randomized controlled trials, emphasize that maintenance treatment can be discontinued before discharge in infants who achieve seizure control on a single medication.[19] Twenty-nine per cent of neonates with seizures were discharged on maintenance treatment from our unit between July 2017 and January 2020, and 75% of these infants were on phenobarbital, 13% on levetiracetam, and 6% on multiple medications at the time of discharge (unpublished data).
- Because the strongest risk factors for post-neonatal epilepsy are status epilepticus, refractory seizures lasting for more than 48 hours and extensive brain injury on neuroimaging, it is recommended to continue maintenance treatment at discharge in these infants.[33,34] In neonates with neonatal-onset epilepsy, maintenance should also be continued at discharge.[31] In cases with none of the above risk factors, discontinuation of maintenance should be considered before hospital discharge.

- Infants discharged on maintenance treatment should have a routine EEG and a follow-up with Neonatal Neurology Clinic at 3 months, while infants who were not discharged on maintenance treatment should be seen in the Combined Clinic at 4 months corrected age.

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Onset of Seizures

- Secure and support ABCs
- Establish intravenous access
- Check glucose, electrolytes and blood gas
- Plan cranial ultrasonography and elective MRI
- Start bedside aEEG monitoring
- Inpatients: Neurology Service consult for cEEG (NICU & Neurology staff conversation)
- Outpatients: Direct referral to SickKids for cEEG
- Start therapeutic hypothermia in HIE when indicated
- Transfer placenta to SickKids and send for pathology

Seizures ongoing for 2 minutes

Lorazepam 0.1 mg/kg IV/PR
Administer over 2 minutes

Seizures 2 minutes after the completion of infusion

Lorazepam 0.1 mg/kg IV/PR
Administer over 2 minutes

Seizures 2 minutes after the completion of infusion

Phenobarbital
20 mg/kg IV over 10 minutes

Seizures 2 minutes after the completion of infusion

Phenobarbital
10 mg/kg IV over 5 minutes

Seizures 2 minutes after the completion of infusion

Phenobarbital
10 mg/kg IV over 5 minutes

Seizures 2 minutes after the completion of infusion

Fosphenytoin
20 mg PE/kg IV over 10 minutes

Alternative: **Levetiracetam**
60 mg /kg IV over 15 minutes

Seizures 2 minutes after the completion of infusion

Midazolam infusion
Initial load: 0.15 mg/kg IV
Followed by 2 mcg/kg/min IV infusion
Increase as needed by 2 mcg/kg/min every 10 minutes
Additional 0.15 mg/kg before each increase in infusion rate
Maximum infusion rate: 24 mcg/kg/min

Metabolism/Genetics consult for sequential trial of B6, P5P, folinic acid and biotin

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Consider starting maintenance
Phenobarbital
5 mg/kg once daily IV/PO
12 hours after the last loading dose

Re-evaluate the need for maintenance treatment prior to discharge

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