GUIDELINE

# Seizures: Neonatal

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| **Scope (Staff):** | Nursing and Medical Staff |
| **Scope (Area):** | NICU KEMH, NICU PCH, NETS WA |

**Child Safe Organisation Statement of Commitment**

CAHS commits to being a child safe organisation by applying the National Principles for Child Safe Organisations. This is a commitment to a strong culture supported by robust policies and procedures to reduce the likelihood of harm to children and young people.

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*Only use this box if relevant (e.g. clinical document or available on an external website)*

## Contents

## Aim

The guideline aims to describe the management of neonatal seizures.

## Risk

If this guideline is not adhered to, it may increase morbidity and mortality in newborn infants with seizures.

## Background

Neonatal seizures (NS) occur in 1.8-5 per 1000 live births, with the majority occurring in the first few days of life.[1] Seizures occur more frequently in the neonatal period than at any other time of life.

## Principles / Key points

- The time, duration and classification of seizures should be recorded. See Appendix 1: Clinical Classification of Seizures for descriptions.
- Often, in the same neonate, more than one seizure type may be seen.
- Factors that provoke seizures (e.g., handling) and progression of events should also be noted.
- Neurological observations should be recorded on MR494 – Neonatal Neurological Observation Chart.

## Aetiology

An underlying aetiology (Table 1) can be identified in nearly 90% of neonates with seizures with appropriate investigations.

### Table 1: Aetiological classification of neonatal seizures[2]

| |
|---|
| Hypoxic Ischaemic Encephalopathy |
| Hypoglycaemia, Hypocalcaemia, hypomagnesemia, hyponatremia, hypernatremia, hyperbilirubinemia |
| Intracranial haemorrhage: Subdural, Subarachnoid, IVH |
| Ischaemic infarction or Sino venous thrombosis |
| Intracranial infections: Meningitis; Encephalitis: HSV; Enterovirus |
| Congenital malformations of the CNS |
| Inborn errors of metabolism |
| Idiopathic |
| Intoxications: local anaesthesia |

Differentiating epileptic seizures from seizure-like activities: While dealing with a neonate with abnormal movement or behaviour, an important step is to know whether they are seizures or paroxysmal non-epileptic motor phenomena.[3] The following common abnormal movements must be considered in the differential diagnosis of neonatal seizures (Table 2).[4]

**Table 2: Non-epileptic movements which can mimic neonatal seizures**

| | Clinical features | EEG |
|---|---|---|
| Jitteriness/Tremor | Irregular, stimulus sensitive disappear when the limb is held firmly | Normal |
| Benign neonatal sleep myoclonus | Repetitive, generalised, focal, or multifocal rhythmic myoclonic jerks that occur during sleep in otherwise healthy normal neonates. Disappear when the neonate is awake. | Normal |
| Motor automatisms | Repetitive stereotypical movements such as pedalling, cycling, boxing, swimming, drum beating type of movements or myoclonic jerks | Normal |
| Dystonic and tonic movements | Generalised stiffening of all four limbs | Abnormal usually but, no seizures |
| Hyperekplexia | Excessive startle response | Normal |
| Paroxysmal extreme pain disorder | Flushing, stiffening or tonic phenomenon and bradycardia | Normal |
| Opsoclonus | Chaotic rapid multidirectional eye movements. Consider Neuroblastoma | Normal |
| Cardiac arrhythmias | Long QT syndrome, WPW syndrome etc | Hypoxic slowing during prolonged episodes |

## Diagnosis

Clinical examination alone has the potential to underdiagnose or over-report seizures.[1] All infants with suspected seizures or at risk of seizures should be monitored with limited channel EEG with amplitude integrated aEEG (Brainz® monitor). However, given the variable sensitivity and specificity, aEEG alone is not recommended for seizure detection in neonates.[5,6]

It is important to request an urgent conventional multichannel video-EEG (V-EEG) as soon as possible.

## Investigations

Investigate and treat the underlying abnormality.

### History

Detailed history could provide clues to the cause of neonatal seizures (Table 3).[4]

### Table 3: Points to review in history

| | |
|---|---|
| Maternal diseases | Preeclampsia, Herpes<br>Chorioamnionitis<br>Antepartum haemorrhage,<br>Excessive fetal movements |
| Maternal medications | Antidepressants<br>Opioid analgesics<br>Benzodiazepines<br>Alcohol |
| History of perinatal asphyxia | Fetal heart rate monitoring<br>Growth restriction<br>Difficult labour<br>Apgar scores<br>Delivery room resuscitation details<br>Type of delivery<br>Cord blood gases |
| Parental description of the observed seizures | Ask if parents have taken a video of the episode. Encourage them to do so. |

## Clinical Examination

A thorough examination of the nervous system as well as other systems is important. Initial investigation (Table 4) should focus on identifying conditions that are treatable and if untreated can lead to severe brain damage.

### Table 4: Emergency investigations of potential treatable conditions

| **Condition** | **Investigations** | |
|---|---|---|
| Metabolic | Blood glucose<br>Plasma sodium<br>Potassium<br>Calcium<br>Magnesium | Blood gas<br>Lactate<br>Ammonia<br>Liver function tests<br>Renal function tests |
| Infections | Full blood count<br>CRP<br>Blood culture<br>CSF microscopy and culture and PCR for HSV and other viruses | Throat and rectal swabs for HSV<br>Blood PCR for HSV<br>Urine microscopy and culture |
| Intracranial haemorrhage | Cranial ultrasound<br>MRI or urgent CT scan if extradural or subdural haemorrhage is suspected | |

Once the above investigations are completed, the next line of investigations will need to focus on conditions where curative therapy may not always be available, but a definitive diagnosis will facilitate provision of supportive treatment and prognostication (Table 5).

**Table 5: Investigations to make a diagnosis, to facilitate prognostication and supportive treatment (curative therapy may not always be available)**

| Condition | Investigations |
|---|---|
| Disorders of amino acid metabolism | Plasma, CSF, and urine amino acids |
| Disorders of organic acid metabolism | Urine organic acids<br>Plasma acyl carnitines |
| Mitochondrial and respiratory chain disorders | Blood and CSF lactate and pyruvate<br>Muscle and/or liver enzymology<br>Specific gene testing |
| Peroxisome disorders | Response to pyridoxine under EEG monitoring<br>Urine, plasma and/or CSF aminoadipate semi aldehyde **or**<br>Piperideine-6-carboxylate |
| Pyridoxal phosphate-responsive seizures (PNPO deficiency) | Response to pyridoxal phosphate,<br>CSF amino acids and biogenic amines, urine vanillactate |
| Infections | CSF, blood, throat swab and rectal swab PCR for enterovirus, para-echo virus, and other viruses. |
| Chromosome disorders, neonatal epileptic encephalopathies | Chromosome analysis<br>Microarray<br>Whole-exome sequencing<br>Epilepsy gene panels |
| Idiopathic and refractory seizures | Liver biopsy<br>Muscle biopsy<br>Skin biopsy for DNA storage and analysis |
| Cerebral malformations, neuronal migration disorders, metabolic encephalopathies | MRI<br>CT scan<br>Cranial ultrasound |

## Imaging

The standard imaging studies are head ultrasound and MRI of the brain. If subdural or extradural haemorrhage is suspected, do an urgent CT scan.

# Treatment

The main principles of management are anti-seizure medication, supportive management, and treatment of the underlying aetiology. Supportive management might necessitate the administration of IV fluids, mechanical ventilation, and correction of hypotension, if required. Conditions such as meningitis, hypoglycaemia, hypocalcaemia, hypomagnesemia, electrolyte imbalances and HSV encephalitis should be treated aggressively.

Pharmacological treatment: Neonatal seizures still lack safe and effective treatment.[8] Treatment options are limited: what to treat, which anti-seizure medication (ASM) to use and for how long, are the issues that are still debated.[9]

## Antiseizure medication (ASM)

The commonly used ASMs are Phenobarbitone , Phenytoin, Levetiracetam, Midazolam, Lignocaine, Clonazepam, Topiramate and Oxcarbazepine. Refer to Neonatal Medication Protocols for dose and administration, adverse effects, and other details.

Request a neurology consult, especially if the seizures are not responding to first-line therapy.

Phenobarbitone continues to be the first line ASM since the NeoLev study found 80% of neonates (24 of 30) randomised to PHB remained seizure-free for 24 hours as compared with only 28% of subjects (15 of 53) randomised to Levetiracetam (p <0.001).[10]

Second-line ASMs include Levetiracetam, Phenytoin, Midazolam, and Lignocaine.

A trial of Pyridoxine may be attempted in neonates with seizures unresponsive to second-line ASMs without an identified aetiology.[11]

Following cessation of acute provoked seizures (electroclinical or electrographic) without evidence for neonatal-onset epilepsy, discuss with neurologists if ASMs could be discontinued before discharge home.[11] In some cases, ASMs may need to be continued after discharge.

# Supportive and Follow-up Care

Treatment of seizures is only one aspect of care. Neuro-critical care for a neonate with seizures involves multiple disciplines, including neurology, neonatology, radiology, haematology, biochemistry, microbiology and many more. Neonates with seizures need to be followed up and assessed appropriately, and early interventional strategies must be instigated proactively. Besides medical care, the family needs supportive care, which includes emotional, psychosocial, and financial aspects, both in the short and long term.

## Summary

The management of neonatal seizures is challenging. They are difficult to diagnose and treat and are associated with adverse outcomes.

Most neonatal seizures have no clinical correlates–they are electrographic-only (subclinical) seizures.

The gold standard investigation to diagnose seizures is continuous V-EEG, preferably for about 24 hours; however, resource limitations hinder its universal applicability. In absence of V-EEG, aEEG is often used despite its variable sensitivity and specificity to detect neonatal seizures.

Initial investigations and management should focus on potentially treatable conditions, where delay in treatment can lead to worse outcomes.

MRI, ultrasound, and CT scans can complement each other as imaging modalities.

Phenobarbitone, phenytoin, midazolam, levetiracetam and lignocaine are commonly used ASMs in the neonatal period., but the evidence about their efficacy and safety is limited.[12] High-quality RCTs evaluating various ASMs in the neonatal population are needed.[1]

## Related CAHS internal policies, procedures and guidelines

Neonatology Guidelines

- Brainz Monitor: Low Impedance Needle Electrodes
- Hypoxic Ischemic Encephalopathy (HIE) and Therapeutic Hypothermia

Neonatology Medication Protocols –

- Clonazepam
- Levetiracetam
- Lignocaine
- Midazolam
- Phenobarbitone
- Phenytoin

## References and related external legislation, policies, and guidelines


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## Appendix 1: Clinical Classification of Seizures

| Type of Seizure | Clinical Features |
|---|---|
| **Subtle**<br>(More common in the premature infant) | • Abnormal behaviour, autonomic or motor (not classified as other categories)<br>• Ocular – eye deviation, staring episode, eyelid fluttering, repetitive blinking<br>• Facial – repetitive sucking, mouthing, drooling, chewing, tongue protrusion<br>• Limbs – cycling, boxing stepping movements<br>• Autonomic – apnoea, tachycardia, hypertension, pupil changes, increased salivation |
| **Clonic**<br>(Rhythmic jerks that do not stop with gentle restraint) | • Focal – 1 to 3-second jerking, localised to a body part<br>• Multifocal or generalised – several body parts jerking simultaneously or migrating |
| **Myoclonic** | • Focal – flexor jerking of a limb<br>• Multifocal or generalised – bilateral jerking of upper limbs +/- lower limbs |
| **Tonic** (posturing) | • Focal – posturing of a limb / trunk / neck<br>• Multifocal or generalised – extension of lower limbs with either upper limb extension / flexion |

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