NWNODN GUIDELINE

Title:	**Seizure Guideline**
Reference number	**GL-ODN-23**
Main Author (s)	**Dr Dev Kumar, Rebecca Hinton, Dr Dipak Ram, Dr Bivan Saha, Dr Manigandan Chandrasekaran.**
Target Audience	**NWNODN Clinicians**
Ratified by:	**SMT + NSG**
Date Ratified:	**28/6/24**
Review Date:	**28/6/27**
Version:	**1**
Document status:	**Draft**

Date	Version	Author	Notes
June 2024	**1.0**	Dr Dev Kumar, Rebecca Hinton, Dr Dipak Ram, Dr Bivan Saha, Dr Manigandan Chandrasekaran.	Document creation

Management of Neonatal Seizures

1. Introduction

Epileptic seizures are relatively common in neonates and the incidence of seizures in term babies is approximately 0.5-3 out of 1000 live births. The incidence is higher in preterm babies ranging from 1-13% of very low birth weight babies [1].

2. Aetiology

There are many causes for neonatal seizures, but only a few conditions account for most seizures. Table 1 summarises the typical and most common causes of neonatal seizures which can be differentiated by the time of onset.

Few seizures are idiopathic and at term, hypoxic-ischaemic encephalopathic (HIE) is the most common underlying cause, typically with onset 6-8 hours after the hypoxic insult but usually within the first 24 hours of life.

Table 1:

Time of Onset	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6 onwards
Seizure aetiology	Structural, developmental brain abnormalities 3-17% Intrauterine (congenital) infection Pyridoxine dependent/pyridoxal phosphate responsive epilepsy 3-4% Idiopathic 2%					
	Perinatal asphyxia/HIE 30-53% Intracranial haemorrhage 7-17% Perinatal stroke 6-17% Sepsis/Meningitis 2-14% Hypoglycaemia 0.1-5% Maternal Drug withdrawal 4% Perinatal trauma					
		Hypocalcaemia/Hypomagnesaemia 4-22% Hypoglycaemia 0.1-5% Hypo-hypernatraemia Benign familial neonatal convulsions				
			Aminoacidopathies 3-4% Galactosaemia 3-4% Ketotic and non-ketotic hyperglycinaemia 3-4% Follinic acid-responsive seizures 3-4% Glucose transporter type 1 deficiency 3-4% Early myoclonic epilepsy			
				Benign neonatal seizures 1% Migrating partial seizures of infancy		

Aetiology and frequency of neonatal seizures determined by time of onset. Adapted from Pressler[1] and Appleton & Gibbs[2]

History:

This is very important to clarify in any neonate presenting with possible seizures.

- It is vital that a full antenatal, maternal and family history is taken. This includes screening for maternal genitourinary infections (i.e. herpes simplex) as well as confirming the partner's status.
- Check if any abnormalities noted on antenatal scans.
- Take a full drug history including prescribed and illicit drugs. It is also important to exclude neonatal abstinence syndrome.
- History of consanguinity, multiple miscarriages and early childhood deaths of previous children may be significant for metabolic or genetic pathology.
- Family history of epilepsy or seizures is important to note.
- Lastly, full labour and delivery details (including cord gases if available) must be sought in view of potential perinatal asphyxia.

3. Clinical Presentation

Seizures in neonates are best defined in clinical terms as an abnormal paroxysmal event (with or without **electroencephalogram (EEG)** seizure activity) or electrographically as sustained epileptiform activity in the EEG. In some clinical settings up to 85% of seizures seen on EEG are clinically silent leading to significant underestimation of seizure burden [1].

Presentation of neonatal seizures is different to seizures in older children and adults as they do not easily fit into the International League against Epilepsy classification of epileptic seizure types.

Movements that are frequently **epileptic** include [3]:

- Focal/multifocal clonic jerking of the limbs that does not improve with holding the affected joint
- Tonic seizures with sustained posturing of limb and trunk (focal or generalised)
- Tonic eye deviation without limb involvement, associated with autonomic phenomena
- Clonic thrusting of tongue associated with clonic movements of limbs/tonic movement of eyes
- Generalised myoclonic jerks (rapid, brief, shock like jerks)
- Epileptic spasms

Some classifications also include many movements as **subtle neonatal seizures** which include [1]:

- Ocular phenomena (staring, blinking, roving eye movements)
- Oral phenomena (mouthing, chewing, sucking, lip smacking, smiling)
- Autonomic phenomena (change in blood pressure and/or heart rate, pallor, increased salivation or secretions, central apnoea but rarely as the only seizure manifestation)
- Fragmentary body movements (swimming, cycling, pedalling)

Non Epileptic movements which mimic Seizures:

a) **Jitters:** 40% of healthy term neonates are jittery within 3 days of birth. Jitters are characterised by high amplitude, low frequency jerky movements that stop on holding the affected body part. They are not accompanied by ocular phenomena and are sensitive to changes in external stimuli. They can be secondary to hypoglycaemia and hypocalcaemia but otherwise do not warrant further investigation.

b) **Exaggerated startle:** this is a jump, jerk or moro reflex that is brought on by an external stimulus such as a loud noise or being handled when not expected. This does not require any

investigation or treatment, however must be differentiated from hyperekplexia. This is a rare condition caused by a mutation in the glycine receptor genes. If present this causes excessive startle, hypertonia and stiffness in response to stimuli leading to apnoea. A simple bedside test that can be used is the glabellar tap test. Neonates with this condition will have excessive startle or tonic stiffening to this test and will fail to habituate to repeated taps. If hyperekplexia is suspected, discussion with paediatric neurology is required and treatment with clonazepam is often suggested.

c) **Benign neonatal sleep myoclonus:** these are episodes of jerking movements that occur only during sleep (often just after falling asleep) or on waking up. The onset of this phenomenon is usually within the first 14 days of birth and in most cases it resolves by 3-6 months.

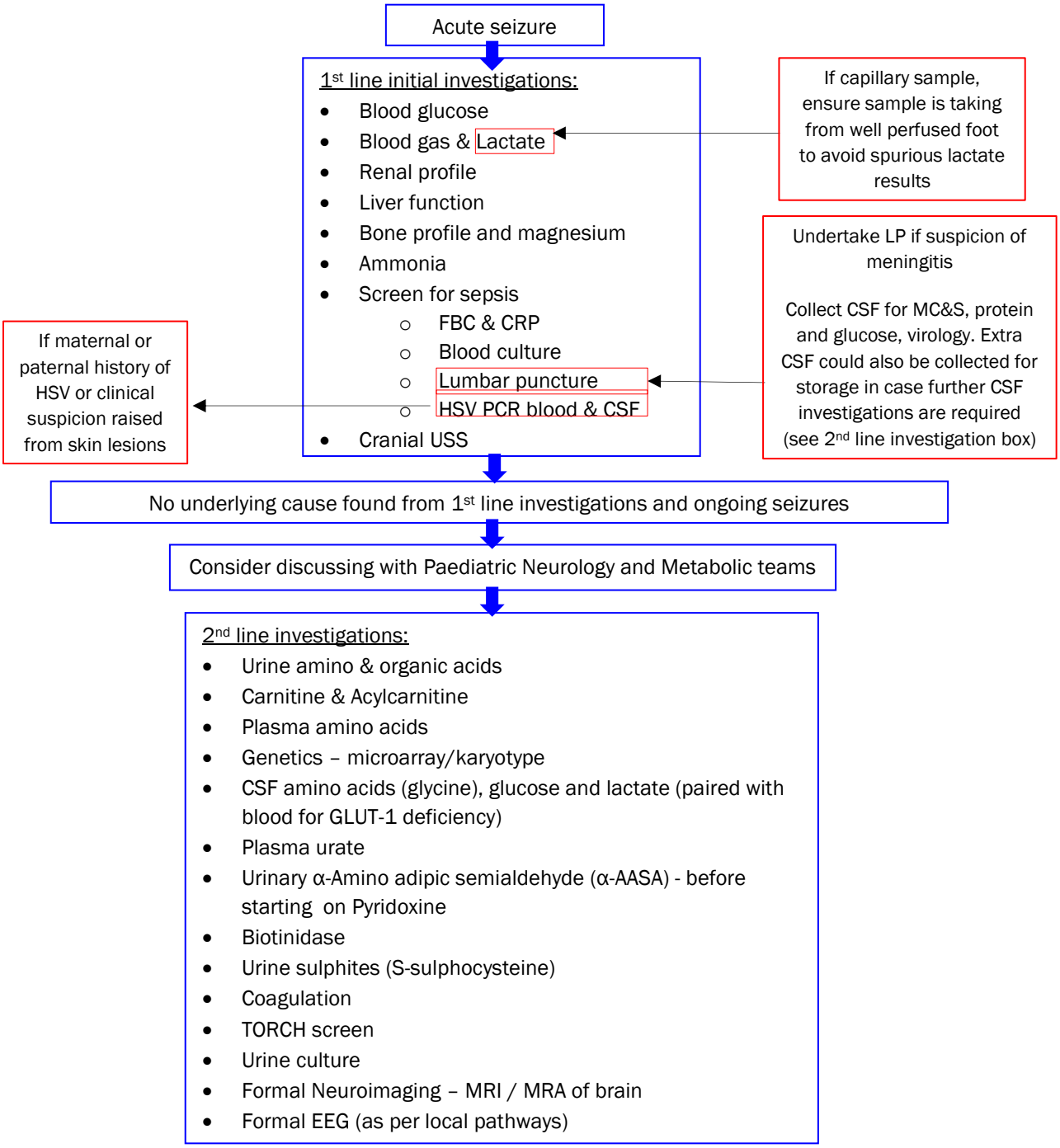
4. Investigations

Initial investigations for neonatal seizures should look for common aetiologies which require prompt/specific treatment (**see Flow Chart 1 - Stepwise Guide to Investigations**).

If the 1st line investigations and review of the antenatal/birth/maternal history do not reveal a potential underlying cause and the neonate continues to have seizures, it may be helpful to discuss with the **Paediatric Neurology** and **Metabolic** teams. It is helpful to do this prior to undertaking 2nd line investigations to avoid the need to repeat blood and CSF investigations.

Certain clues to the underlying aetiology may be present such as history of perinatal asphyxia causing HIE or maternal narcotic abuse causing neonatal abstinence syndrome so this may not need full investigation but other causes such as hypoglycaemia, electrolyte derangement and central nervous system (CNS) infection may co-exist and so still may need excluding.

Flow Chart 1 - Stepwise Guide to Investigations



a) Cerebral Functioning Monitoring (CFM)

CFM (amplitude integrated or aEEG) should be used if there is suspicion of seizure activity so that correlation between clinical symptoms and electrical activity can be made.

If any suspicion of seizures two channel aEEG should be used.

Be aware that CFM is prone to high false positive and false negative errors.

Also, in preterm neonates, it can be difficult to interpret the aEEG findings and decision to use CFM should be guided by the neonatal consultant on duty.

b) Neuroimaging

Cranial USS is readily available as a useful 1st line investigation for exclusion of gross CNS pathology (CNS malformations, intra-ventricular haemorrhage). However, if a neonate continues to have refractory seizures or has abnormal inter-ictal neurological signs, appropriate neuro imaging should be requested, on discussion with the Consultant Radiologist to detect other pathologies e.g. cerebral infarction, subarachnoid/subdural haemorrhage or cerebral malformations. All babies with HIE would require MRI – see guidelines on therapeutic hypothermia for HIE.

c) **Formal 12 lead EEG**

This should be considered if seizures persist, are refractory to medical treatment or if no clear underlying cause is found. Formal EEG should be organised with the clinical neurophysiology department following local pathways. Any requests for an EEG should be directed by a consultant, usually after discussion with the Paediatric Neurologists.

5. Treatment

Untreated seizure activity can increase the insult to the neonatal brain.

Consider treatment if Seizures are **prolonged lasting greater than 5 minutes* or frequent i.e. 2 or more episodes in 30 minutes** (treatable metabolic disturbances should be excluded).

***If high risk of seizure background abnormality (e.g: babies with HIE), consider treating earlier (greater than 3 min).** Where possible, clinical seizures should be correlated with electrical activity on aEEG before initiating treatment.

For pure 'electrical seizures' consider a different threshold – see next page.

Flow Chart 2 - Stepwise Guide to Seizure Treatment

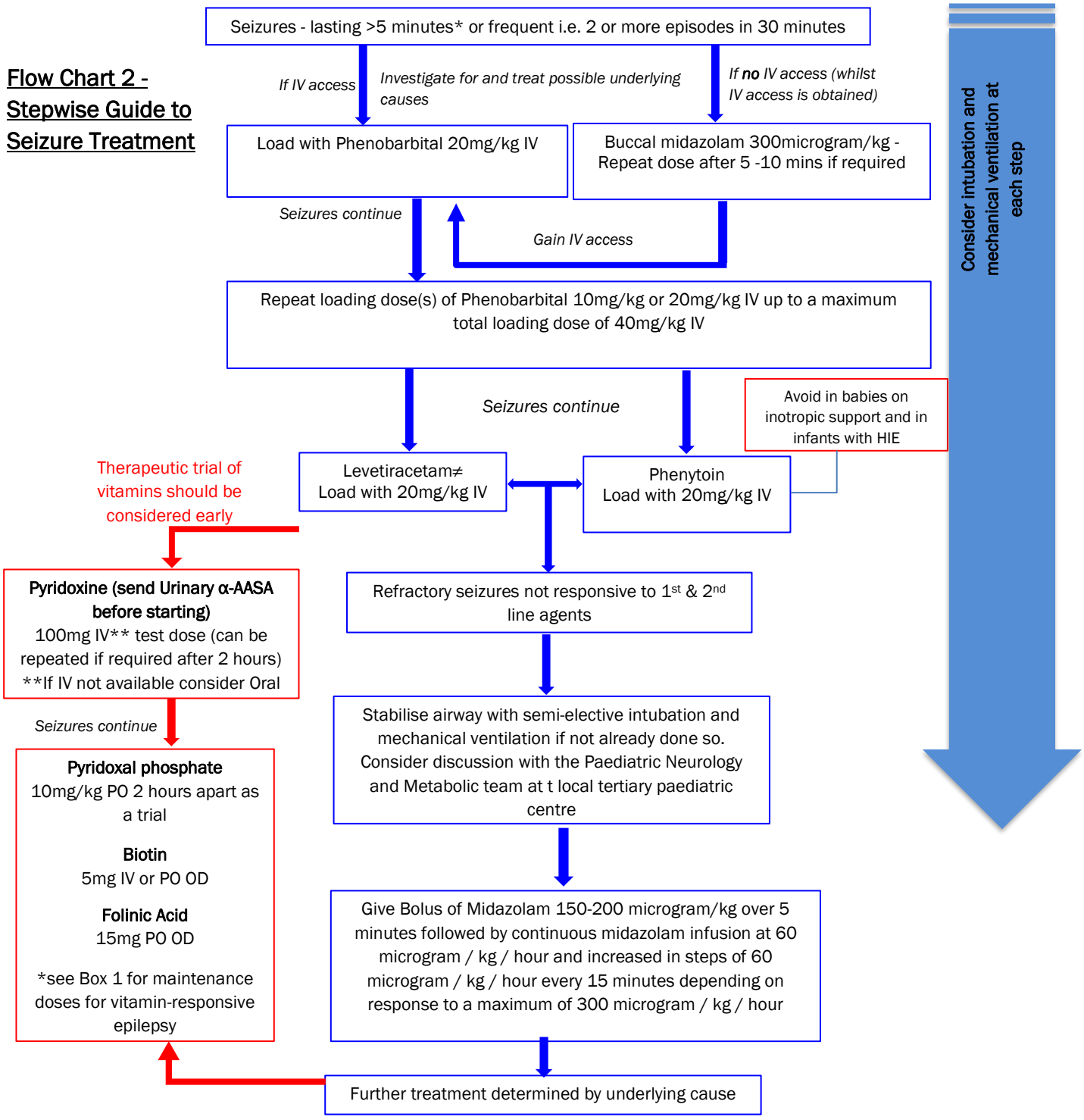


Table 2 : Seizure Medication Summary			
Medication	Acute treatment	Maintenance	Notes
Phenobarbital (phenobarbitone)	Initial loading dose: 20 mg / kg **IV** (1) Subsequent loading doses: 10 – 20 mg / kg **IV** Maximum total loading dose should not exceed 40 mg / kg (2) (3)	Oral or IV*: 2.5-5 mg / kg every 24 hours, adjusted according to response and therapeutic levels.	**Respiratory depression can occur if IV is given too rapidly** **Loading doses**: Dilute and administer over at least 20 minutes. **Maintenance doses:** Dilute and administer over 5 minutes which ensures rate does not exceed 1 mg / kg / minute. Note that in babies who are not ventilated respiratory depression can occur at these high doses. *Oral phenobarbital bioavailability in adults is thought to be approximately 100% however oral availability in the neonate may be as low as 48% (3). Oral Phenobarbital Elixir BP (15 mg / 5 mL) contains 38% v/v of ethanol (alcohol) and is not suitable for neonatal / paediatric patients. The RCPCH and NPPG recommend an ethanol-free unlicensed 50 mg / 5 mL liquid.
Midazolam	**BUCCAL** 300 microgram / kg **BUCCAL**, then 300 microgram / kg **BUCCAL** after 5 -10 minutes if required. (1) Round to nearest 50 microgram to allow for measuring.		Carefully check the strength of product available. There two UK licensed buccal midazolam products available (5 mg in 1 mL and 10 mg in 1 mL). If a buccal midazolam preparation is NOT available, the injection can be used (unlicensed).
	IV 150 to 200 microgram /	Not usually indicated	

	kg over 5 minute followed by continuous infusion of 60 micrograms / kg / hour, increased in steps of 60 micrograms / kg / hour every 15 minutes until seizure controlled to a maximum dose of 300 microgram / kg / hour (1)		
Levetiracetam	20 mg / kg IV over 15 minutes if seizures continue a repeat dose can be given after 20 minutes up to a maximum of 40 mg / kg (2)	Initially at 10mg / kg / day IV or PO in 2 divided doses increasing by 10 mg / kg once a week until a maximum dose of 60 mg / kg / day is reached or until the neonate is seizure free	Levetiracetam is renally cleared - in adults approximately 93 % of a dose is excreted in urine within 48 hours. Infants undergoing therapeutic cooling and/or in the neonatal period are likely to have impaired renal and therefore neonatal levetiracetam dosing reflects this (and is different to the dosing recommendations in the APLS algorithm (5))
Phenytoin IV	Initial loading dose: 20 mg / kg over 20-30 minutes	Not usually indicated	Maximum rate of infusion is 1 mg / kg / min. If bradycardia or hypotension occur during administration, consider slowing rate of administration
Pyridoxine	IV: 100 mg (by slow IV injection) over 5 minutes every 24 hours with concurrent EEG monitoring for 7 days Where possible initiate with IV	IV or oral : 50 – 100 mg ONCE daily (1) (6)	Before giving pyridoxine please send the relevant investigations – see flow chart 1 on page 4 IV: Unlicensed imported product – contact local pharmacy before prescribing Oral: tablets can be crushed and dispersed in water prior to administration.

	treatment however oral should be prescribed if IV preparation is not available Oral (where IV is not available): 200 mg every 24 hours for 7 days (6)		
Pyridoxal-5-phosphate	30 – 60 mg / kg / day, orally, in 4 – 6 divided doses (6)		Check with local pharmacy if stocked, may require sourcing from tertiary pharmacy department. Tablets can be crushed and capsules opened but is poorly soluble in water. Sudden respiratory arrest and profound hypotension can occur, therefore commence treatment within working hours and always ensure adequate resuscitation equipment is available, i.e. ideally initiate on HDU / NICU / PICU Blood pressure, pulse, respiratory rate, oxygen saturation should be observed at baseline and then every 15 minutes for 3 hours following the first dose. (6)
Biotin	Oral or IV: 10 mg ONCE daily, adjusted according to response (1)	5 – 20 mg ONCE daily	Crush & disperse tablets in water Give as a slow intravenous injection/bolus over 3 – 5 minutes (6)
Folinic acid (calcium folinate)	Oral or IV: 15 mg ONCE daily (1) (6)		Do not confuse with folic acid, folinic acid is a CNS accessible source of folate Tablets can be crushed and dispersed in water Injection can be given orally (6)

Management of electrical seizures:

In neonates, there is a stronger argument to treat electrical seizures. Interpret CFM with caution when used as a guide to diagnose seizures. However, it is important to discuss with the neonatal consultant before initiating treatment for purely electrical seizures.

Suggested management strategies:

a) Paralysed baby or heavily sedated - if continuous electrical activity over 5 minutes or recurrent clusters (>3-4 clusters in 30 minutes), we should consider treating

b) In babies who you would expect to see clinical activity as they are on minimal sedation etc, interpret CFM more cautiously before using the above approach. If strong suspicion of CFM showing definite seizure activity, treat as above.
If the baby is very well with no clinical signs and doubts about CFM, consider getting a formal EEG for better clarification.

5.1 First line treatment

a) Phenobarbitone continues to be used as first line treatment in most neonatal units. Early administration of phenobarbitone in neonatal HIE may improve clinical outcomes [5] therefore it continues to be used as the 1st line treatment. However, one needs to be mindful that it achieves clinical control in only 30-40% of cases [1] & has adverse effects on cognitive and memory ability.
b) If no IV access is present, 2 doses of buccal midazolam, 10 minutes apart, can be given while IV access is achieved. No more than 2 doses of benzodiazepines should be given to a non-ventilated child in a 24 hour period due to the risk of respiratory depression.

5.2 Second line treatment

Levetiracetam has shown improved neurodevelopmental outcomes in early animal studies and has a favourable pharmokinetic profile with additional safety and efficacy in neonates [5]. It appears to exert a disease-modifying effect on HIE seizures by reducing the number of apoptotic cells in the cerebral cortex significantly reducing hypoxic seizure activity in animal models [5]. No routine drug monitoring is required; it has a large therapeutic window and can also be continued safely as maintenance therapy. It has been shown to be a viable alternative therapy to phenobarbitone and effective treatment for seizures in babies with HIE [6,7].

PLEASE NOTE:
Phenytoin is less commonly used in current practice due to concerns regarding side-effects. It should be avoided in babies with inotropic support and in babies at risk of myocardial dysfunction eg: HIE. It may be considered for refractory seizures not responding to other agents after liaison with the consultant neonatologist or paediatric neurologist.
Intravenous phenytoin has a high pH and is prone to precipitation, when given intravenously care should be taken as extravasation ma cause significant tissue damage.

5.3 Refractory seizures treatment

For neonates who continue to have seizures despite 2 anti-epileptic agents, consider seeking advice from Paediatric Neurology and Metabolic teams who could help guide further investigations and management. Midazolam infusion should be considered at this stage but as this causes respiratory depression and sedation, stabilisation of the airway and semi-elective intubation will be required in most cases.

5.4 Vitamin-responsive seizure treatment

Therapeutic trial of vitamins such as pyridoxine, pyridoxal-5-phosphate and folinic acid should be considered early in the cases of refractory seizures where no other cause is known (see Box 1 in Flow Chart 2 - Stepwise Guide to Seizure Treatment).

Pyridoxine dependent seizures are a rare but a treatable group of neonatal seizures which usually begins shortly after birth resistant to conventional anti-epileptics. Seizures can be of multiple types with associated encephalopathy. The EEG typical shows burst suppression pattern ± focal seizures [4]. Treatment includes administration of a test dose of pyridoxine at 100mg IV which in cases of pyridoxine dependency will cause the seizures to abruptly stop (within minutes) followed by the EEG returning to a normal pattern. Use oral pyridoxine (typically at a dose of 50mg twice daily) if IV preparation is not available. Before giving pyridoxine, please send the relevant investigations – see flow chart 1 on page 4. A repeat dose can be administered and if successful, oral maintenance can be prescribed.

If treatment with pyridoxine is not successful, pyridoxal-5-phosphate, biotin and folinic acid can also be used but subsequently stopped if all investigations rule these conditions out.

Once again, discussion with the Paediatric Neurology and Metabolic team is advised to guide management of these rare conditions.

5.5 Maintenance Treatment:

Most infants with neonatal seizures do not need ongoing maintenance therapy. If maintenance treatment is required, try and aim for monotherapy wherever possible.

Discussion with the Paediatric Neurologist may be helpful to guide treatment.

No maintenance treatment is superior to the other; phenobarbitone needs therapeutic levels monitoring and can be difficult to source in the community.

Phenytoin is not suitable for long term maintenance treatment.

a) First line maintenance is with levetiracetam starting at 5 mg / kg every 12 hours IV or PO; increase dose in steps of 5 mg/kg every 3-7 days until a maximum dose of 30mg/kg every 12 hours (60 mg/kg/day) is reached or until the neonate is seizure free. Ongoing need for this can be reviewed on an outpatient basis.

b) Phenobarbitone 2-5mg/kg OD IV or PO can be used if this was the only agent used for initial control of seizures, and adjusted according to level/response. Check levels 48-72hrs after

initiation, especially if child has ongoing seizures. Levels should be monitored at least once a week to achieve an optimum level of 15-40 mg/L. Most neonates without an ongoing risk of seizures after discharge can wean off phenobarbitone within 12 weeks. If there is a need to continue anti-seizure medications beyond this, levetiracetam or other anti-seizure medications could be introduced to facilitate the weaning of phenobarbitone. Discussion with a paediatric neurologist at this stage is usually helpful.

Risk of seizure reoccurrence in children with neonatal seizures is relatively small [2] and as anti-epileptics are potentially harmful, they should be withdrawn as soon as feasible i.e. as soon as neurological recovery takes place or before discharge from hospital if the baby is seizure free and neurologically normal.

Long term treatment on discharge will be dependent on the underlying cause, response to treatment and should be guided by advice from Paediatric Neurologist.

5. References

[1] Pressler RM, Chapter 6. Neonatal Seizures. Dept of Clinical Neurophysiology, GOSH, London

[2] Appleton R, Gibbs J (Eds). Epilepsy in Childhood and Adolescence. Second edition. London: Martin Dunitz Ltd, 1998

[3] Hart AR, Pilling EL, Alix JJ Neonatal seizures-part 1: Not everything that jerks, stiffens and shakes is a fit. Arch Dis Child Educ Pract Ed. 2015 Aug;100(4):170-5

[4] Hart AR, et al. Neonatal seizures—part 2: Aetiology of acute symptomatic seizures, treatments and the neonatal epilepsy syndromes Arch Dis Child Educ Pract Ed 2015;0:1–7

[5] Levetiracetam in Neonatal Seizures: A Review Allison L. Mruk, PharmD,1 Karen L. Garlitz, PharmD,2 and Noelle R. Leung, PharmD2 J Pediatr Pharmacol Ther 2015;20(2):76–89

[6] A comparison of levetiracetam and phenobarbital for the treatment of neonatal seizures associated with hypoxic-ischemic encephalopathy.Rao LM, Hussain SA, Zaki T, Cho A, Chanlaw T, Garg M, Sankar R. Epilepsy Behav. 2018 Nov;88:212-217. doi: 10.1016/j.yebeh.2018.09.015. Epub 2018 Oct 5.

[7] Levetiracetam for the Treatment of Seizures in Neonatal Hypoxic Ischemic Encephalopathy. Venkatesan C, Young S, Schapiro M, Thomas C.
J Child Neurol. 2017 Feb;32(2):210-214. doi: 10.1177/0883073816678102. Epub 2016 Nov 22.

Adapted from NICU Guidelines, ELHT with their permission and updated.
Dev Kumar Mar 2024