Neonatal Seizures Evaluation & Management Clinical Pathway

Neonatal Intensive Care Unit

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Inclusion Criteria:

- Neonates ≥ 36 weeks GA **And** <10 days of life with high risk/suspected seizures

Patients at High Risk for Neonatal Seizures (ACNS 2011 Guidelines):

- Known or suspected metabolic abnormality, infectious, hypoxic or vascular brain injury or malformation
- Clinical suspicion for seizure or neonatal epilepsy syndrome
- Iatrogenically paralyzed, on ECMO or post-cardiac arrest

Acute Management of a Neonate with Suspected Seizure

Identify and treat any metabolic and infectious etiologies for seizures

- Check serum electrolytes, glucose, iCa, Mg, Phos, CBC, LFTs, ammonia
- Consider sepsis workup
- Consider lumbar puncture for routine studies; culture, MEID and HSV PCR
- Consider Antibiotics and Acyclovir as clinically indicated
- Consult Neurology
- Order LTM EEG (Continuous video EEG should be considered in all patients at high risk for neonatal seizures)
- Order Head ultrasound

Abbreviations:

- GA : Gestational Age
- LTM: Long Term Monitoring
- EEG: Electroencephalogram
- MEID: Meningitis Encephalitis ID
- LFT: Liver Function Test
- PCR: Polymerase Chain Reaction
- ECMO: ExtraCorporeal Membrane Oxygenation

Is the neonate clinically stable?

No

Yes

Seizure event captured?

No

EEG typically continued until a minimum of 24 hours of seizure freedom, until event capture, or until completion of rewarming in patients undergoing therapeutic hypothermia

See Hypothermia Pathway

Yes

Proceed to **Acute Treatment page**

Acute Treatment of a Neonate with Seizures

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Inclusion Criteria:

- Neonates ≥ 36 weeks GA **And** <10 days of life with EEG confirmed seizures OR suspected seizures and unstable

Anti-Seizure Medications can be administered sequentially:

- In unstable neonates with high clinical suspicion for seizure
- In neonates experiencing recurrent seizures on EEG without underlying correctable metabolic abnormality

Abbreviations

MRI: Magnetic Resonance Imaging
MRS: Magnetic Resonance Spectroscopy

Phenobarbital 20 mg/kg IV

Seizure continues for 10 minutes?

No

Yes

Phenobarbital 20 mg/kg IV repeat

Seizure continues for 10 minutes?

No

- Monitor EEG for return of seizure activity
- EEG typically continued until a minimum of 24 hours of seizure freedom, until event capture, or until completion of rewarming in patients undergoing therapeutic hypothermia **See Hypothermia Pathway**
- **MRI/MRS when stable**

Yes

Fosphenytoin 20 mg/kg IV

Seizure continues for 10 minutes?

No

Continue to **Treatment of Medication Resistant Seizure**

Special Considerations

- At Neurologist's discretion, in the acute treatment algorithm, levetiracetam may be given in place of phenobarbital or foshpenytoin in neonates with cardiac disorders or those with contraindications to other medications, especially if other therapies have been ineffective or are delayed
- Levetiracetam is less effective then Phenobarbital in the treatment of neonatal acute symptomatic seizures.
- Levetiracetam dose is 50mg/kg
- Can repeat in 10 minutes

Return to Acute Management

Treatment of a Neonate with Medication Resistant Seizure

Neonatal Intensive Care Unit

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- Midazolam 0.2 mg/kg IV bolus
  And
- Start Midazolam infusion at 0.1 mg/kg/hr

Seizure continues?

No

- Continue present Midazolam infusion rate
- Consider weaning after 24 hours of seizure freedom
- Suggested wean of Midazolam 0.05 mg/kg/hr every 4-6 hours
- MRI/MRS when stable
- Consider **Further Evaluation & Management** for etiology of seizures

Yes

- Midazolam Bolus 0.2 mg/kg & increase Midazolam infusion by 0.05 mg/kg/hour
- Repeat bolus and increase infusion every 5-15 minutes if needed[†]
- Maximum rate of Midazolam infusion 1 mg/kg/hr

Seizure continues?

No

Yes

Proceed to next page, **Further Evaluation & Management**

[†] Additional Considerations

- Continue to titrate Midazolam infusion if high seizure burden or status* persists
- Not every isolated seizure will require escalation of treatment

*High seizure burden (cumulative >12 minutes/hour) or status epilepticus (50% of any hour) may require escalating treatment. Decisions must balance the risk versus benefit of infusions for each patient

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Further Evaluation & Management of a Neonate with Medication Resistant Seizures and/or if No Clear Etiology Identified

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Further Evaluation:

- Serum amino acids, serum lactate, serum pipecolic acid
- Urine organic acids, urine AASA
- CSF amino acids (including glycine), CSF AASA, CSF lactate, CSF neurotransmitters (recommended but not required prior to pyridoxine treatment)
- Consider Genetics consult, consider rapid genome sequencing
- MRI/MRS when stable

Abbreviations

- AASA: Alpha-aminoadipic semialdehyde
- CSF: Cerebrospinal fluid

Consider IV pyridoxine treatment in patient with persistent seizures

This should occur during the day to allow multidisciplinary coordination (Neurology, LTM reader, Neonatology, Pharmacy, and Genetics)

- Further management guided by Neurology recommendation which may include:
  i. Bolus with IV Pyridoxine 50 mg/kg/dose (up to 100 mg) (IV push over 3-5 minutes)
  ii. Maintenance Pyridoxine 30 mg/kg/d IV (up to 300mg/day) divided TID
  iii. +/- Folinic acid 3-5 mg FLAT IV daily until return of genetic testing and/or CSF neurotransmitters regardless of acute response
  iv. If unresponsive to Pyridoxine, consider trial of Pyridoxal-5-phosphate treatment
  iii. Irrespective of whether seizures are responsive or not, move to Long term/ Maintenance management
- Obtain Genetics recommendations regarding need for lysine free diet and arginine supplement

i. Neonatology provider should be at bedside during infusion given risk for acute cardiorespiratory collapse and 20% risk of cerebral depression (isoelectric EEG and apnea) in the hours following pyridoxine bolus.

Return to Acute Management

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Return to Medication Resistant Seizure

Long term/ Maintenance seizure management

If risk of ongoing seizure is present per Neurology's assessment[ff]:

- Daytime NICU/Neuro consult team can initiate maintenance anti-seizure medication
- The following anti-seizure medications can be used alone or in combination based on clinical course:
  i. Levetiracetam* 40mg/kg/day with titration up to 90-100 mg/kg/day as clinically indicated. Dose divided twice daily as maintenance
  ii. Phenobarbital[+] 5 mg/kg/day divided twice daily
  iii. Topiramate[$] starting at 3-6 mg/kg/day titrating to at least 8 mg/kg/d over 3 days divided twice daily
  iv. Oxcarbazepine 30mg/kg/day divided twice daily in a patient with family history or presentation suspicious for channelopathy

[ff] Up to 2/3 of neonatal seizures are acute provoked seizures, which can remit after the first 72 hours, and may not require maintenance medications.

* While not as effective in the acute setting, levetiracetam can be a good option for maintenance medication given ease of dosing and minimal side effect profile

[+] Consider lower Phenobarbital doses and monitor levels in 3-5 days for premature neonates and neonates on hypothermia protocol due to slower clearance

[$] Consider getting topiramate levels and checking bicarbonate once at steady state. Typical Neonates may require higher and/or more frequent doses of topiramate because of rapid metabolism. Caution recommended in preterm neonates due to possible increased risk of necrotizing enterocolitis. Recent retrospective cohort suggests that topiramate is safe in this population.

Medication Weaning of a Neonate with Seizures

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Medication Weaning

Patients are candidate for medication wean if:

- Seizure-free for 24-48 hours
- EEG, imaging and examination, and clinical presentation suggests low risk of seizure recurrence

↓

- Anti-seizure maintenance medication should be weaned one at a time
  i. Wean Phenobarbital first if more than one maintenance medication is being given
  ii. Medications should be weaned by 50% and discontinued 2 days later
- In patients who are on more than one anti-seizure medication, all weaning should be with the guidance of Neurology

Concerns for Phenobarbital neurotoxicity and long term neuro-developmental consequences based on animal models.

↓

Family Education:

Information about seizure etiology, presentation and first aid must be completed for all families prior to discharge.
The neonatal seizure handout can be used as a guide but is not a substitute for in person education.

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Return to Refractory Seizure

Return to Further Evaluation

Diagnosis & Definition

Definition

Neonatal seizure is "an electrographic event with a pattern characterized by sudden, repetitive, evolving stereotyped waveforms with a beginning and end. The duration is not defined but has to be sufficient to demonstrate evolution in frequency and morphology of the discharge and needs to be long enough to allow recognition of onset, evolution and resolution of an abnormal discharge (pp 622-623)." [1]

Background Information and Context

Seizures are a common problem in the neonatal period with 1 to 3 of 1000 live births affected. [2]
Acute provoked seizure etiologies, including hypoxic/anoxic injury and perinatal stroke (both ischemic and hemorrhagic), are the most common etiology for seizure in this population. Recent publications confirm that more than 40% of neonates with neonatal seizure experience a high seizure burden and warrant intervention. [3] Genetically and metabolically mediated epilepsies may also present in the neonatal period and accurate identification, diagnosis and appropriate management is a key factor in improving outcomes. [4]

Treatment of neonatal seizure with anti-seizure medications is recommended, as higher seizure burden has been correlated to increased morbidity and mortality and poorer developmental outcomes, [5] Furthermore, evidence suggests that seizure activity is harmful to the developing brain. [6] [7] [8] However, there is growing concern regarding the potential neurotoxicity of anti-seizure medications, and evidence that these agents lead to neuroapoptosis in animal models, with unknown effects on developmental outcome. [9]

The need to balance the benefits of seizure management with the risks of the seizure medications has led to a focus on appropriate medication choice and optimal therapy duration in keeping with recommendations that anti-seizure medications should be discontinued when the risk of recurrent seizures decreases.
In neonates with acute provoked seizures, evidence shows that discontinuation of medications prior to discharge is not harmful [9] and does not impact the long term risk of post neonatal epilepsy in this population. [10] [11]

Typical Presentation·

Neonatal seizures can be difficult to identify. Many neonatal seizures only have subtle clinical findings or are subclinical.(Massey et al., 2018) Additionally, many unusual movements in the neonatal population are not seizures. [12] Multichannel continuous EEG (cEEG) with concurrent video is considered necessary for accurate diagnosis of seizure activity in neonates [1]

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Differential Diagnoses

Acute Provoked Seizures: [13] [14]
- ~65% of neonatal seizures
- Typically remit after 72 hours
- May not require a maintenance anti-seizure medication
- Etiologies:
  - Hypoxic/anoxic injury
  - Neonatal stroke (ischemic or hemorrhagic)
  - Intracranial or intraventricular hemorrhage (IVH)
  - Central nervous system (CNS) infection/meningitis
  - Metabolic derangement

Epilepsy with onset in the neonatal period and infancy: [13] [14]
- Inborn errors of metabolism
- Genetic epilepsies
- Central nervous system (CNS) structural lesion

Neonatal behaviors or movement disorders [15]
- Startle response
- Tremulousness
- Benign neonatal sleep myoclonus
- Hyperekplexia
- Medication or substance withdrawal
- Apnea
- Cardiac event/arrhythmia
- Paroxysmal eye movements
- Paroxysmal extreme pain disorder
- Gastroesophageal Reflux
- Hiccups
- Movement disorder

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Diagnostic Testing

Initial Testing in a Neonate with Suspected Seizure:

- Check serum electrolytes, glucose, iCa, Mg, Phos, CBC, LFTs, ammonia.
- Consider sepsis workup
- Consider lumbar puncture for routine studies; culture, MEID and HSV PCR
- Consider Antibiotics and Acyclovir as clinically indicated
- Order LTM EEG (Continuous video EEG should be considered in all patients at high risk for neonatal seizures)
- Order Head ultrasound
- All neonates with seizures will need MRI/MRS when stable

Further Evaluation in a Neonate with Medication Resistant Seizures and/or if no clear etiology for seizure identified:

- Serum amino acids , serum lactate , serum pipecolic acid
- Urine organic acids, urine AASA
- CSF amino acids (including glycine), CSF AASA, CSF lactate, CSF neurotransmitters (recommended but not required prior to pyridoxine treatment)
- Consider Genetics consult, consider rapid genome sequencing
- MRI/MRS when stable

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Monitoring

Continuous EEG should be considered in all patients at high risk for neonatal seizures:

- Known or suspected metabolic abnormality
- Infectious, hypoxic or vascular brain injury or malformation
- Clinical suspicion for seizure
- Neonatal epilepsy syndrome
- Iatrogenically paralyzed
  - For intermittent, brief events of possible seizure activity in a clinically stable neonate, obtain EEG confirmation before starting medication.
  - For persistent clinical events with high suspicion for seizures, proceed with treatment

EEG is typically continued until:

- 24 hours of seizure freedom or
- Until event capture or
- Until completion of rewarming in patients undergoing therapeutic hypothermia

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Recommended Treatment/Medications

Acute Treatment

For neonates experiencing recurrent seizures on EEG without underlying correctable metabolic abnormality, anti-seizure medications can be administered sequentially:

- **Phenobarbital 20 mg/kg IV**
  - **If seizure continues for 10 minutes**
- **Phenobarbital 20 mg/kg IV repeat**
  - **If seizure continues for 10 minutes**
- **Fosphenytoin 20 mg/kg IV**
  - **If seizure continues for 10 minutes**
- **Levetiracetam 50mg/kg with repeat in 10 minutes**
  - **Based on clinical judgement**
    - Consider levetiracetam in neonates with cardiac disorders or when other anti-seizure medications are contraindicated, therapies have been ineffective or waiting for other medications to arrive..(Pressler et al., 2023) (Sharpe et al., 2020)

Treatment Resistant Seizure

- **Midazolam 0.2 mg/kg IV bolus**
  - **Start drip at 0.1 mg/kg/hr**
- **Midazolam Bolus 0.2 mg/kg & increase 0.05 mg/kg/hour**
  - **Every 5-15 min if needed**
  - **Max rate: 1 mg/kg/hr**
  - Consider weaning midazolam after 24 hours of seizure freedom
  - suggested wean of 0.05 mg/kg/hr every 4-6 hours

Long Term/Maintenance Seizure Management

Initiate maintenance anti-seizure medication if risk of ongoing seizure is present.

- Levetiracetam 40mg/kg/day with titration up to 90-100 mg/kg/day as clinically indicated. Dose divided twice daily as maintenance.
- Phenobarbital 5 mg/kg/day divided twice daily.
- Topiramate starting at 3 - 6 mg/kg/day titrating to at least 8 mg/kg/d over 3 days(Tulloch et al., 2012) divided twice daily.
- Oxcarbazepine 30mg/kg/day divided twice daily in a patient with family history of presentation suspicious for channelopathy (Pressler et al., 2023)

Medication Weaning

If EEG, imaging and exam suggest low risk of seizure recurrence, evaluate for early discontinuation of anti-seizure medications.(Brod et al., 1988)(Hellström-Westas et al., 1995; Organization, 2011) (Glass et al., 2021) (Pressler et al., 2023)

- Decrease 1 anti-seizure maintenance medication by 50% on DOL 5-7 and discontinue 2 days later.
- Preferentially wean phenobarbital first if more than one maintenance medication is being given
  - Concerns for phenobarbital neurotoxicity and long term neurodevelopmental consequences based on animal models.(Kilicdag et al., 2013; Komur et al., 2014; Maitre et al., 2013)
- In patients receiving more than one drug, anti-seizure medications should be stopped sequentially based on clinical judgement.

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Pharmacology Pearls to Consider

Phenobarbital: recommend infusing in a larger vein due to hyperosmolarity. Standard infusion is over 30 minutes to avoid respiratory depression. Doses less than 6.5 mg need to be drawn up with our 10 mg/ml concentration.

Fosphenytoin: can be infused peripherally or centrally and has to be refrigerated. Do not exceed 150 mg PE /MIN during administration.

Phenytoin: if only phenytoin is available, it is HIGHLY recommended to be given via a central line as it is a known vesicant. Phenytoin is only good for 4 hours after preparation. Do not refrigerate. Standard infusion time is over 1 hour (no faster than 1 mg/kg/ MIN). Phenytoin needs to be infused through a 0.22 micron filter.

Midazolam: administer over 5 minutes

Levetiracetam: administer over 15 minutes

Compatibility:

- Midazolam infusion: INcompatible with fosphenytoin/phenytoin and phenobarbital. No compatibility data for midazolam and levetiracetam, also treat as INcompatible.
- TPN/IL compatibility:
  - Fosphenytoin: TPN only, no data on IL/SMOF
  - Levetiracetam: TPN/SMOF, no data on IL
  - Midazolam: TPN/SMOF/IL only at concentrations at 0.5 mg/ml or less (standard drip concentration is 0.4 mg/ml)
  - Phenobarbital: INcompatible w/ TPN/IL, no data with SMOF
  - Phenytoin: INcompatible w/ TPN/IL, no data with SMOF

Pyridoxal-5-phosphate: special order may need to be coordinated with pharmacy.

Abbreviations:

- "Standard" refers to standard of care at Nationwide Children's Hospital
- IL: Intralipid
- PE: Phenytoin Equivalent
- SMOF: Soy, MCT, Olive, Fish; special IL formulary
- TPN: Total Parenteral Nutrition

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Discharge Criteria & Planning

- Information about seizure etiology, presentation and first aid must be completed for all families prior to discharge. A neonatal seizure handout should be provided to all families and used as a guide. The handout is not a substitute for in person education.
- Discharge determined by primary team with neurology collaboration
- Appropriate neurology follow up to be determined based on clinical course

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Patient & Caregiver Education

Caregiver Education (include Epic Patient Instructions/DC templates, Helping Hands, illustrations etc. if applicable):

- ***Family Education***: Information about seizure etiology, presentation and first aid must be completed for all families prior to discharge. The neonatal seizure handout can be used as a guide but is not a substitute for in person education.

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Quality Metrics

Outcome Measures

- Percentage of neonates with acute provoked seizure:
  - Weaned from ONE anti-seizure medication by day of life 10 in the C4 and H7B NICUs
  - Weaned from ALL anti-seizure medication by day of discharge in the C4 and H7B NICUs

Process Measures

- Percentage of neonates with Phenobarbital used as the first line of medication
- Percentage of neonates with LTM placed within 24 hours of admission
- Percentage of neonates with HUS obtained within 24 hours of admission

Balancing Measures

- Neonates' records will be queried every 3 months after discharge, using the resumption of anti seizure medications as a marker for the return of seizure activity
- If a return of seizure activity is noted in more than 50% of neonates at any time point in the 12 months following medication discontinuation, the project aims will be re-evaluated

Data Collection Plan

- CLARITY_Neonates on Anti-Seizure Medication at DOL

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Clinical Pathway Development

This clinical pathway was developed using the process described in the NCH Clinical Pathway Development Manual Version 6, 2022. Clinical Pathways at Nationwide Children's Hospital (NCH) are standards which provide general guidance to clinicians. Patient choice, clinician judgment, and other relevant factors in diagnosing and treating patients remain central to the selection of diagnostic tests and therapy. The ordering provider assumes all risks associates with care decisions. NCH assumes no responsibility for any adverse consequences, errors, or omissions that may arise from the use or reliance on these guidelines. NCH's clinical pathways are reviewed periodically for consistency with new evidence; however, new developments may not be represented, and NCH makes no guarantees, representations, or warranties with respect to the information provided in this clinical pathway.

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