Bradford Teaching Hospitals NHS
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Management of Neonatal Seizures

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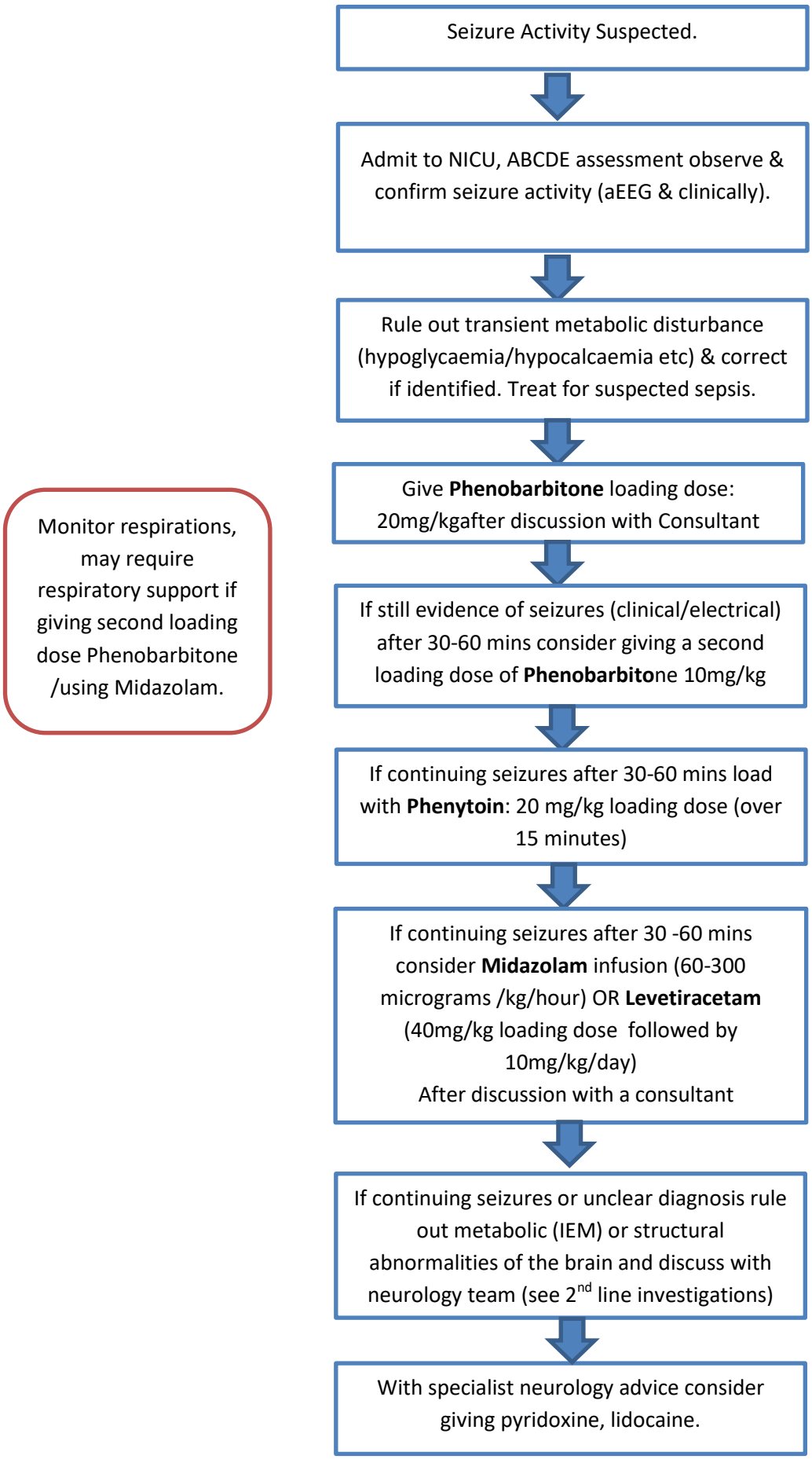
ACUTE MANAGEMENT OF NEONATAL SEIZURES



Background

Neonatal seizures represent the most common neurological pathology in the neonatal period. There are a variety of causes for neonatal seizures, these include: [1,2,3,4,5,]

- **Hypoxic Ischaemic Encephalopathy** (HIE) secondary to perinatal asphyxia (most common).
- **Metabolic disturbances**:
    - More common: hypoglycaemia, hypocalcaemia, hypomagnesaemia, hyper/hyponatraemia.
    - Rarer: pyridoxine dependency, inborn errors of metabolism (IEM).
- **Infections**: Meningitis. Meningoencephalitis secondary to congenital infections (TORCH).
- **Intracranial Haemorrhage**, intracranial infarction.
- **Developmental defects**: Cerebral dysgenesis and neuronal migration disorders (very rare).
- **Drugs**: drug withdrawal (NAS), drug toxicity.
- **Neonatal epilepsies**.
- **Idiopathic** (~10%)

Due to this wide range of aetiologies careful investigation is required in order to manage neonatal seizures effectively, as not all will require antiepileptic drugs (AEDs):

Hypoglycaemia and treatable metabolic disturbances should be treated prior to anticonvulsant therapy[4,5].

There is limited evidence to guide us on the choice of anticonvulsants due to lack of extensive research and varying practices across the world. [1,2,3,4,5]:

Phenobarbital/phenobarbitone is considered as a first line treatment mainly due to tradition and its known safety profile. **Phenytoin** is often used as second line, again due to its tradition/familiarity. It has been found to show seizure reduction when used second line with phenobarbitone.[6] There is however concerns regarding a risk of neurotoxicity and known difficulty in preparation/prescription. Benzodiazepines such as **Midazolam** are then popular regarding their comparable efficacy. They do however cause sedation and often the neonate required ventilation.[7] **Levetiracetam** (Keppra) is being used and studied as a choice especially in seizures not responding to conventional treatment. It has been found to reduce seizures when used 2nd or 3rd line and limited side effects have been reported.[6,7]

Approach to Management of neonatal seizures

Acute assessment using ABCDE approach to ensure baby is stable (do **blood glucose** at this stage and treat with a bolus of 10% dextrose if required – 2.5ml/kg).

History:

- 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 (prelabour 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)

- 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: A thorough neurological and general examination to help identify aetiology:

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

Investigations. You should obtain an aEEG trace after admission to NNU.

1st line investigations

- Blood gas – pH, pCO_2, BE, lactate, glucose, ionised calcium
- FBC
- U&E – renal function, Na, K, Mg, Ca
- LFT's
- Ammonia
- Septic screen – Blood culture, CRP, LP (consider viral PCR's if appropriate), urine culture

Neuroimaging

- Cranial USS – to identify intraventricular haemorrhage, arterial stroke, malformations and infections. Should be carried out as early as possible.
- MRI – to identify changes of HIE, arterial and venous stroke, meningitis/encephalitis, inborn errors of metabolism and congenital malformations. Can be carried out later into investigations.

Electrophysiology

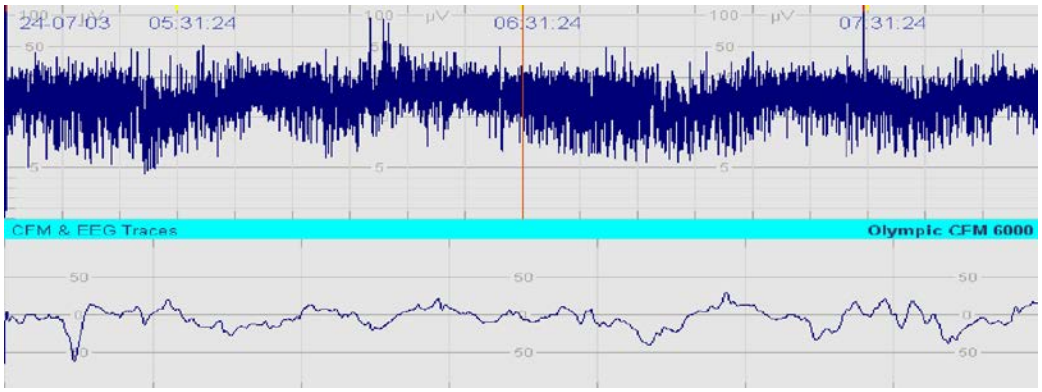
- aEEG – all babies being investigated for seizures require EEG monitoring.
- Multichannel EEG – contact Neurophysiology Department (SLH)

2nd line investigations

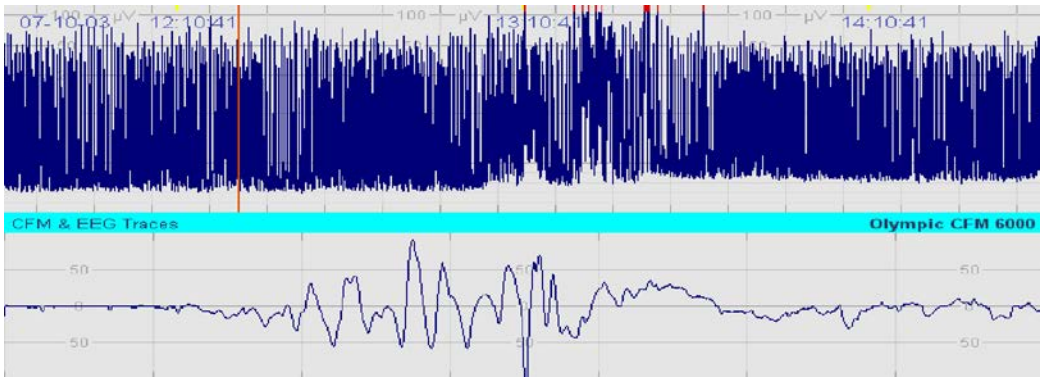
- Metabolic screen – serum amino acids, acylcarnitine, TORCH, urine organic and amino acids, urine reducing substances
- Genetic testing
- LP – neurotransmitters, paired glucose/lactate/amino acids

aEEG/CFAM Examples[8]

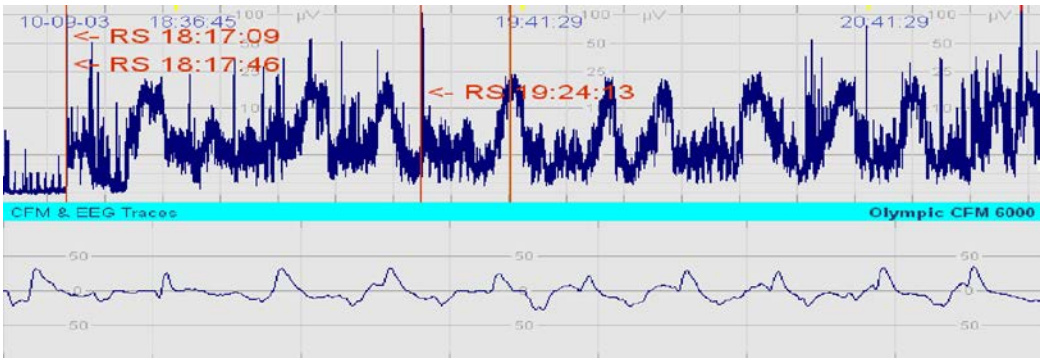
1. Normal CFM voltage, sleep wake cycle. Lower margin >5, upper margin >10



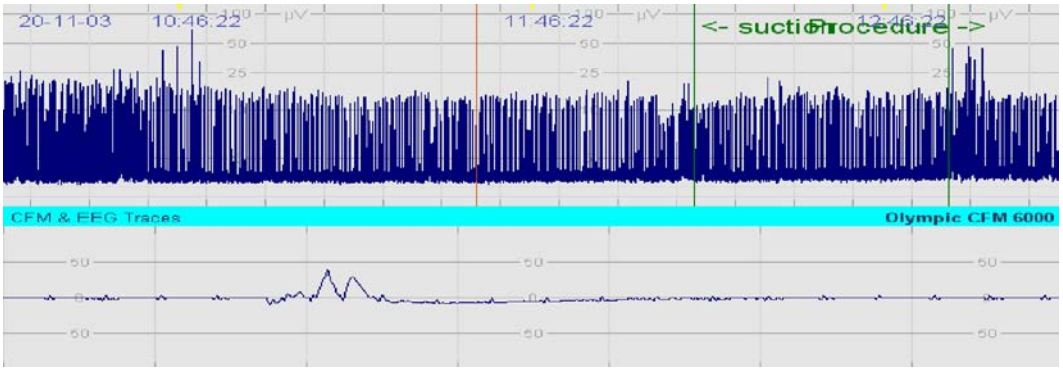
2. CFM amplitude varying between moderately and severely abnormal trace. EEG shows burst suppression pattern



3. Frequent seizures confirmed by inspecting EEG.



4. Severely abnormal CFM. EEG shows brief burst on isoelectric background.



Management will then be guided by probable aetiology (some baby's may require all or few interventions depending on the findings of the investigations/underlying cause): Commence **aEEG monitoring** in any baby with suspected seizures.

- If **HIE** is suspected and current criteria for cooling are met this should be commenced (with senior clinician approval).
- If **hypoglycaemia** is found an IV 10% dextrose bolus should be given (2.5 ml/kg) .
- If **electrolyte imbalances** are discovered these should be corrected e.g. hypocalcaemia
- All babies with confirmed seizures where **infection** is considered a possible cause should be investigated for infection and antibiotics commenced with a view to obtain CSF for analysis at the earliest possible opportunity.
- It is also important to consider viral infections (eg. Herpes simplex) and history should be obtained to rule out active maternal lesions. If Herpes infections are suspected, then appropriate investigations (Herpes PCR – blood / CSF obtained) should be completed and Aciclovir should be considered.
- If an **IEM** is suspected (high ammonia/lactate/family history) then relevant investigations and specialist metabolic advice should be sought.
- **When the decision to treat neonatal seizures with AEDs has been made (by a senior clinician) the medications may be used in order as seen in flowchart / table 1 [6,7,9,10].**
- When a baby has been seizure free for >24 hours you should consider withdrawing medications. For those only on phenobarbital this can be stopped without tailoring the dose. If the baby was on more than one medication these should be stopped separately (consider discussion with neurology and decision made based on the underlying cause)
- If seizures re-occur then AEDs should be recommenced in order as before
- Treatment with **maintenance Phenobarbitone (5-7mg/kg/day)** or other anticonvulsants (Levetiracetam) needs to be considered if seizures have been recurrent or difficult to control / depending on the underlying aetieology and may be used to wean off the other anticonvulsants.

It is known that neonatal seizures can be hard to recognise both clinically and eletrographically and this becomes more difficult following medications. aEEG monitoring cannot detect all electrical seizure activity and recent studies have started to use cEEG monitoring in neonates[12].

If seizures are refractory following first three AEDs:

- Discussion with neurology team by senior clinician for advice on further investigations/management options. Also consider discussion with metabolic/genetic team.
- Consider
  - Rare conditions: e.g. pyridoxine dependency, non-ketotic hyperglycinemia , neuronal migration disorders
  - Trial of pyridoxine, with specialist advice (100mg iv with EEG monitoring, followed by 30mg/kg/day for at least 3 days)
  - Further AEDs such as lidocaine with specialist advice

The National Metabolic Biochemistry Website has some useful guidelines - http://www.metbio.net/metbioGuidelines.asp - including presentation and investigations for suspected metabolic disorders.

Follow up

- *Around 20-30% of neonates with perinatal seizures will develop postnatal epilepsy. More likely in those with infectious etiology, stroke, brain malformations. A decision needs to be made regarding when to stop phenobarbitone if it has been started regularly. Long-term phenobarbitone treatment does not prevent neonatal epilepsy and early discontinuation maybe favourable to avoid neurotoxic side effects*[11]
- The neonate will require follow up to assess neurodevelopmental progress.
- Discussion with neurology and radiology regarding future imaging requirements.

Table 1

	1st Line Phenobarbital/ Phenobarbitone	**2rd Line Phenytoin**
Dose	20mg/kg loading dose 5mg/kg/day maintenance	20 mg/kg loading dose 2.5 mg/kg bd maintenance
Preparation	To prepare phenobarbitone from 200mg/ml vials Take 1ml of 200mg/ml Dilute to 10ml with water for injection = 20mg/ml Use proportion of this to give dose	Dilute to a concentration not exceeding 10mg/ml with 0.9% sodium chloride. NOT compatible with glucose. Phenytoin 250mg/5ml Line should be flushed with Sodium chloride 0.9% before and after administration.
Administration	IV loading dose over 20 minutes (no faster than 1mg/kg/minute)	IV loading dose over 15 minutes (at a rate not exceeding 1mg/kg/minute). Should be infused via a filter
Monitoring	No routine monitoring of levels. If clinical suspicion of toxicity/no response to treatment levels should	Monitoring of levels is recommended if on for more than 2-3 days or if clinical suspicion of toxicity/no response to treatment levels should be done.

	be considered. Be aware that there is reduced drug clearance in cooled babies. Therapeutic Blood Levels 20 - 40mg/Litre	 Trough levels: Neonate <3 months 6-15mg/litre. >3months 10-20mg/litre.
Side Effects	Drowsiness Respiratory depression	Drowsiness/reduced consciousness Vomiting Rash Neurotoxicity

	3rd[rd]Line Midazolam	**3[rd] Line Levetiracetam**
Dose	60-300 micrograms/kg/hour May need loading dose 200 micrograms/kg (senior decision)	40mg/kg loading dose followed by 10mg/kg/day once daily (Alternative dosage – 10mg/kg twice daily increasing by 10mg/kg/ day over 3 days to 30mg/kg twice daily)
Preparation	10mg into 50mls of 5% or 10% glucose= 200micrograms per ml	Dilute to 10mg/ml. Take 1ml (100mg) of 100mg/ml levetiracetem and add to 9ml of 5% glucose.6
Administration	Loading dose – over 2 minutes. Continuous infusion	Admininister over 15 minutes.
Monitoring	No routine blood levels Be aware that there is likely a reduced drug clearance in cooled babies.	Continue to monitor sediatory effects with multiple AEDs
Side Effects	Hypotonia, Hypotension Respiratory depression Coma Antidote: flumazenil (10micrograms/kg) May be used to unmask fits caused by benzodiazepine	Drowsiness, diarrhoea/vomiting.

SEIZURE INVESTIGATIONS LIST

Name

Hospital number

Date of birth

INVESTIGATION	DATE SENT	DATE EXPECTED	RESULT
Blood gas			
FBC			
U&E's			
LFT's			
Ammonia			
Septic screen ● Blood cultures ● Urine culture ● LP ● CRP			
Metabolic screen ● Acylcarnitine ● Serum AA's ● Urine OA's ● Urine AA's ● Urine reducing substances			
Genetic testing (discuss with genetics)			
TORCH			
CSF			
Cr USS			
MRI			
EEG			

INVESTIGATION SHEET TO BE FILED BEHIND DAILY BLOOD TESTS

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