Yorkshire & Humber Pan-Network Neonatal Clinical Guideline

Title: Management of Neonatal Seizures

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This clinical guideline has been developed to ensure appropriate evidence based standards of care throughout the Yorkshire & Humber Neonatal Operational Delivery Network. The appropriate use and interpretation of this guideline in providing clinical care remains the responsibility of the individual clinician. If there is any doubt discuss with a senior colleague.

Best practice recommendations represent widely used evidence-based practice and high quality standards that all Neonatal Units across the Network should implement. Subsequent suggested recommendations may be put into practice in local units. However, alternative appropriate local guidelines may also exist.

A. Guideline summary

1. Aims

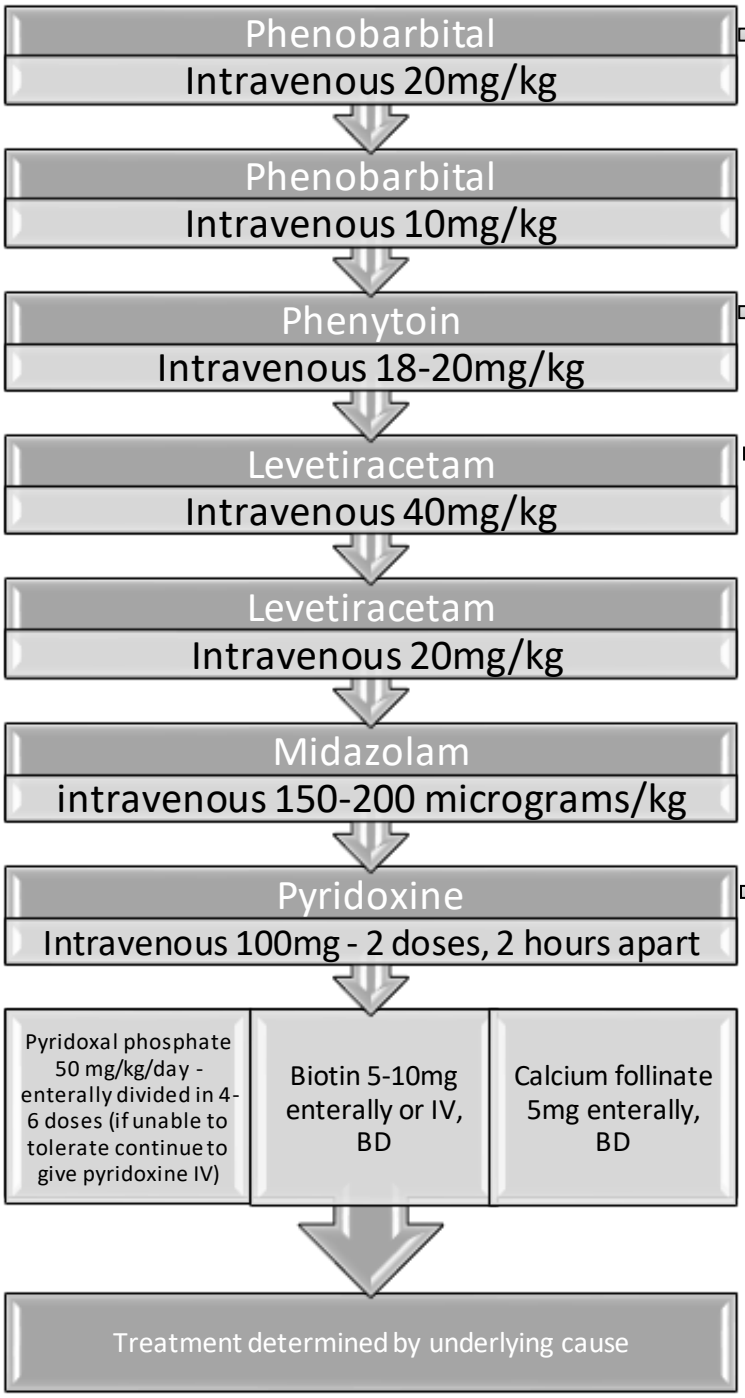
Seizures are a common neurological emergency in the neonatal period. This guideline aims to aid prompt recognition, investigation and treatment.

2. Guideline Summary

- ABCD approach
- Apply aEEG (CFM) as soon as feasible
- Correct any reversible causes (e.g. hypoglycaemia or electrolyte abnormalities)
- Screen for and treat infection, if suspected
- Follow the treatment algorithm to achieve seizure control
- Further investigation as warranted

Seizure treatment algorithm

Move to the next step after 20-30mins if seizures continue & possible underlying causes corrected.



If one or two loading doses of phenobarbital stop seizures, no maintenance dose may be required. If repeated doses are needed, consider a maintenance dose.
2.5-5mg/kg once a day, intravenous or enterally, adjusted according to level/response.
Try to stop as soon as feasible. If needed long term, convert to another anti-epileptic e.g. levetiracetam.

If maintenance dose required:
Phenytoin: intravenous or enterally 5-20mg/kg/day divided into two doses according to levels/response.

Levetiracetam: intravenous or enterally up to 50mg/kg/day divided into 2 or 3 doses.

Consider seizures as refractory and seek specialist advice

Continue vitamins until either the biochemical tests come back ruling out these conditions or there has been no response after two weeks. If a response is seen, consider maintenance doses whilst working out which drug has had the most effect.

B Full guideline and evidence

1. Background

Seizures are a common neurological emergency in the neonatal period, occurring in 1–5 per 1000 live births.[1] The majority of neonatal seizures are provoked by an acute illness or brain insult with an underlying aetiology either documented or suspected, that is, these are acute provoked seizures (as opposed to epilepsy). They are also invariably focal in nature. The majority of neonatal seizures are due to hypoxic-ischaemia, stroke, or infections in term infants. In preterm infants, intraventricular haemorrhage is the commonest cause.[2] Other causes include cortical malformations, acute and inborn errors of metabolism, genetic aetiologies, neonatal drug withdrawal and birth-related head trauma.

2. Diagnosis

The clinical diagnosis of neonatal seizures is difficult. This is in part because there may be no, or very subtle, clinical features, and also because neonates frequently exhibit non-epileptic movements that can be mistaken for epileptic seizures. In light of this, video-EEG recording is considered the gold standard for diagnosis. However, as most neonatal units do not have access to video-EEG recording, aEEG (CFM) is recommended. It should be noted that aEEG /CFM does not detect all seizures, but approximately 85% where two channels and a single lead EEG is available, assuming good clinical competence at its interpretation. Where seizures are persistent or the cause remains unknown, an EEG should be requested.

The International League Against Epilepsy (ILAE) has modified their 2017 classification of seizures and epilepsies as relevant to neonates[1]. Only events with an EEG correlate are included in the classification. The initial stage of describing a neonatal seizure should specify whether a seizure is with (electroclinical) or without clinical signs (electrographic-only).
Descriptors are determined by the predominant clinical feature and divided into motor, non-motor, and sequential. See Appendix 1 for the full ILAE classification.

It is equally important to identify which movements are not seizures, particularly in the absence of EEG/CFM recording. See Appendix 2 for descriptions of movements which may not be seizure related.

Overall diagnostic certainty will be determined by:

- type of movements,
- duration,
- frequency
- EEG/CFM correlation.
- If baby is treated for, or has features of, a condition associated with seizures, then it is more likely that any abnormal movements are seizure activity.

For example, the diagnosis may be less certain in an otherwise well baby on the postnatal ward compared to an unwell baby with HIE where there is CFM correlation. Senior input would be required in such circumstances to aid decision making regarding investigation and treatment.

3. Management

History[3]

- Maternal/antenatal: maternal age, scans, infection screens/known antenatal infections (TORCH), consanguinity, family history, diabetes/gestational diabetes, illicit drug use/prescription medications and significant family history of metabolic problems.
- Intrapartum: risk factors for infection (pre-labour rupture of membranes, known GBS, maternal sepsis), evidence of fetal distress during labour/delivery, difficulties at delivery (prolonged second stage, placental abruption, cord prolapse, suspected hypoxic episode, difficult extraction, requirement for active resuscitation), evidence of neurological dysfunction following delivery.
- Postnatal: Prematurity, post term (>42 weeks) low birth weight, feeding history. Where possible a witness account of a clinical seizure should be gained (what was happening pre, during and post seizure) this should be documented clearly.

Examination[3]

- Neurological: tone, posture, movements, peripheral and primitive reflexes, gaze, pupillary reaction, facial movements, fontanelle, head circumference (for baseline)
- General: dysmorphic features, neurocutaneous lesions, birth marks, bruising/bleeding, cardiac, respiratory and abdominal systems.

Investigation[3,4,5,6]

If there is a clear history and examination/preliminary findings that explain the seizures (e.g. history suggestive of HIE) then no further investigation is required. If there is no clear cause identified from the first line investigations and the seizures are refractory, further investigations are required.

First line investigations		
Blood gas	Glucose Lactate	Lactate is typically high following HIE, falls to normal within days. Persistent elevation should trigger further investigation
Haematology	FBC	
Biochemistry	Urea & electrolytes Calcium Magnesium Liver function tests	
Septic screen	CRP Blood culture Consider lumbar puncture (if significant infection concerns)	
Imaging	Cranial ultrasound scan	Including Dopplers to exclude AVM
Neurophysiology	aEEG/CFM	See Appendix 3 for information on how to apply and interpret CFM

Early diagnostic investigations		
Metabolic	Ammonia	Up to about 110 µmol/L may be seen in sick babies. Very high levels (>200 µmol/L) may indicate a urea cycle defect and warrants further investigation.
CSF	MC&S (if not already done) Paired CSF and serum glucose Paired CSF and serum lactate	Meningitis CSF glucose for GLUT1 deficiency CSF lactate for mitochondrial disorders
Infection	Herpes PCR	Herpes infection unlikely to present until around or beyond 7 days of age

Second line investigations if cause still unknown		
Blood metabolic screen	Plasma amino acids	
	Acylcarnitine	
	Serum uric acid	Molybdenum cofactor and sulphite oxidase deficiencies (often lactate high too), as well as purine and pyrimidine disorders
	Serum biotinidase	Biotin deficiency
	VLCFA phytanic acid and pristanic acid	Peroxisomal disorders, (dysmorphic with skeletal/renal/liver anomalies and cataracts)
	Copper and caeruloplasm	Menke's disease
Urine metabolic screen	Urine reducing substances	
	Urine alpha amino-adipic semialdehyde (AASA)	Vitamin B6 epilepsy; Pyridoxine dependant seizures

	Urine sulphocysteine	Molybdendum cofactor defieiceny and sulphite oxidase defiency
	Urinary purines and pyrimidines	Purine and pyrimidine disorders
	Urine amino and organic acids	
TORCH screen		
Genetic testing	Karyotype and array with DNA for analysis	Chromosomal abnormalities
	Consider R14 rapid exome sequencing in cases of refractory seizures without clear cause	Single gene disorders causing epilepsy and metabolic conditions
CSF	Paired CSF and plasma pipecolic acids	Vitamin B6 epilepsy: Pyridox(am)ine phosphate oxidase deficiency (PNPO). Also deranged in peroxisomal disorders
	CSF neurotransmitters and folate levels	Folinic acid responsive seizures and other neurotransmitter disorders, goes on ice. Discuss with lab prior to taking
	CSF lactate	Mitochondrial disorders, plasma lactate can be normal.
	CSF glucose	GLUT 1 deficiency (FH of seizures/learning disorders)
	Paired plasma and CSF amino acids	Non-ketotic hyperglycinaemia and serine deficiencies
Imaging	MRI	Consider HIE timing
Neurophysiology	EEG	

See Appendix 4 for a printable table of investigations

Approach to treatment

No nationally agreed guidelines exist on the acute treatment of neonatal seizures. [7] In complex epilepsy syndromes treatment should be guided by advice from a specialist neurologist.

- Initial management should be with an ABCD approach
- Apply aEEG (CFM) as soon as feasible
- If HIE is suspected and the criteria for cooling are met then this should be commenced (see YH neonatal ODN “Management of HIE and total body cooling” guideline)
- Identify and correct any reversible cause such as hypoglycaemia or electrolyte abnormalities
- If infection is suspected then appropriate investigations should be undertaken (as above) and antibiotics +/- aciclovir should be commenced
- Neonatal seizures can contribute to poor neurodevelopmental outcome so getting them under control promptly is important. However, the decision to start anticonvulsant treatment may not be straightforward. Consider:

- Is this truly seizure activity? (see appendix 2) What is the level of diagnostic certainty (as discussed in section 2)? CFM correlation will be helpful in making this decision.
- The duration of the seizure: a single brief seizure, with no cardiorespiratory compromise, will not require treatment, whereas a single seizure >5mins will.
- The frequency of seizures: repeated seizures, even if shorter (>3 per hour), will also merit treatment.
- Overall there will be an increased readiness to treat if seizure activity is more probable and/or more severe.

Use of CFM at low gestations is not universal practice. Reasons for this include that the background pattern of CFM in preterm infants is not typical of that of term infants, and also the potential for injury from needle electrodes. Use of CFM below 36 weeks can be considered for the detection of seizures on a case by case basis.

Anticonvulsant treatment

Without good evidence that other antiepileptic drugs are better and safer, it seems logical to retain phenobarbital for first-line use for acute seizures[7]. A small randomized controlled trial suggests phenytoin is as effective as phenobarbital, but there may be reasons not to give, it such as where cardiovascular / dysrhythmia concerns exist or the intravenous access is difficult and the risk of extravasation is significant.

Wait 20-30 minutes before moving to the next step in the algorithm if seizures are not yet controlled. Drugs not mentioned in the algorithm (e.g. sodium valproate and lignocaine) should be used only under specialist advice.

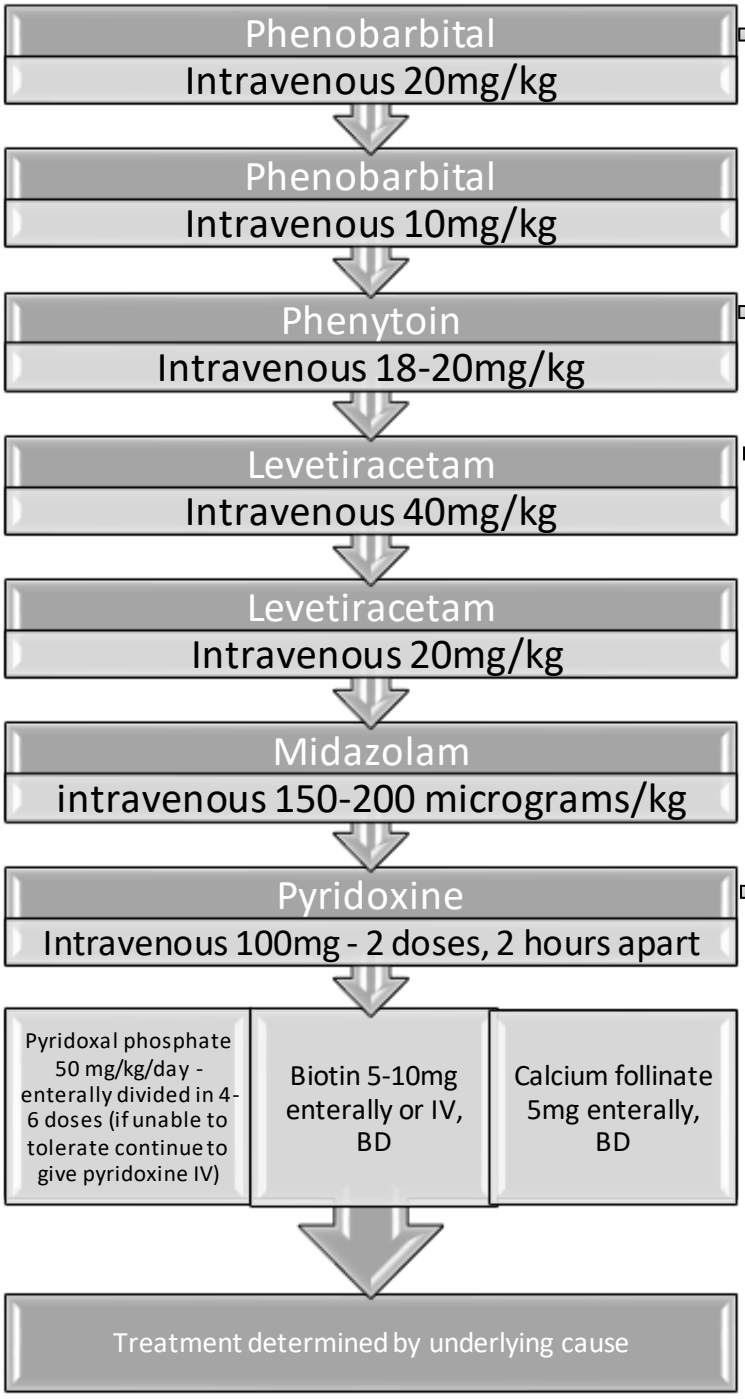
Treatment of epilepsy syndromes will be guided by the specific syndrome – consider discussing with a neurologist.

As per the algorithm (below), maintenance phenobarbital can be considered if repeated loading doses are required. The dose is 2.5-5mg/kg once daily and this should start no earlier than 12-24 hours after the last loading dose. Therapeutic drug monitoring is required:

- Time to steady state is approximately 10-14 days
- Take a trough sample immediately prior to the next dose
- Therapeutic range is 15- 40mg/L

Seizure treatment algorithm

Move to the next step after 20-30mins if seizures continue & possible underlying causes corrected.



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Continue vitamins until either the biochemical tests come back ruling out these conditions or there has been no response after two weeks. If a response is seen, consider maintenance doses whilst working out which drug has had the most effect.

Vitamin trial[4]

In refractory seizures an early trial of vitamin treatments is used when no other obvious aetiology can be identified.

In babies who present as HIE with refractory seizures, a vitamin trial may be considered as babies with underlying metabolic pathologies are prone to decompensation around the time of delivery and can present with encephalopathy. This should be discussed with paediatric neurology.

- The initiation of treatment should not be delayed for investigations to be done as treatment will probably not interfere with the ability to detect the disorders and some of the tests need to be done in working hours.
- Diagnosing these disorders can be difficult and should be discussed with the specialist paediatric neurology team. However, in short, if the seizures stop, then we can work out what it is later. If not, then you've probably answered your question.

Steps in vitamins trial: (to be done with aEEGmonitoring)

1. Pyridoxine 100mg IV 2 doses 2 hours apart as test doses – May cause apnoeas and therefore it is recommended that babies are on close monitoring or intubated and ventilated first.
    a. If there is a good response to IV Pyridoxine can then it can be given orally/IV 15mg/kg/day (maximum 500mg) in divided doses and continued until the results of the pipecolic acids and / or urine AASA are back (discuss with neurology team)
    b. If no response, do not start regular pyridoxine but continue with step 2
    c. Ensure urine AASA sent (Alpha amino-adipic semialdehyde). It is not affected by supplementation
2. If seizures persist >2 hours after the second dose in the pyridoxine trial, start the following oral vitamins together and continue them until either the results of investigations are back or there is no response seen after 2 weeks of treatment.
    a. Pyridoxal phosphate 50mg/kg/day PO in 4 or 6 divided doses
        i. If NBM or unable to tolerate pyridoxal phosphate (it can cause significant vomiting) continue IV pyridoxine as above
        ii. Send paired plasma and CSF pipecolic acid. It is probably affected by supplementation. Discuss with the lab prior to sending CSF
    b. Biotin 5mg BD PO/IV

i. Ensure plasma biotinidase has been sent. It is not affected by supplementation. Clues to the diagnosis include a marked metabolic acidosis, rash that looks like eczema, lack of hair or friable hair
ii. Can increase up to 10mg BD

c. Folinic Acid 5mg BD PO/IV (prescribe as calcium folinate on drug card to avoid confusion)
   i. Send CSF neurotransmitters and urine amino acids. Discuss with the lab prior to sending CSF. These will be affected by supplementation.
   ii. Can increase up to 8mg/kg/day

Withdrawal of anticonvulsant treatment

Once the baby has been seizure free for 24- 48 hours anticonvulsant treatment can start being withdrawn. For those only on phenobarbitone, this can be stopped without tapering the dose. For those on more than one medication, each medication should be stopped one at a time. aEEG (CFM) should be used while weaning midazolam infusions. Vitamin treatments can be withdrawn once test results rule out the conditions or if no response after 2 weeks.

4. Audit Criteria

5. Appendices

ILAE classification of Seizures
Epileptic and Non Epileptic movements
CFAM
Table of investigations

Appendix 1 – ILAE classification of seizures

Type		Description	Clinical context of seizure type
Motor	Automatisms	A more or less coordinated motor activity usually occurring when cognition is impaired. This often resembles a voluntary movement and may consist of an inappropriate continuation of pre-ictal motor activity. Typically oral in neonates.	Seen in HIE and preterm infants. Often part of sequential seizures.
	Clonic	Jerking, either symmetric or asymmetric, that is regularly repetitive and involves the same muscle groups.	Typical seizure type in neonatal stroke or cerebral haemorrhage. May be seen in HIE.
	Epileptic spasms	A sudden flexion, extension, or mixed extension-flexion of predominantly proximal and truncal muscles that is usually more sustained than a myoclonic movement but not as sustained as a tonic seizure. Limited forms may occur: Grimacing, head nodding, or subtle eye movements. Brief in neonates thus may be difficult to differentiate from myoclonic seizures.	Rare. May be seen in inborn errors of metabolism or early infantile developmental and epileptic encephalopathy (DEE).
	Myoclonic	A sudden, brief (<100 msec) involuntary single or multiple contraction(s) of muscle(s) or muscle groups of variable topography (axial, proximal limb, distal). Clinically difficult to differentiate from non-epileptic myoclonus.	Typical seizure type in inborn errors of metabolism and preterm infants. May also be seen in early infantile DEE.
	Tonic	A sustained increase in muscle contraction lasting a few seconds to minutes. Focal, unilateral or bilateral asymmetric. Generalised tonic posturing not of epileptic origin.	Typical seizure type in early infantile DEE and genetic neonatal epilepsies.
Non-motor	Autonomic	A distinct alteration of autonomic nervous system function involving cerebrovascular, pupillary, gastrointestinal, sudomotor, vasomotor, and thermoregulatory functions. May involve apnoea.	Rare in isolation. Seen in intraventricular haemorrhage as well as temporal or occipital lobe lesions. Also described in early infantile DEE.
	Behavioural arrest	Arrest (pause) of activities, freezing, immobilization, as in behavior arrest seizure.	Rare as an isolated seizure type. More commonly seen as part of sequential seizure.
Sequential		No predominant feature can be determined, instead the seizure presents with a variety of clinical signs. Several features typically occur in a sequence, often with changing lateralization within or between seizures.	Often seen in genetic epilepsies such as self-limiting neonatal epilepsy or KCNQ2 encephalopathy.
Electrographic only		Subclinical, without clinical classification.	Often seen in preterm infants, HIE (particularly those with basal ganglia/thalamus injury), critically ill and neonates undergoing cardiac surgery.
Unclassified		Due to inadequate information or unusual clinical features with inability to place in other categories	

Table adapted from Pressler, R.M., Cilio, M.R., Mizrahi, E.M., Moshé, S.L., Nunes, M.L., Plouin, P., Vanhatalo, S., Yozawitz, E., de Vries, L.S., Puthenveettil Vinayan, K., Triki, C.C., Wilmshurst, J.M., Yamamoto, H. and Zuberi, S.M. (2021), The ILAE classification of seizures and the epilepsies: Modification for seizures in the neonate. Position paper by the ILAE Task Force on Neonatal Seizures. Epilepsia, 62: 615-628. https://doi.org/10.1111/epi.16815

Appendix 2 – Epileptic and non-epileptic movements

Movements that are frequently epileptic include

- Generalised myoclonic jerks
- Myoclonic jerks of the diaphragm leading to frequent hiccups
- Clonic jerking of the limbs that does not improve with holding or moving the affected joint, particularly if associated with autonomic features and tonic eye deviation
- Rhythmical tonic thrusting of the tongue, especially associated with other clonic movements of the limbs and/or tonic eye deviation
- Focal tonic seizures, especially if associated with eye deviation
- Tonic eye deviation without limb involvement when associated with autonomic features, often occurring after rapid eyelid fluttering
- Epileptic spasms
- Electrical seizures on EEG without clinical features (subclinical seizures)

Movements that should not be assumed to be epileptic or treated without further investigation include

- Cycling
- Pedalling
- Swimming
- Thrashing of limbs
- Movement of head from side to side
- Sucking
- Lip puckering
- Grimacing
- Tongue protrusion
- Blinking without tonic eye deviation
- Roving eye movements
- Nystagmus
- Generalised tonic stiffening

Movements that are not likely to be epileptic

- Tremor or jitteriness
- Clonus
- Myoclonus seen only in sleep
- Dystonia
- Startle with or without tonic stiffening – consider hyperekplexia

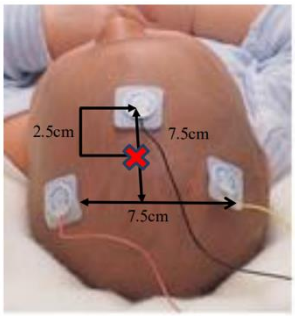
Table adapted from Hart AR, Pilling EL, Alix JJ. Neonatal seizures-part 1: Not everything that jerks, stiffens and shakes is a fit. Arch Dis Child Educ Pract Ed. 2015 Aug;100(4):170-5. doi: 10.1136/archdischild-2014-306385

Appendix 3 – CFM

How to apply CFM (as per YH ODN "Management of Hypoxic Ischaemic Encephalopathy Including Therapeutic Hypothermia" guideline)

Either single channel or dual aEEG can be used. The site of electrode placement is as described below for both types but please refer to local guidelines for your monitor. Needle EEG electrodes are commonly used and the use of collodion may be considered to hold the electrodes in place.

Single channel



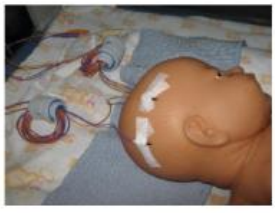
fontanelle

Dual Channel

2 leads each side and a central reference electrode as with single channel above or a gel reference electrode placed on the shoulder.

Position the strip vertical and parallel to the baby's face. Align strip so that the letter (A-H) at the saggital suture is the same as the letter at the tragus

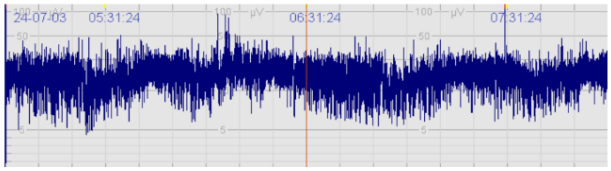
Using a marker pen, mark the two sensor sites at the ends of the arrows.



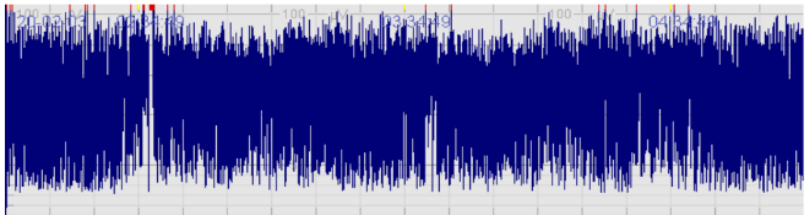
Insert a needle electrode subdermally at insertion sites. Leads are directed to the top of the head
Ensure all metal is under the dermal layer

Examples of CFM traces[9]

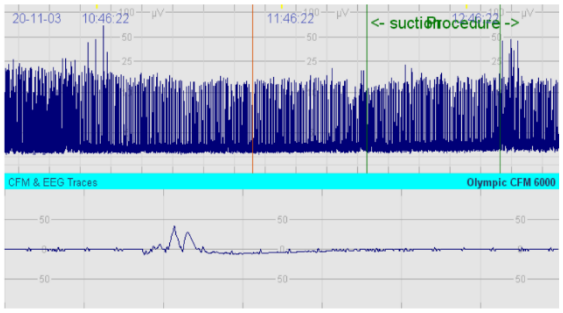
1. Normal CFM – lower margin >5, upper margin >10, sleep wake cycling



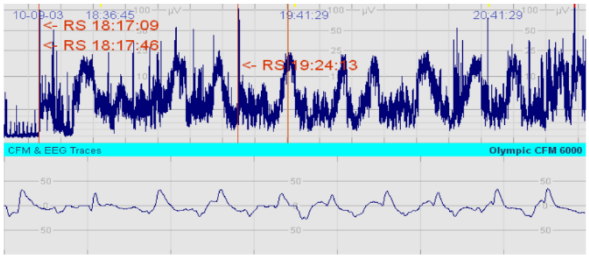
2. Moderately abnormal CFM – lower margin <5, upper margin >10, no sleep wake cycling



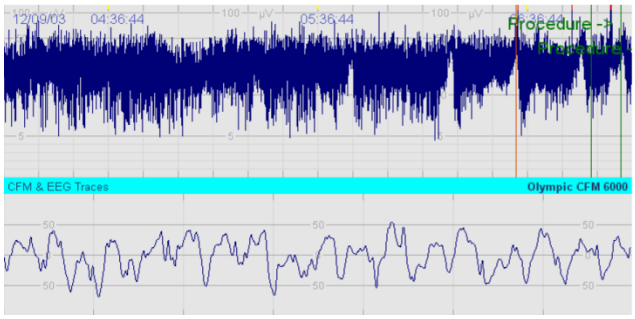
3. Severely abnormal CFM – EEG shows brief burst on isoelectric background



4. Frequent seizures – trace narrows and rises up. Confirmed on EEG



5. Normal CFAM amplitude. Seizures present and confirmed on EEG



Appendix 4 – Table of investigations

	Date sent	Result
First line Investigations		
Blood gas		
FBC		
U&E		
Calcium		
Magnesium		
LFT		
CRP		
Blood culture		
CSF MC&S		
Cranial ultrasound scan		
aEEG/CFM		
Early diagnostic investigations		
Ammonia		
CSF glucose		
CSF lactate		
Serum glucose		
Serum lactate		
Herpes PCR		
Second line investigations		
Plasma amino acids		
Acylcarnitine		

Serum uric acid		
Serum biotinidase		
VLCFA phytanic acid and pristanic acid		
Copper and caeruloplasm		
Urine reducing substances		
Urine alpha amino-adipic semialdehyde (AASA)		
Urine sulphocysteine		
Urinary sulphites, purines and pyrimidines		
Urine amino and organic acids		
Karyotype and array with DNA for analysis		
Paired CSF and plasma pipecolic acids		
CSF neurotransmitters and folate levels		
CSF lactate		
CSF glucose		
Paired plasma and CSF amino acids		
MRI		
EEG		

6. Contributors and Sources

With the guideline groups thanks to Dr Hart for his contribution to this document

7. References

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