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PEDIATRIC - MEDICAL OR CLINICAL GUIDELINE - MUHC

☒ Medication included ☐ No medication included

Title:	Neonatal Seizures: Acute Management Guidelines
This document is attached to:	MCH Vital Signs Care of an Infant in an Incubator Clinical Protocol High Alert Medication: Safe Prescribing, Preparation, Labeling, Distribution, Storage, Administration and Monitoring

1. PURPOSE

Provide guidance for the acute management of neonatal seizures in term and late preterm newborns (gestational age greater than or equal to 34 weeks, less than 28 days of life) admitted in the Neonatal Intensive Care Unit (NICU) at the Montreal Children's Hospital (MCH). This guideline also applies to the neonatal transport team working in collaboration with community pediatricians caring for babies at referring hospitals.

2. GUIDELINE APPLICABLE IN THE FOLLOWING SETTING:

- This guideline applies to the above defined population admitted to the NICU at the MCH.
- This guideline applies to nurses, neonatal nurse practitioners (NNPs), pharmacists and physicians who have read and understood it.

3. GUIDELINE HAS BEEN APPROVED BY:

- Neonatal Intensive Care Unit
- Division of Pediatric Neurology
- Pediatric Pharmacy

4. ELEMENTS OF CLINICAL ACTIVITY

Professionals are responsible to know the limits and extent of their practice as related to this guideline.

Definitions

Seizure: A seizure is a sudden, uncontrolled electrical disturbance in the brain. It can cause changes in behavior, movements, and in level of consciousness.

Neonatal status epilepticus: Summed duration of seizures comprising greater than or equal to 50% of an arbitrarily defined one-hour EEG recording.

Investigations

Upon recognition of clinical signs of neonatal seizures, the following must be initiated without delay:

1. Placement of amplitude-integrated EEG (aEEG)
2. Investigation and treatment of correctable causes (for example, but not limited to, hypoglycemia, electrolyte imbalances and infections)
3. Requisition of conventional EEG (cEEG), to be placed as soon as possible; if evening, weekend or stat day, discuss urgency with neurology
4. Consultation with neurology

Medications

The pharmacological management of neonatal seizures involves a staged approach. Before progression to the next line of treatment, the clinicians must observe the patient's clinical and electrographic response to each therapeutic stage to follow the persistence or cessation of seizures.

These suggestions can also be interpreted as an algorithm (see Annex 1). Please refer to Annex 2 for frequently asked questions on this algorithm.

Table 1. Acute pharmacological management of neonatal seizures

Stage		Medication and dosages	Next steps and notes	Monitoring
First-line	**Optional before Phenobarbital 20mg/kg**	**Midazolam.** 0.1mg/kg x 1 Give dose over 5 minutes	Consider administering Midazolam prior to Phenobarbital if the nature of the event(s) is unclear and especially if not confirmed by aEEG or cEEG, e.g., on transport. If seizure(s) persist 5 minutes after end of Midazolam bolus, proceed to phenobarbital 20 mg/kg IV x 1.	Monitor blood pressure every 15 minutes for at least 1 hour post bolus administration in addition to routine vital signs and cardiorespiratory monitoring as per MCH Vital Signs Protocol.
		Phenobarbital 20 mg/kg IV x1 Give dose over 20 minutes	If seizure(s) persist 5 minutes after end of phenobarbital bolus, give phenobarbital 10 mg/kg IV x 1. If seizure persists 5 minutes after 2nd bolus, can optionally give phenobarbital 10 mg/kg IV x1, or proceed to second-line.	Monitor blood pressure every 15 minutes for at least 2 hours post-initiation of bolus administration, in addition to routine vital signs and cardiorespiratory monitoring as per MCH Vital Signs Protocol.
Second-line		**Fosphenytoin** 20 mg Phenytoin Equivalents (PE)/kg IV x1	If seizure(s) persist 15 minutes after the end of fosphenytoin bolus, can optionally give fosphenytoin 10 mg PE/kg IV x1, or proceed to third line.	Monitor blood pressure every 15 minutes for at least 2 hours post-initiation of bolus administration, in addition to routine vital

		Give dose over 20 minutes		signs and cardiorespiratory monitoring as per MCH Vital Signs Protocol.
Third-line[1]	**Persistent seizure(s) NOT meeting criteria for status epilepticus**	**Levetiracetam** 60 mg/kg IV x1 Give dose over 20 minutes OR **Topiramate** 10 mg/kg PO x1	If seizure(s) persist, discuss further management with neurology.	Routine vital signs and cardiorespiratory monitoring as per MCH Vital Signs Protocol
	Status epilepticus	**Midazolam** 0.1 mg/kg IV x1 over 5 minutes, followed by midazolam infusion 1 mcg/kg/min IV	If seizure(s) persist, increase midazolam infusion by 1 mcg/kg/min IV every 30 minutes until seizure-free, or up to a maximum of 5 mcg/kg/min[2]. Once seizure-freedom is achieved, maintain same infusion rate for at least 24 hours of EEG seizure-freedom before starting to wean.	Monitor blood pressure every 15 minutes for at least 1 hour post-bolus administration and after each increase in infusion rate, then at least every 1 hour while on midazolam, in addition to routine vital signs and cardiorespiratory monitoring as per MCH Vital Signs Protocol.

[1]Consult medical genetics for further investigations/management (including consideration of pyridoxine trial or other vitamin-responsive epilepsies).

[2]Consider higher infusions in selected patients after discussion with neurology.

Maintenance treatment

Clinical indication and agent choice can be discussed with the neurology team.

Suggested initial dosing reference:

- Levetiracetam: 20 mg/kg/dose PO/IV q12 h
- Topiramate: 2.5 mg/kg/dose PO q12 h
- Phenobarbital: 2.5 mg/kg/dose PO/IV q12 h

The first maintenance dose can be administered approximately 12 hours after the last loading dose. The per os (PO) route of medication is preferable to the intravenous (IV) route unless it is not possible (e.g., NPO or not feeding).

Special considerations for nursing care in the NICU

- Babies admitted to the NICU for suspicion of or confirmed seizures must be admitted to an incubator in "Baby Mode" as per the Care of an Infant in an Incubator Clinical Protocol.
- Head of the baby must be placed at the foot of the bed, so that aEEG can be placed easily
- Baby must remain unclothed and uncovered in order to adequately observe clinical signs of seizures.

- If seizure suspected, if medications are given or if care is provided, the nurse must use the “Markers” function on the aEEG machine to note this or push the appropriate button on the EEG machine. Additionally, if possible, out-loud description of the event is helpful for EEG interpretation (clinical correlation).
- If the nurse observes signs of seizure, either clinically or through EEG, they must advise the physician or NNP immediately and document the following elements in nursing notes:
    - Time of onset
    - Alterations in behaviour and description of observed signs of seizure, including response to stimulation/suppression by restraint when appropriate
    - Duration of suspected seizure
    - Alterations in vital signs
    - Any interventions undertaken

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7. SPECIAL CONSIDERATIONS

This guideline provides a proposed pathway for the acute management of neonatal seizures. All treatment decisions should be made on an individual patient basis after an assessment of the patient’s condition. This is not a collective order. All medications must be legally prescribed by a licensed prescriber.

8. APPROVAL PROCESS

Institutional and professional approval

Committees	Date [yyyy-mm-dd]
☐ Adult Clinical Practice Review Committee (CPRC) (if applicable)	

Committees	Date [yyyy-mm-dd]
☐ Pediatric Clinical Practice Review Committee (CPRC) (if applicable)	
☐ Adult Pharmacy and Therapeutics (P&T) (if applicable)	
☐ Pediatric Pharmacy and Therapeutics (Peds P&T) (if applicable)	
☐ Multidisciplinary Council (MDC) (if applicable)	

9. REVIEW DATE

To be updated in maximum of 4 years (2025) or sooner if presence of new evidence or need for practice change.

10. REFERENCES

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Version History (for Administrative use only)			
Version	**Description**	**Author/responsable**	**Date**
No	Description (Creation, Approval, Revision with modifications, Revision without modifications, etc.)	Management Acronym, Function	
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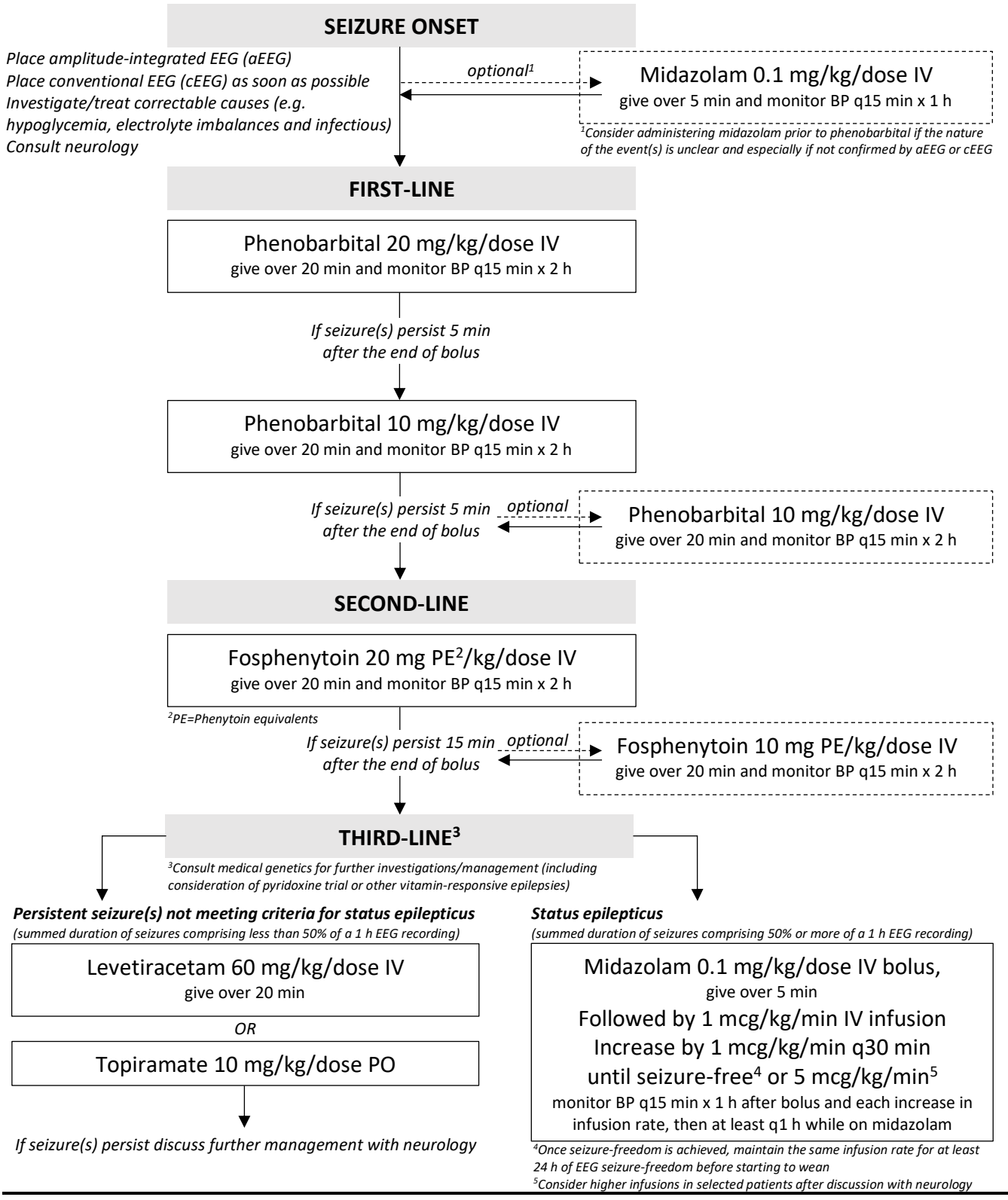
ANNEX 1. NEONATAL SEIZURES: ACUTE MANAGEMENT GUIDELINES

Please refer to next page

NEONATAL SEIZURES: ACUTE MANAGEMENT GUIDELINES

For Term and Late Preterm Newborns: (gestational age 34 weeks or more)

Abbreviations: min = minutes; h = hour(s); BP = blood pressure.



Maintenance treatment: Discuss clinical indication and agent choice with neurology team.

Initial dosing reference: • Levetiracetam 20 mg/kg/dose PO/IV q12 h • Topiramate 2.5 mg/kg/dose PO q12 h • Phenobarbital 2.5 mg/kg/dose PO/IV q12 h

Give first dose of maintenance treatment approximately 12h after last loading dose. PO route preferable unless NPO or not feeding.

ANNEX 2. FREQUENTLY ASKED QUESTIONS

Question: What is our "goal" in treating neonatal seizures?

Answer: Cessation of all electrographic and clinical seizures.

Question: Can this guideline be applied in cases of seizure recurrence after a period of seizure control?

Answer: Yes. However, it is important to remember that the management of recurrent seizures should be individualized, and can be discussed with neurology. Specific considerations include 1) the suspected etiology, and 2) the type, response, and timing of administration of previously used agents.

Question: Can this guideline be applied to preterm babies?

Answer: This guideline applies to neonates of gestational age greater than or equal to 34 weeks. Treatment of seizures in preterm newborns requires specific considerations and is a clinical challenge due to many knowledge gaps.[1]

Question: If IV access is not available, are there any alternatives?

Answer: In neonates without IV access at seizure onset, intranasal midazolam (at a dose of 0.1 mg/kg) instead of IV midazolam can be considered, while obtaining IV access. In neonates with hypoxic-ischemic encephalopathy, we especially suggest avoiding the intramuscular route due to potential coagulopathy and bleeding risk.

Question: Why is phenobarbital the suggested first-line agent?

Answer: Only few clinical trials are available to guide seizure treatment algorithms. Existing evidence supports phenobarbital as the first-line agent for neonatal seizures treatment. A recent multicenter, randomized, blinded, controlled, phase IIb trial showed that 80% of patients randomized to phenobarbital (20 mg/kg loading dose, with an additional 20 mg/kg if seizures persisted) as the first antiseizure medication remained seizure-free for 24 hours, compared to only 28% of patients randomized to levetiracetam (40 mg/kg loading dose, with an additional 20 mg/kg if seizures persisted).[2]

Question: What is the purpose of the optional midazolam, which can be administered prior to phenobarbital?

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[1] Pisani, F. & Spagnoli, C. Acute symptomatic neonatal seizures in preterm neonates: etiologies and treatments. *Seminars Fetal Neonatal Medicine* **23**, 191–196 (2018).

[2] Sharpe, C. *et al.* Levetiracetam Versus Phenobarbital for Neonatal Seizures: A Randomized Controlled Trial. *Pediatrics* 145, e20193182 (2020).

Answer: Compared to phenobarbital, midazolam has a shorter elimination half-life. As such, its use can be considered in cases where the epileptic nature of clinical events is unclear (for example, during transport), pending confirmation with amplitude-integrated EEG (aEEG) or conventional EEG (cEEG).

Question: Why is the suggested administration rate over 20 minutes for phenobarbital loads?

Answer: Rapid IV administration of parenteral phenobarbital has been associated with hypotension and respiratory depression.

Question: In which cases should "optional" top-up bolus doses be administered?

Answer: Clinical judgment can guide administration of "optional" top-up boluses. For example, "optional" top-up boluses with the same agent, before advancing to the next agent, can be considered in cases of partial response to the initial loading dose(s). In contrast, in cases where there is no improvement with initial loading dose(s), advancing to the next agent without administration of an "optional" top-up bolus dose can be considered.

Question: What is the difference between phenytoin and fosphenytoin?

Answer: Fosphenytoin, a prodrug of phenytoin, has a reduced incidence of cardiovascular (i.e., hypotension and arrythmia) and extravasation-related side effects when compared to phenytoin.

Question: Should we routinely check phenobarbital or phenytoin levels?

Answer: Clinical judgment of the health care team can guide the request for drug levels, taking into account the patient-specific clinical context.

Question: When should treatable vitamin-responsive epilepsies (e.g., pyridoxine-dependent epilepsy) be considered?

Answer: Treatable vitamin-responsive epilepsies should be considered early, particularly in neonates with seizures unresponsive to conventional antiseizure medications, or if the cause of the seizures is not known. Medical genetics should be consulted for further investigations/management.

Question: Should the maintenance antiseizure medication be identical to the loading agent?

Answer: The choice of maintenance agent(s) should be individualized, and can differ from the agent(s) used for loading doses. Specific options can be discussed with neurology.