NEONATAL SEIZURES

Neonatal seizures are the commonest neurological emergency and are associated with poor neurodevelopmental outcome. They are mostly provoked seizures caused by an acute brain insult such as hypoxic ischemic encephalopathy (HIE), ischemic stroke, intracranial hemorrhage, infections of the central nervous system, or acute metabolic disturbances. Early onset epilepsy syndromes are less common.

Definition

The International League Against Epilepsy (ILAE) defines seizures as a transient occurrence of signs and/or symptoms due to abnormally excessive or synchronous neuronal activity in the brain.

The American Clinical Neurophysiology Society classifies seizures into

- Clinical-only
- Electro-clinical
- Electrographic-only seizures.

Electrographic seizures are defined as a paroxysmal abnormal, sustained change in the EEG characterized by a repetitive and an evolving pattern with a minimum 2 μV voltage (peak to peak) and a duration of at least 10 s.

Incidence

The incidence of neonatal seizures is estimated to be 1–5 per 1000 live births in HIC and widely varies from 36–90 per 1000 live births in LMIC.

Only 10%–15% of seizures in the neonatal period are the first manifestation of an epilepsy syndrome (unprovoked seizures), typically due to an underlying structural or genetic etiology.

Etiology based on age:

- **Day 1-4**:
  - HIE
  - Maternal drug withdrawal
  - IVH, Focal infarction

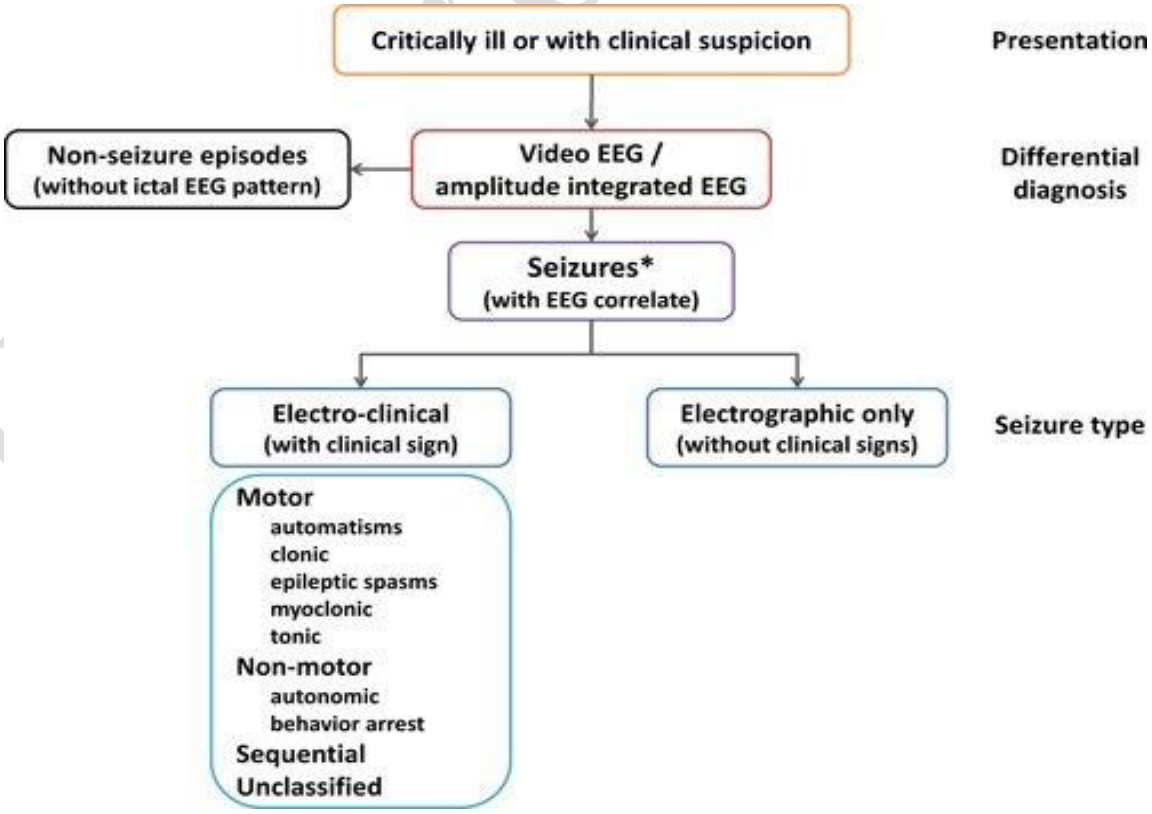
- Acute metabolic- calcium/magnesium/sodium/hypoglycaemia
- IEM- galactosemia, urea cycle disorders

➢ **Day 4-14**:

- Meningitis
- Encephalitis
- Hyperbilirubinemia, late onset hypocalcaemia
- Epilepsy syndromes- fifth day fits, early myoclonic epilepsy

➢ **2-8 weeks**:

- HSV meningitis
- IEM- urea cycle defects, amino acidopathies
- Adrenoleukodystrophy
- Cortical malformations(lissencephaly)
- Tuberous sclerosis, Sturge weber syndrome



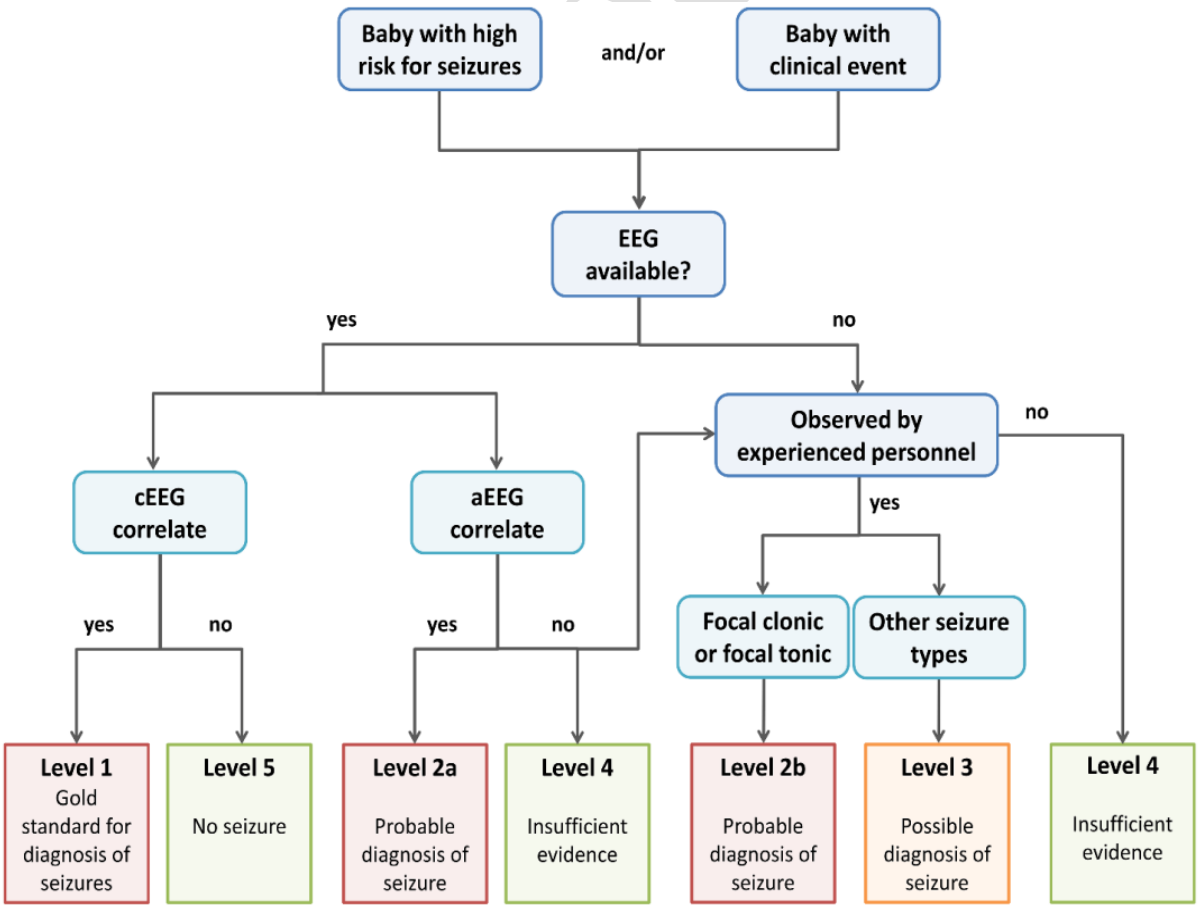
Electrographic-only seizures

Most neonatal seizures are electrographic-only, characterized by the presence of an electrographic seizure on electroencephalography (EEG) that has no overt clinical manifestations.

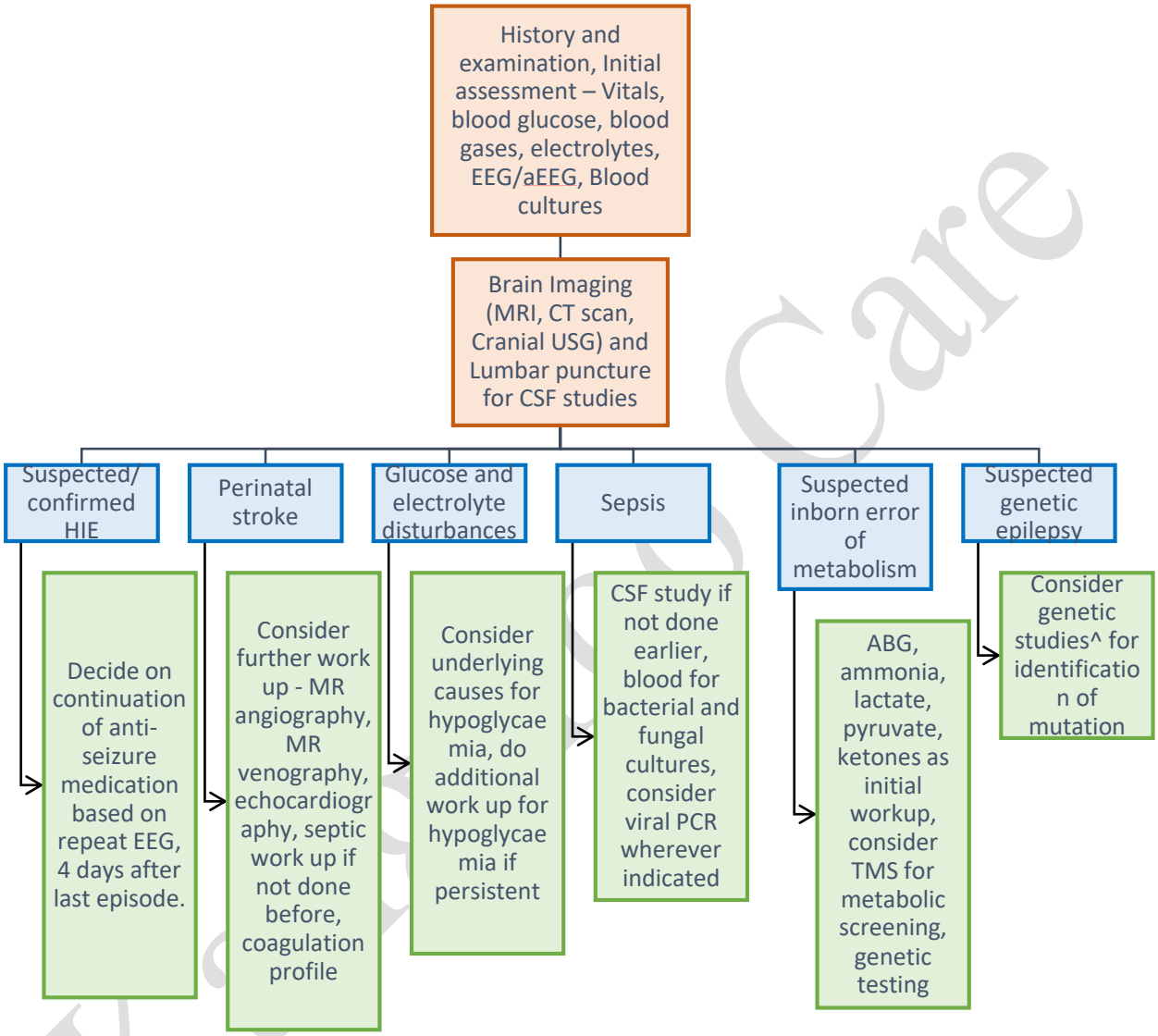
DIAGNOSIS

Clinical diagnosis is unreliable due to the risk of both under and overdiagnosis of seizures. Underdiagnosis is due to missing discreet seizure manifestations and because over 50% of seizures are electrographic only while overdiagnosis is due to misdiagnosing abnormal nonepileptic movements as seizures. EEG (multi-channel video continuous EEG -cEEG) is considered the gold standard for the diagnosis of seizures in newborns.

This flowchart will help to determine the diagnostic certainty of neonatal seizures depending on the available diagnostic method and seizure type.



Evaluation of seizures



- aEEG provides an assessment of background activity (which provides information on the degree of brain injury for example in HIE) and can identify seizures. However, the sensitivity of aEEG is lower than full EEG as short seizures (<30 s) or low amplitude seizures are often missed.
- The American Clinical Neurophysiology Society recommends EEG monitoring for 24 h in all neonates who are at high risk for seizures, such as neonates with acute brain injury, clinical encephalopathy, or abnormal paroxysmal events.

Management

- Diagnosis and treatment of underlying etiology is crucial for effective control of neonatal seizures, especially secondary to metabolic derangements.
- Any hypoglycemia must be promptly corrected. Brief seizures secondary to transient metabolic derangements (hypocalcemia, hypoglycemia, hypomagnesemia, or hyponatremia) may not warrant anticonvulsant medication, if seizures cease upon correction.

Anti- seizure therapy

- In the absence of evidence, it is recommended that one should commence antiseizure medications when the overall seizure burden is more than 1–2 min on EEG or aEEG.
- Timely intervention is crucial as 43% of the neonatal seizures may progress to status epilepticus, if untreated.
- Since it is assumed that clinical and subclinical seizures differ primarily in anatomical origin, it is important to treat subclinical seizures as well.
- Clinical manifestations are more likely when the motor cortex is involved. Furthermore, with antiseizure treatment, seizures are more likely to be electrographic-only due to uncoupling.
- Neonates in a deep coma, on heavy sedation or muscle relaxation may also not exhibit clinical manifestations

Phenobarbitone

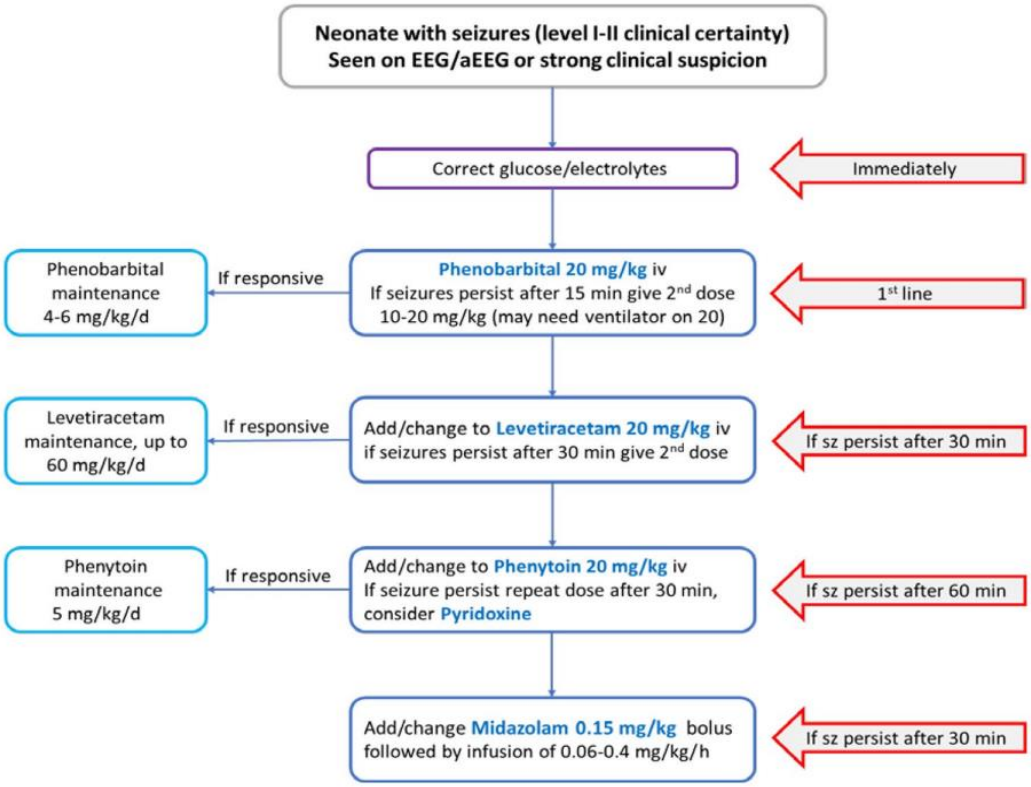
- Phenobarbital remains the preferred first-line agent for managing neonatal seizures worldwide
- Eliminated by the liver and kidney - infants with impaired hepatic or renal function, such as those with HIE, may have a reduced rate of elimination.
- Based on the NEOLEV2 study, phenobarbital and not levetiracetam, should be used as the first treatment option for neonatal seizures

OTHER DRUGS

When a reversible, acute metabolic etiology for seizures is suspected and investigation results are pending, acute treatment with benzodiazepines with a short half-life (lorazepam, midazolam) may be considered.

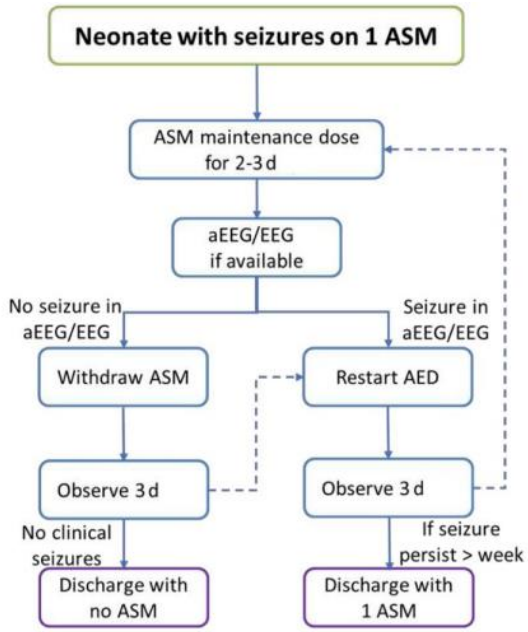
- Phenytoin/ Fosphenytoin, levetiracetam, and midazolam may be selected as a second-line antiseizure drug.
- Phenytoin/Fosphenytoin needs to be given under cardiac monitoring, which may be difficult in some low resource settings.
- Levetiracetam is, therefore, considered a better option, but data for its efficacy as a second-line choice are limited.

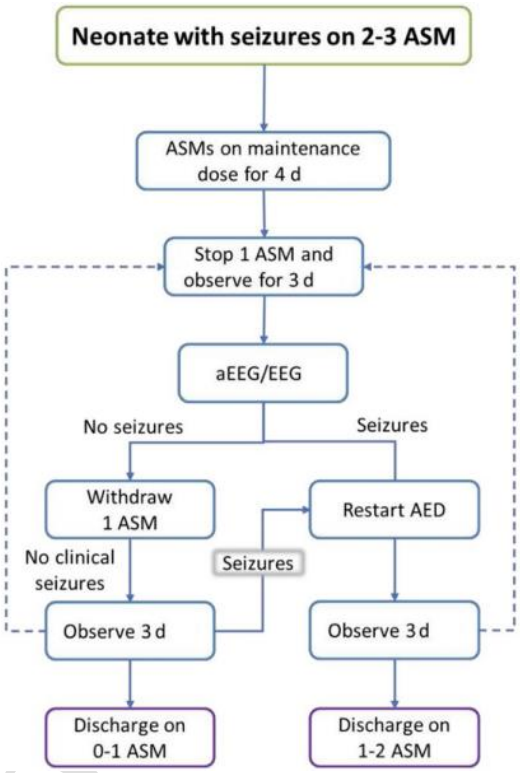
Medication	Dosage	Common side effects	Remarks
Phenobarbitone	Loading dose: 20 mg/kg intravenously, repeated once as needed (consider 10 mg/kg, if notventilated) Maintenance dose: 3–6 mg/kg/d Target level: 40 mcg/mL	Respiratory depression Depressed consciousness Hypotension Hepatotoxic Blood dyscrasia	Prolonged half-life first week of life and preterm (43–217 h) may lead to increased duration of NICU stay Risk of dose error because of available strength [200 mg/mL] Renal and hepatic excretion can be affected in HIE
Phenytoin/Fosphenytoin	Loading dose: 20 mg/kg PE intravenous, over 20 min or at rate of 3 mg/kg/min PE Maintenance dose: 2.5–5 mg/kg/d in 2 divided doses Target level: 10–20 mcg/mL Administer over 10 min	Infusion site irritation Arrhythmia Rash Hepatotoxic Blood dyscrasia	Cardiac monitoring required Phenytoin poor oral bioavailability Fosphenytoin preferred over phenytoin Levels likely higher in therapeutic cooled infant, and hence, maintenance dose needs to be titrated to drug levels
Levetiracetam	Loading dose: 40–60 mg/kg/d intravenously Maintenance dose: 30–60 mg/kg/d in 3 divided doses Optimal dosing & target level not known	Mild sedation Irritability	Limited information regarding dosing side effect for the neonatal population Adjust dose in renal impairment
Midazolam	Loading dose: 0.15 mg/kg as bolus intravenously over 10 min Maintenance dose: Infusion started at 0.06 mg/kg/h and titrated upwards to effect up to maximal 0.3 mg/kg/h	Respiratory depression Depressed consciousness Hypotension	Developing brain may have an excitatory response to benzodiazepines rather than inhibition, hence, can potentiallyworsen seizures. Wean gradually



STOPPING ANTISEIZURE DRUGS

- The decision to stop antiseizure medication should be governed by the risk of seizure recurrence.
- In the case of acute symptomatic seizures, early discontinuation of antiseizure drugs before or shortly after discharge is now generally recommended as this seizure usually resolves within two to three days and the risk of recurrence is low.
- If seizures were difficult to control, then reducing the number of antiseizure medications to one or two in the neonatal period is preferable and phenobarbital should be the last drug to be discontinued.
- In a newborn where seizures could not be controlled or newborns with early onset epilepsy, antiseizure medications should be maintained and the newborn should be referred to a child neurologist for the decision to, if, and when to wean medication.





PROGNOSIS

- Advances in neonatal intensive care have yielded a reduction in mortality in infants with neonatal seizures from about 40% to < 20%, with < 10% mortality in term infants.
- Long term sequelae in infants with neonatal seizures, including cerebral palsy and intellectual disabilities occur at a high rate of up to 30% to 35% with post neonatal seizures occurring in up to 20%.
- Most important factor is underlying aetiology. Normal development can be expected in infants with benign idiopathic neonatal seizures and in 90% of those with primary SAH, whereas only 50% of those in HIE and fewer in brain malformation.

REF: Indian Journal of Paediatrics (2022), Cloharty, Fanaroff, ILAE

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